لجنة عمداء كليات الصيدلة
لجنة توحيد منهاج مادة (Therapeutics II)

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تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي . لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتيبها وتنظيمها لتكون واضحة يسيرة على طلبتنا الاعزاء .. نأمل من طلبتنا الاعزاء الاستفادة منه في طريقهم الى النجاح والتفوق ، والله الموفق

Adrenal Gland Disorders

INTRODUCTION

- Hyperfunction of the adrenal glands involves excess production of the adrenal hormones cortisol (resulting in Cushingsyndrome) or aldosterone (resulting in hyperaldosteronism).
- Adrenal gland hypofunction is associated with primary (Addison disease) or secondary adrenal insufficiency.

CUSHING SYNDROME: PATHOPHYSIOLOGY

- Cushing syndrome results from effects of supraphysiologic glucocorticoid concentrations originating from eitherexogenous administration or endogenous overproduction by the adrenal gland (adrenocorticotropic hormone [ACTH] dependent) or by abnormal adrenocortical tissues (ACTH independent).
- ACTH dependent Cushing syndrome (80%of all Cushing syndrome cases) is usually caused by overproduction of ACTH by the pituitary gland, causing bilateral adrenal hyperplasia. Pituitary adenomas account for about 85% of these cases (Cushing disease). Ectopic ACTH secreting tumors and nonneoplastic corticotropin hypersecretion cause the remaining 20% of ACTH dependent cases.
- Ectopic ACTH syndrome refers to excessive ACTH production resulting from an endocrine or nonendocrine tumor,usually of the pancreas, thyroid, or lung (eg, small•cell lung cancer).
- ACTH-independent Cushing syndrome is usually caused by adrenal adenomas and carcinomas.

CLINICAL PRESENTATION

- The most common findings in Cushing syndrome are central obesity and facial rounding (90% of patients). Peripheralobesity and fat accumulation occur in 50% of patients. Fat accumulation in the dorsocervical area (buffalo hump) is nonspecific, but increased supraclavicular fat pads are more specific for Cushing syndrome. Patients are often described as having moon facies and a buffalo hump.
- Other findings may include myopathy or muscular weakness, abdominal striae, hypertension, glucose intolerance, psychiatric changes, gonadal dysfunction, facial plethora (reddish complexion), and amenorrhea and hirsutism inwomen.
- Up to 60% of patients develop Cushing•induced osteoporosis; about 40% present with back pain, and 20% progress tospinal compression fractures.

DIAGNOSIS

- Hypercortisolism can be established with one or more of the following tests: 24 hour urinary free cortisol (UFC), midnight plasma cortisol, late• night (11 PM) salivary cortisol, and/or low dose dexamethasone suppression test(DST).
- Other tests to determine etiology are plasma ACTH; adrenal vein catheterization; metyrapone stimulation test; adrenal, chest, or abdominal computed tomography (CT); corticotropin releasing hormone (CRH) stimulation test; inferior petrosal sinus sampling; and pituitary magnetic resonance imaging (MRI).
- Adrenal nodules and masses are identified using high resolution CT scanning or MRI.

TREATMENT

- Goals of Treatment: Limit morbidity and mortality and return the patient to a normal functional state by removing thesource of hypercortisolism while minimizing pituitary or adrenal deficiencies.
- Treatment plans in Cushing syndrome based on etiology:

Table1: Treatment Options in Cushing Syndrome Based on Etiology

Etiology	Nondrug	Drug Name	Dosing		
			Initial Dose	Usual Range	Maximum
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone 250-mg capsules	1–2 g/day, divided every 4–6 hours	6 g/day	Metyrapone 250-mg capsules
		Ketoconazole 200-mg tablets	200–1200 mg/day, divided	1600 mg/day divided four	Ketoconazole 200-mg tablets
Pituitary dependent	Surgery, irradiation	Mitotane 500-mgtablets	0.5–1 g/day, increased by 0.5–1 g/day every 1–4 weeks	1–4 g daily, with food to decrease GI effects	12 g/day
		Metyrapone	See above	See above	See above
		Mifepristone 300-mg tablets	300 mg once daily,increased by 300mg/day every 2–4	600–1200 mg/day	1200 mg/day or 20 mg/kg/day
		Cabergoline 0.5-mg tablets	0.5 mg once weekly	0.5–7 mg once weekly	7 mg/week
		Pasireotide 0.3-, 0.6-, and 0.9-mg/mLsolution	0.6–0.9 mg twice daily	0.3–0.9 mg twice daily	1.8 mg/day
Adrenal adenoma	Surgery, postoperative replacement	Ketoconazole	See above	See above	See above
Adrenal carcinoma	Surgery	Mitotane	See above	See above	See above

Nonpharmacologic Therapy

- Treatment of choice for both ACTH dependent and ACTH independent Cushing syndrome is surgical resection ofoffending tumors.

- Transsphenoidal resection of the pituitary tumor is the treatment of choice for Cushing disease. Radiotherapy may be preferred for tumors invading the dura or cavernous sinus and provides clinical improvement in ~50% of patients within 3–5 years but increases the risk for pituitary dependent hormone deficiencies (hypopituitarism

- Laparoscopic adrenalectomy is often preferred for unilateral adrenal adenomas or when transsphenoidal surgery andpituitary radiotherapy have failed or cannot be used.

Pharmacologic Therapy

- Pharmacotherapy is generally used as second•line treatment in patients who are not surgical candidates and may also be used preoperatively or as adjunctive therapy in postoperative patients awaiting response Rarely, monotherapy is used as a palliative treatment when surgery is not indicated.

Steroidogenesis Inhibitors

Metyrapone inhibits 11 *β*•hydroxylase, thereby inhibiting cortisol synthesis. After administration, a sudden decreasein cortisol concentration prompts a compensatory rise in plasma ACTH levels. With cortisol synthesis blocked, adrenal steroidogenesis shunts toward androgen production, resulting in androgenic side effects such as acne and hirsutism. Inhibition of aldosterone synthesis can result in natriuresis and blood pressure changes. Nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash have been reported after oral administration.

Ketoconazole inhibits cytochrome P•450 enzymes, including 11 *β*•hydroxylase and 17 *α*•hydroxylase. It is effective inlowering serum cortisol levels after several weeks of therapy. It also has antiandrogenic activity, which may be beneficial in women but can cause gynecomastia and hypogonadism in men. The most common adverse effects are reversible elevation of hepatic transaminases, GI discomfort, and dermatologic reactions. Because of the risk of severe hepatotoxicity, monitoring should include liver function tests at baseline followed by weekly monitoring of serum ALT throughout therapy. Ketoconazole may be used concomitantly with metyrapone to achieve synergistic reduction in cortisol levels; in addition, ketoconazole's antiandrogenic actions may offset the androgenic potential of metyrapone.

Etomidate is an imidazole derivative similar to ketoconazole that inhibits 11 *β*•hydroxylase and may have other mechanisms. Because it is only available in a parenteral formulation, use is limited to patients with acute hypercortisolemia requiring emergency treatment or in preparation for surgery. Frequent monitoring of serum cortisol is advised to prevent hypocortisolemia. Side effects include sedation, injection site pain, hypotension, myoclonus, nausea, and vomiting.

Osilodrostat (Itsurisa) prevents cortisol synthesis via inhibition of 11*β*-hydroxylase and is indicated for patients with Cushing disease who are either not candidates for surgery or in whom symptoms persist after surgery. Osilodrostat is available as an oral tablet taken twice daily, with or without food. Hypokalemia and hypomagnesemia should be corrected prior to use, and an ECG should be obtained at baseline and again one week after treatment initiation to monitor possible QTc prolongation. Adverse effects are similar to other 11*β*-hydroxylase inhibitors, including hypocortisolism, QTc prolongation, nausea, and headache.

Adrenolytic Agents

Mitotane is a cytotoxic drug that inhibits the 11-hydroxylation of 11-deoxycortisol and 11-desoxycorticosterone in the adrenal cortex, reducing synthesis of cortisol and corticosterone. Similar to ketoconazole, mitotane takes weeks to months to exert beneficial effects. Sustained cortisol suppression occurs in most patients and may persist after drug discontinuation in up to one third of patients. Mitotane degenerates' cells within the zona fasciculata and reticularis, resulting in atrophy of the adrenal cortex; the zona glomerulosa is minimally affected during acute therapy but can be damaged during long term treatment. Mitotane can cause significant neurologic and GI side effects, and patients should be monitored carefully or hospitalized when initiating therapy. Nausea and diarrhea are common at doses greater than 2 g/day and can be avoided by gradually increasing the dose and/or administering it with food. Lethargy, somnolence, and other CNS effects are also common. Reversible hypercholesterolemia and prolonged bleeding times can occur.

Neuromodulators of ACTH Release

Pituitary secretion of ACTH is normally mediated by neurotransmitters such as serotonin, *γ* aminobutyric acid (GABA), acetylcholine, and catecholamines. Although ACTH secreting pituitary tumors (Cushing disease) self-regulate ACTH production to some degree, these neurotransmitters can still promote pituitary ACTH production. Consequently, agents that target these transmitters have been proposed for treatment of Cushing disease, including cyproheptadine, bromocriptine, cabergoline, valproic acid, octreotide, lanreotide, pasireotide, rosiglitazone, and tretinoin. With the exception of pasireotide, none of these drugs have demonstrated consistent clinical efficacy for treating Cushing disease.

Cyproheptadine, a nonselective serotonin receptor antagonist and anticholinergic drug, can decrease ACTH secretion in some patients with Cushing disease. However, side effects such as sedation and weight gain significantly limit its use.

Pasireotide (Signifor) is a somatostatin analog that binds and activates somatostatin receptors, thereby inhibiting ACTH secretion, leading to decreased cortisol secretion. It is approved for treatment of adults with Cushing disease for whom pituitary surgery is not an option or has not been curative. Side effects include nausea, diarrhea, cholelithiasis, increased hepatic transaminases, hyperglycemia, sinus bradycardia, and QT prolongation.

Glucocorticoid Receptor Blocking Agents

Mifepristone (Korlym) is a progesterone and glucocorticoid receptor antagonist that inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in normal subjects. Evidence suggests that mifepristone is highly effective in reversing the manifestations of hypercortisolism (hyperglycemia, hypertension, and weight gain). It is FDA approved 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. Common adverse effects include fatigue, nausea, headache, arthralgia, peripheral edema, endometrial hyperplasia, and hypokalemia.

EVALUATION OF THERAPEUTIC OUTCOMES

Close monitoring of 24-hour UFC and serum cortisol is essential to identify adrenal insufficiency in patients with Cushing syndrome. Monitor steroid secretion with all drug therapy (except mifepristone) and give corticosteroid replacement if needed.

HYPERALDOSTERONISM: PATHOPHYSIOLOGY

- Hyperaldosteronism involves excess aldosterone secretion and is categorized as either primary (stimulus arising from within the adrenal gland) or secondary (stimulus from extra adrenal etiologies).
- Primary hyperaldosteronism (PA) is usually caused by bilateral adrenal hyperplasia and aldosterone producing adenoma (Conn syndrome). Rare causes include unilateral (primary) adrenal hyperplasia, adrenal cortex carcinoma, renin responsive adrenocortical adenoma, and three forms of familial hyperaldosteronism (FH): Type I (glucocorticoid remediable aldosteronism); Type II (familial occurrence of adenoma or hyperplasia type II); and Type III.
- Secondary hyperaldosteronism results from excessive stimulation of the zona glomerulosa by an extra adrenal factor, usually the renin– angiotensin system. Elevated aldosterone secretion can result from excessive potassium intake, oral contraceptives, pregnancy, and menses. Heart failure, cirrhosis, renal artery stenosis, and Bartter syndrome also can lead to elevated aldosterone concentrations.

CLINICAL PRESENTATION

- Patients may complain of muscle weakness, fatigue, paresthesias, headache, polydipsia, and nocturnal polyuria.
- Signs may include hypertension, tetany/paralysis, and olydipsia/nocturnal polyuria.
- A plasma aldosterone concentration to plasma renin activity (PAC to PRA) ratio or aldosterone to renin ratio (ARR) >30 ng/dL per ng/(mL·h) (830 pmol/L per mcg/(L·h) and a PAC >15 ng/dL (420 pmol/L) is suggestive of PA. Other laboratory findings include suppressed renin activity, elevated plasma aldosterone, hypernatremia (>142 mEq/L), hypokalemia, hypomagnesemia, elevated serum bicarbonate (>31 mEq/L), and glucose intolerance.

DIAGNOSIS

- Initial diagnosis is made by screening patients with suspected PA. Any patient with a blood pressure >150/100 mm Hg measured on three separate days, and those meeting the criteria for treatment resistant hypertension should be screened. Additional patients at risk for PA include those with diuretic induced hypokalemia, hypertension and adrenal incidentaloma, hypertension and sleep apnea, hypertension and a family history of early onset hypertension or cerebrovascular accident at an age <40 years, and all patients with hypertension and a first degree relative diagnosed with PA.

- Screening for PA is most often done using the PAC to PRA ratio (also known as the ARR). An elevated ARR is highly suggestive of PA.

- If the ARR is positive, confirmatory tests to exclude false positives include the oral sodium loading test, saline infusion test, fludrocortisone suppression test (FST), and captopril challenge test. A positive test indicates autonomous aldosterone secretion under inhibitory pressures and is diagnostic for PA.

TREATMENT

Nonpharmacologic Therapy

Aldosterone producing adenomas are treated by laparoscopic resection of the tumor, leading to permanent cures in up to 72% of patients. Medical management with an aldosterone receptor antagonist is often effective if surgery is contraindicated.

Pharmacologic Therapy

Aldosterone receptor antagonists are the treatment of choice for bilateral adrenal hyperplasia.

✓ **Spironolactone** (Aldactone) is a nonselective aldosterone receptor antagonist that competes with aldosterone for binding at aldosterone receptors, thus preventing the negative effects of aldosterone receptor activation. The initial dose is 25 mg once daily titrated upward at 4• to 8•week intervals. Most patients respond to doses between 25 and 400 mg/day given in single or divided doses. Adverse effects include GI discomfort, impotence, gynecomastia, menstrual irregularities, and hyperkalemia.

✓ **Eplerenone** (Inspra) is a selective aldosterone receptor antagonist with high affinity for aldosterone receptors and low affinity for androgen and progesterone receptors. Consequently, it elicits fewer sex steroid–dependent effects than spironolactone. Dosing starts at 50 mg daily, with titration at 4• to 8•week intervals to 50 mg twice a day; some patients may require total daily doses as high as 200–300 mg.

✓ **Amiloride** (Amiloride), a potassium sparing diuretic, is less effective than spironolactone, and patients often require additional therapy to adequately control blood pressure. The initial dose is 5 mg twice daily, with a usual range of 20 mg/day given in two divided doses; doses up to 30 mg/day may be necessary.

✓ Additional second line options include calcium channel blockers, ACE inhibitors, and diuretics such aschlorthalidone, although all of these lack outcome data in PA.

Treatment of secondary aldosteronism is dictated by etiology. Control or correction of the extra adrenal stimulationof aldosterone secretion should resolve the disorder. Medical therapy with spironolactone is undertaken until theetiology is identified.

ADRENAL INSUFFICIENCY: PATHOPHYSIOLOGY

- Primary adrenal insufficiency (Addison disease) usually involves destruction of all regions of the adrenal cortex. Thereare deficiencies of cortisol, aldosterone, and the various androgens, and levels of CRH and ACTH increase in a compensatory manner.
- Autoimmune dysfunction is responsible for 80%–90% of cases in developed countries, whereas tuberculosis is thepredominant cause in developing countries.
- Medications that inhibit cortisol synthesis (eg, ketoconazole) or accelerate cortisol metabolism (eg, phenytoin, rifampin,phenobarbital) can also cause primary adrenal insufficiency.
- Secondary adrenal insufficiency most commonly results from exogenous corticosteroid use, leading to suppression of the hypothalamic– pituitary–adrenal axis and decreased ACTH release as well as impaired androgen and cortisol production. Mirtazapine and progestins (eg, medroxyprogesterone acetate, megestrol acetate) have also been reported toinduce secondary adrenal insufficiency. Secondary disease typically presents with normal mineralocorticoid concentrations.

CLINICAL PRESENTATION

- Patients with adrenal insufficiency commonly complain of weakness, weight loss, GI symptoms, salt craving, headaches,memory impairment, depression, and postural dizziness.
- Early symptoms of acute adrenal insufficiency also include myalgias, malaise, and anorexia. As the situationprogresses, vomiting, fever, hypotension, and shock develop.
- Signs of adrenal insufficiency include increased skin pigmentation, postural hypotension, fever, decreased body hair,vitiligo, amenorrhea, and cold intolerance.

DIAGNOSIS

The short cosyntropin stimulation test can be used to assess patients with suspected hypercortisolism. An increase to acortisol level of ≥18 mcg/dL (500 nmol/L) rules out adrenal insufficiency.
Patients with Addison disease have an abnormal response to the short cosyntropin stimulation test. Plasma ACTH levels are usually elevated (400– 2000 pg/mL or 88–440 pmol/L) in primary insufficiency versus normal to low (5–50 pg/mL or 1.1–11 pmol/L]) in secondary insufficiency. A normal cosyntropin stimulation test does not rule out secondary adrenalinsufficiency. Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.

TREATMENT

Goals of Treatment: Limit morbidity and mortality, return the patient to a normal functional state, and preventepisodes of acute adrenal insufficiency.

Nonpharmacologic Therapy

Inform patients of treatment complications, expected outcomes, proper medication administration and adherence, andpossible side effects.

Pharmacologic TherapyCorticosteroids

- The agents of choice are **hydrocortisone** and **cortisone acetate**, usually administered two times daily, with the goal of establishing the lowest effective dose while mimicking the normal diurnal adrenal rhythm. Once daily **prednisolone** isan alternative when adherence to a multidose regimen is a concern.
- Recommended starting total daily doses are hydrocortisone 15–25 mg daily, which is approximately equivalent to cortisone acetate 20–35 mg daily, or prednisolone 3–5 mg daily (**Table•2**). For hydrocortisone or cortisone, two thirdsof the dose is given in the morning and one third is given 6–8 hours later.
- Monitor the patient's symptoms every 6–8 weeks to assess proper glucocorticoid replacement. Measure body weight, postural blood pressures, subjective energy levels, and signs of glucocorticoid excess.
- In primary adrenal insufficiency, **fludrocortisone acetate** 0.05–0.2 mg orally once daily can be used to replace mineralocorticoid loss and maintain volume status. If parenteral therapy is needed, 2–5 mg of **deoxycorticosterone trimethylacetate** in oil can be administered intramuscularly every 3–4 weeks. Mineralocorticoid replacement attenuates development of hyperkalemia, and patients on fludrocortisone therapy do not need to restrict salt intake. Mineralocorticoid therapy may be unnecessary in some cases because glucocorticoids (especially in large doses) alsobind to mineralocorticoid receptors.
- Because most adrenal crises occur because of glucocorticoid dose reductions or lack of stress related dose adjustments, patients receiving corticosteroid replacement therapy should add 5–10 mg hydrocortisone (or equivalent) to their normal daily regimen shortly before strenuous activities, such as exercise. During times of severephysical stress (eg, febrile illness, injury), patients should be instructed to double their daily dose until recovery.
- Treatment of secondary adrenal insufficiency is similar to primary disease treatment, except that mineralocorticoidreplacement is usually not necessary.

TABLE -2: Relative Potencies of Glucocorticoids

Glucocortico id	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
Methylprednis olone	5	4	180	0
Betamethasone	25	0.6	100–300	0
Dexamethasone	30	0.75	100–300	0

Pharmacologic Therapy of Acute Adrenal Insufficiency

- Acute adrenal insufficiency (adrenal crisis or Addisonian crisis) represents a true endocrine emergency. Major clinicalfeatures include volume depletion and hypotension that resolve within 1–2 hours after parenteral glucocorticoid administration.
- Stressful situations, surgery, infection, and trauma are potential events that increase adrenal requirements, especially inpatients with some underlying adrenal or pituitary insufficiency.
- The most common cause of adrenal crisis is HPA axis suppression brought on by abrupt withdrawal of chronicglucocorticoid use.
- **Hydrocortisone** given parenterally is the corticosteroid of choice because of its combined glucocorticoid and mineralocorticoid activity. The starting dose is 100 mg IV by rapid infusion, followed by 200 mg over 24 hours as a continuous infusion. IV administration is continued for an additional dayat a reduced dose of 100 mg over 24 hours. If the patient is stable at that time, oral hydrocortisone can be started at a dose of 50 mg every 6–8 hours, followed by tapering to the individual's chronic replacement needs.
- **Fluid replacement** often is required and can be accomplished with IV dextrose 5% in normal saline solution at a rateto support blood pressure. If therapy is needed for hypoglycemia, dextrose 25% in water can be infused at a dose of 2–4 mL/kg. If hyperkalemia is present after the hydrocortisone maintenance phase, additional mineralocorticoid supplementationcan be achieved with **fludrocortisone acetate** 0.1 mg daily.
- Patients with adrenal insufficiency should carry a card or wear a bracelet or necklace that contains information abouttheir condition. They should also have easy access to injectable hydrocortisone or glucocorticoid suppositories in caseof an emergency or during times of physical stress.

EVALUATION OF THERAPEUTIC OUTCOMES

The endpoint of therapy for adrenal insufficiency is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker. Development of features of Cushing syndrome indicates excessive replacement.

Thyroid Disorders

INTRO DUCTIO N

Thyroid disorders involve thyroid hormone production or secretion and result in alterations in metabolic stability.

THYROID HORMONE PHYSIOLOGY

- The thyroid hormones thyroxine (T4) and triiodothyronine (T3) are formed within thyroglobulin, a large glycoprotein synthesized in the thyroid
- cell. Inorganic iodide enters the thyroid follicular cell and is oxidized by thyroid peroxidase and covalently bound (organified) to tyrosine residues of thyroglobulin.
- Iodinated tyrosine residues mono-iodo-tyrosine (MIT) and diiodotyrosine (DIT) combine (couple) to form iodothyronines in reactions catalyzed by thyroid peroxidase. Thus, two molecules of DIT combine to form T4, and MIT and DIT join to form T3.
- Proteolysis within thyroid cells releases thyroid hormone into the bloodstream. T4 and T3 are transported by thyroid binding globulin (TBG),
- transthyretin, and albumin. Only the unbound (free) thyroid hormone can diffuse into cells, elicit biologic effects, and regulate thyroid stimulating hormone (TSH) secretion from the pituitary.
- T4is secreted solely from the thyroid, but <20% of T3 is produced there; most T3 is formed from breakdown of T4 catalyzed by the enzyme 5′- mono deiodinase in peripheral tissues. T3is five times more active than T4. T4may also be acted on by 5′-monodeiodinase to form reverse T3, which has no significant biologic activity.
- Thyroid hormone production is regulated by TSH secreted by the anterior pituitary, which in turn is under negative feedback control by the circulating level of free thyroid hormone and the positive influence of hypothalamic thyrotropin releasing hormone (TRH). Thyroid hormone production is also regulated by extrathyroidal deiodination of T4to T3, which can be affected by nutrition, nonthyroidal hormones, drugs, and illness.

THYROTOXICOSIS (HYPERTHYROIDISM): PATHOPHYSIOLOGY

- Thyrotoxicosis results when tissues are exposed to excessive levels of T4, T3, or both. Hyperthyroidism, which is one cause of thyrotoxicosis, refers to overproduction of thyroid hormone by the thyroid gland.

- TSH secreting pituitary tumors occur sporadically and release biologically active hormone that is unresponsive to normal feedback control. The tumors may cosecrete prolactin or growth hormone; therefore, patients may present with amenorrhea, galactorrhea, or signs of acromegaly.
- Resistance to thyroid hormone occurs rarely and can be due to various molecular defects, including mutations in the TRβ gene. Pituitary resistance to thyroid hormone (PRTH) refers to selective resistance of the pituitary thyrotrophs to thyroid hormone.
- Graves' disease is the most common cause of hyperthyroidism, which results from the action of thyroid stimulating antibodies (TSAb) directed against the thyrotropin receptor on the surface of thyroid cells. These immunoglobulins bind to the receptor and activate the enzyme adenylate cyclase in the same manner as TSH.
- An autonomous thyroid nodule (toxic adenoma) is a benign thyroid mass that produces thyroid hormone independent of pituitary and TSH control. Hyperthyroidism usually occurs with larger nodules (>3 cm in diameter).
- In multinodular goiter, follicles with autonomous function coexist with normal or even nonfunctioning follicles. Thyrotoxicosis occurs when autonomous follicles generate more thyroid hormone than is required.
- Painful subacute (granulomatous or de Quervain) thyroiditis often develops after a viral syndrome, but rarely has a specific virus been identified in thyroid parenchyma.
- Painless (silent, lymphocytic, or postpartum) thyroiditis is a common cause of thyrotoxicosis. Its etiology is not fully understood; autoimmunity may underlie most cases.
- Thyrotoxicosis factitia is hyperthyroidism due to ingestion of exogenous thyroid hormone. This may occur when thyroid hormone is used for inappropriate indications, excessive doses are used for accepted medical indications, there is accidental ingestion, or it is used surreptitiously.
- Amiodarone may induce thyrotoxicosis (2%–3% of patients), overt hypothyroidism (5% of patients), subclinical hypothyroidism (25% of patients),or euthyroid hyperthyroxinemia. Because of amiodarone's high iodine content (37% by weight), increased thyroid hormone synthesis commonly exacerbates thyroid dysfunction in patients with preexisting thyroid disease. Amiodarone also causes a destructive thyroiditis with leakage of thyroglobulin and thyroid hormones.

CLINICAL PRESENTATION

- Symptoms of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, heat intolerance, weight loss concurrent with increased appetite, increased frequency of bowel movements, proximal muscle weakness (noted on climbing stairs or arising from a sitting position), and scanty or irregular menses in women.

- Physical signs include warm, smooth, moist skin, and unusually fine hair; separation of the ends of the fingernails from the nail beds (onycholysis); retraction of the eyelids and lagging of the upper lid behind the globe upon downward gaze (lid lag); tachycardia at rest, widened pulse pressure, and systolic ejection murmur; occasional gynecomastia in men; fine tremor of the protruded tongue and outstretched hands; and hyperactive deep tendon reflexes. Thyromegaly is usually present.
- Graves' disease is manifested by hyperthyroidism, diffuse thyroid enlargement, and extrathyroidal findings of exophthalmos, pretibial myxedema, and thyroid acropachy. In severe disease, a thrill may be felt and a systolic bruit may be heard over the gland.
- In subacute thyroiditis, patients have severe pain in the thyroid region, which often extends to the ear. Systemic symptoms include fever, malaise, myalgia, and signs and symptoms of thyrotoxicosis. The thyroid gland is firm and exquisitely tender on physical examination.
- Painless thyroiditis has a triphasic course that mimics painful subacute thyroiditis. Most patients present with mild thyrotoxic symptoms; lid-retraction and lid lag are present, but exophthalmos is absent. The thyroid gland may be diffusely enlarged without tenderness.
- Thyroid storm is a life-threatening medical emergency characterized by decompensated thyrotoxicosis, high fever (often >39.4°C [103°F]), tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea. Precipitating factors include infection, trauma, surgery, radioactive iodine (RAI) treatment, and withdrawal from antithyroid drugs.

DIAGNOSIS

- Elevated 24•hour radioactive iodine uptake (RAIU) indicates true hyperthyroidism: the patient's thyroid gland is overproducing T4, T3, or both (normal RAIU 10%–30%). A low RAIU indicates that excess thyroid hormone is not a consequence of thyroid gland hyperfunction but is likely caused by thyroiditis, struma ovarii, follicular cancer, or exogenous thyroid hormone ingestion.
- In thyrotoxic Graves' disease, there is an increase in the overall hormone production rate with a disproportionate increase in T3 relative to T4 (Table •1). Saturation of TBG is increased due to elevated serum levels of T4and T3, which is reflected in elevated T3resin uptake. As a result, concentrations of free T4, free T3, and the free T4 and T3 indices are increased to an even greater extent than the measured serum total T4 and T3concentrations. The TSH level is undetectable due to negative feedback by elevated levels of thyroid hormone at the pituitary. In patients with symptomatic disease, measurement of serum free T4, total T4, total T3, and TSH will confirm the diagnosis of thyrotoxicosis. If the patient is not pregnant or lactating, an increased 24•hour RAIU indicates that the thyroid gland is inappropriately using iodine to produce more thyroid hormone when the patient is thyrotoxic.

- For toxic adenomas, because there may be isolated elevation of serum T3 with autonomously functioning nodules, a T3 level must be measured to rule out T3toxicosis if the T4level is normal. If autonomous function is suspected but the TSH is normal, the diagnosis can be confirmed by failure of the autonomous nodule to decrease iodine uptake during exogenous T3administration sufficient to suppress TSH.
- In multinodular goiters, a thyroid scan shows patchy areas of autonomously functioning thyroid tissue.
- TSH induced hyperthyroidism is diagnosed by evidence of peripheral hypermetabolism, diffuse thyroid gland enlargement, elevated free thyroid hormone levels, and elevated serum immunoreactive TSH concentrations. Because the pituitary gland is extremely sensitive to even minimal elevations of free T4, a "normal" or elevated TSH level in any thyrotoxic patient indicates inappropriate production of TSH.
- TSH secreting pituitary adenomas are diagnosed by demonstrating lack of TSH response to TRH stimulation, inappropriate TSH levels, elevated TSH α•subunit levels, and radiologic imaging.
- In subacute thyroiditis, thyroid function tests typically run a triphasic course in this self-limited disease. Initially, serum T4 levels are elevated due to release of preformed thyroid hormone. The 24•hour RAIU during this time is <2% because of thyroid inflammation and TSH suppression by the elevated T4level. As the disease progresses, intrathyroidal hormone stores are depleted, and the patient may become mildly hypothyroid with appropriately elevated TSH level. During the recovery phase, thyroid hormone stores are replenished, and serum TSH elevation gradually returns to normal.
- During the thyrotoxic phase of painless thyroiditis, the 24-hour RAIU is suppressed to <2%. Antithyroglobulin and antithyroid peroxidase antibody levels are elevated in more than 50% of patients.
- Thyrotoxicosis factitia should be suspected in a thyrotoxic patient without evidence of increased hormone production, thyroidal inflammation, or ectopic thyroid tissue. The RAIU is low because thyroid gland function is suppressed by exogenous thyroid hormone. Measurement of plasma thyroglobulin reveals presence of very low levels.

TABLE 1: Thyroid Function Tests in Different Thyroid Conditions

	Total T4	Free T4	Total T3	TSH
Normal	4.5–10.9 mcg/dL	0.8–2.7 ng/dL	60–181 ng/dL	0.5–4.7 milli-international units/L
Hyperthyroid	↑↑	↑↑	↑↑↑	↓↓[a]
Hypothyroid	↓↓	↓↓	↓	↑↑[a]
Increased TBG	↑	Normal	↑	Normal

TREATMENT

Goals of Treatment: Eliminate excess thyroid hormone; minimize symptoms and long term consequences; and provide individualized therapy based on the type and severity of disease, patient age and gender, existence of nonthyroidal conditions, and response to previous therapy.

Nonpharmacologic Therapy

- Surgical removal of the thyroid gland should be considered in patients with a large gland (>80 g), severe ophthalmopathy, or lack of remission on antithyroid drug treatment.
- If thyroidectomy is planned, methimazole is given until the patient is biochemically euthyroid (usually 6–8 weeks), followed by addition of iodides (500 mg/day) for 10–14 days before surgery to decrease vascularity of the gland.
- Propranolol has been used for several weeks preoperatively and 7–10 days after surgery to maintain pulse rate <90 beats/min. Combined pretreatment with propranolol and 10–14 days of potassium iodide also has been advocated.

Pharmacologic TherapyThionamides

- **Methimazole** and **propylthiouracil (PTU)** block thyroid hormone synthesis by inhibiting the peroxidase enzyme system of the thyroid, preventing oxidation of trapped iodide and subsequent incorporation into iodo-tyrosines and ultimately iodothyronine ("organification"); and by inhibiting coupling of MIT and DIT to form T4and T3. PTU (but not methimazole) also inhibits peripheral conversion of T4to T3.
- Usual initial doses include methimazole 30–60 mg daily given in two or three divided doses or PTU 300–600 mg daily(usually in three or four divided doses). Evidence exists that both drugs can be given as a single daily dose.
- Improvement in symptoms and laboratory abnormalities should occur within 4–8 weeks, at which time a tapering regimen to maintenance doses can be started. Make dosage changes monthly because the endogenously produced T4will reach a new steady state concentration in this interval.
- Typical daily maintenance doses are methimazole 5–30 mg and PTU 50–300 mg. Continue therapy for at least 12–24months to induce long term remission.
- Monitor patients every 6–12 months after remission. If a relapse occurs, alternate therapy with RAI is preferred over asecond course of antithyroid drugs, but continued long term low dose methimazole may also be considered.
- Minor adverse reactions include pruritic maculopapular rashes, arthralgias, fever, and benign transient leukopenia (white blood cell count <4000/mm^3 or 4 × 10^9/L). The alternate thionamide may be tried in these situations, but cross sensitivity occurs in about50% of patients.
- Major adverse effects include agranulocytosis (with fever, malaise, gingivitis, oropharyngeal infection, and granulocyte count <250/mm^3 or 0.25 × 10^9/L), aplastic anemia, lupus•like syndrome, polymyositis, GI intolerance, hepatotoxicity, and hypoprothrombinemia. If agranulocytosis occurs, it usually develops in the first 3 months of therapy; routine WBC count monitoring is not recommended because of its sudden onset.

- Because of the risk of serious hepatotoxicity, PTU should not be considered first line therapy in either adults or children. Exceptions to this recommendation include (1) the first trimester of pregnancy (when the risk of methimazole induced embryopathy may exceed that of PTU• induced hepatotoxicity), (2) intolerance to methimazole, and (3) thyroid storm.

Iodides

- **Iodide** acutely blocks thyroid hormone release, inhibits thyroid hormone biosynthesis by interfering with intrathyroidal iodide use, and decreases size and vascularity of the gland.

- Symptom improvement occurs within 2–7 days of initiating therapy, and serum T4 and T3 concentrations may be reduced for a few weeks.

- Iodides are often used as adjunctive therapy to prepare a patient with Graves' disease for surgery, to acutely inhibit thyroid hormone release and quickly attain the euthyroid state in severely thyrotoxic patients with cardiac decompensation, or to inhibit thyroid hormone release after RAI therapy.

- **Potassium iodide** is available as a saturated solution (**SSKI**, 38 mg iodide per drop) or as **Lugol solution**, containing 6.3 mg of iodide per drop.

- Typical starting dose of SSKI is 3–10 drops daily (120–400 mg) in water or juice. When used to prepare a patient for surgery, it should be administered 7–14 days preoperatively. As an adjunct to RAI, SSKI should not be used before but rather 3–7 days after RAI treatment so that the RAI can concentrate in the thyroid.

- Adverse effects of iodide therapy include hypersensitivity reactions (skin rashes, drug fever, and rhinitis, conjunctivitis), salivary gland swelling,"iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea),and gynecomastia. Iodide is contraindicated in toxic multinodular goiter because the autonomous tissue utilizes the iodine for subsequent thyroid hormone synthesis.

Adrenergic Blockers

- *B*-Blockers are used to ameliorate symptoms such as palpitations, anxiety, tremor, and heat intolerance. They have no effect on peripheral thyrotoxicosis and protein metabolism and do not reduce TSAb or prevent thyroid storm.
- **Propranolol** and **nadolol** partially block conversion of T4 to T3, but this contribution to overall effect is small.
- *β*-Blockers are usually used as adjunctive therapy with antithyroid drugs, RAI, or iodides when treating Graves' disease or toxic nodules, in preparation for surgery, or in thyroid storm. The only conditions for which *β*•blockers are primary therapy for thyrotoxicosis are those associated with thyroiditis.
- **Propranolol** doses required to relieve adrenergic symptoms vary, but an initial dose of 20–40 mg orally four times daily is effective for most patients (goal heart rate <90 beats/min). Younger or more severely toxic patients may require 240–480 mg/day, perhaps because of increased clearance.

- *β*•Blockers are contraindicated in decompensated heart failure unless it is caused solely by tachycardia (high output). Other contraindications aresinus bradycardia, concomitant therapy with monoamine oxidase inhibitors or tricyclic antidepressants, and patients with spontaneous hypoglycemia. Side effects include nausea, vomiting, anxiety, insomnia, lightheadedness, bradycardia, and hematologic disturbances.

- Centrally acting sympatholytics (eg, **clonidine)** and calcium channel antagonists (eg, **diltiazem)** may be useful for symptomcontrol when contraindications to *β*•blockade exist.

Radioactive Iodine

- **Sodium iodide–131** is an oral liquid that concentrates in the thyroid and initially disrupts hormone synthesis by incorporating into thyroid hormones and thyroglobulin. Over a period of weeks, follicles that have taken up RAIand surrounding follicles develop evidence of cellular necrosis and fibrosis of interstitial tissue.

- RAI is the agent of choice for Graves' disease, toxic autonomous nodules, and toxic multinodular goiters. Pregnancy is an absolute contraindication to use of RAI because radiation would be delivered to the fetal tissue.

- *β*•Blockers are the primary adjunctive therapy to RAI because they may be given anytime without compromising RAItherapy.

- If iodides are administered, they should be given 3–7 days after RAI to prevent interference with uptake of RAI in thethyroid gland.

- Patients with cardiac disease and elderly patients are often treated with thionamides prior to RAI ablation because thyroidhormone levels transiently increase after RAI treatment due to release of preformed thyroid hormone.

- Administering antithyroid drug therapy immediately after RAI may result in a higher rate of posttreatment recurrence orpersistent hyperthyroidism.

- Use of lithium as adjunctive therapy to RAI has benefits of increased cure rate, shortened time to cure, and prevention ofposttherapy increases in thyroid hormone levels.
- The goal of therapy is to destroy overactive thyroid cells, and a single dose of 4000–8000 rad results in a euthyroid state in60% of patients at 6months or sooner. A second dose of RAI should be given 6 months after the first RAI treatment if the patient remains hyperthyroid.
- Hypothyroidism commonly occurs months to years after RAI. The acute, short-term side effects include mild thyroidal tenderness and dysphagia. Long-term follow-up has not revealed an increased risk for development of mutations orcongenital defects.

Treatment of Thyroid Storm

- Initiate the following therapeutic measures promptly: (1) suppression of thyroid hormone formation and secretion, (2) antiadrenergic therapy, (3) administration of corticosteroids, and (4) treatment of associated complications or coexistingfactors that may have precipitated the storm.

- **PTU** in large doses may be the preferred thionamide because it blocks peripheral conversion of T4 to T3 in addition to interfering with thyroid hormone production. However, β-blockers and corticosteroids serve the same purpose. **Methimazole** has a longer duration of action, which offers a theoretical advantage.

- **Iodides**, which rapidly block the release of preformed thyroid hormone, should be administered after a thionamide is initiated to inhibit iodide utilization by the overactive gland. Antiadrenergic therapy with the short-acting agent **esmolol** is preferred because it can be used in patients with pulmonary disease or at risk for cardiac failure and because its effects can be rapidly reversed.

- **Corticosteroids** are generally recommended, but there is no convincing evidence of adrenocortical insufficiency in thyroid storm; their benefits may be attributed to their antipyretic action and stabilization of blood pressure (BP).

- General supportive measures, including **acetaminophen** as an antipyretic (avoid **aspirin** or other nonsteroidal anti-inflammatory drugs, which may displace bound thyroid hormone), **fluid and electrolyte replacement, sedatives, digoxin, antiarrhythmics, insulin,** and **antibiotics** should be given as indicated.

EVALUATION OF THERAPEUTIC OUTCOMES

- After therapy (surgery, thionamides, or RAI) for hyperthyroidism has been initiated, evaluate patients monthly until they reach a euthyroid condition.

- Assess for clinical signs of continuing thyrotoxicosis or development of hypothyroidism.

- If T4 replacement is initiated, the goal is to maintain both the free T4 level and the TSH concentration in the normal range. Once a stable dose of T4 is identified, monitor the patient every 6–12 months.

HYPOTHYROIDISM: PATHOPHYSIOLOGY

- The vast majority of patients have primary hypothyroidism due to thyroid gland failure caused by chronic autoimmune thyroiditis (Hashimoto disease). Defects in suppressor T lymphocyte function led to survival of a randomly mutating clone of helper T lymphocytes directed against antigens on the thyroid membrane. The resulting interaction stimulates B lymphocytes to produce thyroid antibodies.

- Iatrogenic hypothyroidism follows exposure to destructive amounts of radiation, after total thyroidectomy, or with excessive thionamide doses used to treat hyperthyroidism. Other causes of primary hypothyroidism include iodine deficiency, enzymatic defects within the thyroid, thyroid hypoplasia, and ingestion of goitrogens.

- Secondary hypothyroidism due to pituitary failure is uncommon. Pituitary insufficiency may be caused by destruction of thyrotrophs by pituitary tumors, surgical therapy, external pituitary

radiation, postpartum pituitary necrosis (Sheehan syndrome), trauma, and infiltrative processes of the pituitary (eg, metastatic tumors, tuberculosis).

CLINICAL PRESENTATION

- Symptoms of hypothyroidism include dry skin, cold intolerance, weight gain, constipation, weakness, lethargy, depression, fatigue, exercise intolerance, loss of ambition or energy, muscle cramps, myalgia, and stiffness. Menorrhagia and infertility are common in women. In children, thyroid hormone deficiency may manifest as growth or intellectual retardation.

- Physical signs include coarse skin and hair, cold or dry skin, periorbital puffiness, bradycardia, and slowed or hoarse speech. Objective weakness (with proximal muscles affected more than distal muscles) and slow relaxation of deep tendon reflexes are common. Reversible neurologic syndromes such as carpal tunnel syndrome, polyneuropathy, and cerebellar dysfunction may also occur.

- Most patients with secondary hypothyroidism due to inadequate TSH production have clinical signs of generalized pituitary insufficiency, such as abnormal menses and decreased libido, or evidence of a pituitary adenoma, such as visual field defects, galactorrhea, or acromegaloid features.

- Myxedema coma is a rare consequence of decompensated hypothyroidism manifested by hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Mortality rates of 60%–70% necessitate immediate and aggressive therapy.

DIAGNOSIS

- A rise in TSH level is the first evidence of primary hypothyroidism. Many patients have a free T4 level within the normal range (compensated or subclinical hypothyroidism) and few, if any, symptoms of hypothyroidism. As the disease progresses, the free T4 drops below normal. The T3 concentration is often maintained in the normal range despite low T4. Eventually, free and/or total T4 and T3 serum concentrations should be low.
- In secondary hypothyroidism in patients with pituitary disease, serum TSH concentrations are generally low or normal. A serum TSH in the normal range is inappropriate if the patient's T4 is low.

Treatment of Hypothyroidism

- Goals of Treatment: Restore thyroid hormone concentrations in tissue, provide symptomatic relief, prevent neurologic deficits in newborns and children, and reverse the biochemical abnormalities of hypothyroidism.
- **Levothyroxine** (L-thyroxine, T4) is the drug of choice for thyroid hormone replacement and suppressive therapy because it is chemically stable, relatively inexpensive, active when given orally, free of antigenicity, and has uniform potency. Because T3 (and not T4) is the biologically active form, levothyroxine administration results in a pool of thyroid hormone that is readily converted to T3.

- In patients with longstanding disease and older individuals without known cardiac disease, start therapy with levothyroxine 50 mcg daily and increase after 1 month.

- The recommended initial dose for older patients with known cardiac disease is 25 mcg/day titrated upward in increments of 25 mcg at monthly intervals to prevent stress on the cardiovascular system.
- The average maintenance dose for most adults is ~125 mcg/day, but there is a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an appropriate dose.
- Most patients with subclinical hypothyroidism can be observed without treatment. Treatment may be indicated for subclinical hypothyroidism and serum thyrotropin levels 10 mU/L or higher or for young and middle-aged individuals with symptoms consistent with mild hypothyroidism.
- Levothyroxine is the drug of choice for pregnant women, and the goal is to decrease TSH to the normal reference range for pregnancy.
- Cholestyramine, calcium carbonate, sucralfate, aluminum hydroxide, ferrous sulfate, soybean formula, dietary fiber supplements, and espresso coffee may impair the GI absorption of levothyroxine. Acid suppression with histamine blockers and proton pump inhibitors may also reduce levothyroxine absorption. Drugs that increase non-deiodinative T4 clearance include rifampin, carbamazepine, and possibly phenytoin. Selenium deficiency and amiodarone may block conversion of T4to T3.

- **Thyroid USP** (or desiccated thyroid) is usually derived from pig thyroid gland. It may be antigenic in allergic or sensitive patients. Inexpensive generic brands may not be bioequivalent.

- **Liothyronine** (synthetic T3) has uniform potency but has a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring

- with conventional laboratory tests. It must be administered three times a day and may require a prolonged adjustmentperiod to achieve stable euthyroidism.

- **Liotrix** (synthetic T4:T3in a 4:1 ratio) is chemically stable, pure, and has a predictable potency but is expensive. It also lacks therapeutic rationale because most T3is converted peripherally from T4.

- Excessive doses of thyroid hormone may lead to heart failure, angina pectoris, and myocardial infarction (MI).Hyperthyroidism leads to reduced bone density and increased risk of fracture.

Treatment of Myxedema Coma

- Immediate and aggressive therapy with IV bolus **levothyroxine,** 300–500 mcg, has traditionally been used. Initial treatmentwith IV **liothyronine** or a combination of both hormones has also been advocated because of impaired conversion of T4to T3.

- Give glucocorticoid therapy with IV **hydrocortisone** 100 mg every 8 hours until coexisting adrenal suppression isruled out. Consciousness, lowered TSH concentrations, and improvement in vital signs are expected within 24 hours.

- Maintenance levothyroxine doses are typically 75–100 mcg IV until the patient stabilizes and oral therapy is begun.
- Provide supportive therapy to maintain adequate ventilation, euglycemia, BP, and body temperature. Diagnose and treatunderlying disordersthat may have precipitated the event, such as sepsis and MI.

EVALUATION OF THERAPEUTIC OUTCOMES

- Serum TSH concentration is the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose.Concentrations begin to fall within hours and are usually normalized within 2–6 weeks.
- Check both TSH and T4concentrations every 6 weeks until a euthyroid state is achieved. An elevated TSH level indicatesinsufficient replacement. Serum T4 concentrations can be useful in detecting noncompliance, malabsorption, or changes in levothyroxine product bioequivalence. TSH may also be used to help identify noncompliance.
- In patients with hypothyroidism caused by hypothalamic or pituitary failure, alleviation of the clinical syndrome and restoration of serum T4to the normal range are the only criteria available for estimating the appropriate replacement dose oflevothyroxine.

ALZHEIMER DISEASE

INTRODUCTION

Alzheimer disease (AD) affects ~7.5 million Americans of all ages and is a progressive illness of unknown cause characterized by loss of cognitive and physical functioning, commonly with behavior symptoms.

PATHOPHYSIOLOGY

- Genetic susceptibility to late onset AD is primarily linked to the apolipoprotein E (APOE) genotype, but a genetic × environmental interaction may be at play. AD occurrence at a young age is seen in less than 1% of cases. These dominantly inherited forms are attributed to chromosomal alterations that affect processing of the amyloid precursor protein.

- AD risk factors include age, decreased brain reserve capacity, head injury, Down syndrome, depression, mild cognitive impairment, and risk factors for vascular disease, including hypertension, elevated homocysteine, elevated low density lipoprotein cholesterol, low high density lipoprotein cholesterol, obesity, metabolic syndrome, and diabetes.
  - Signature lesions include intracellular neurofibrillary tangles (NFTs), extra cellular plagues in the cortex and medial temporal lobe, degeneration of neurons and synapses, and cortical atrophy. AD affected individuals appear to have a higher burden of plaques and NFTs in their younger years compared to age matched controls.
- Proposed mechanisms for these changes include: (1) β•amyloid protein aggregation, leading to formation of plaques; (2) hyperphosphorylation of tau protein, leading to NFTs; (3) synaptic failure and depletion of neurotrophin and neurotransmitters; (4) mitochondrial dysfunction; and (5) oxidative stress.
- The amyloid cascade hypothesis involves a β-amyloid production and clearance imbalance, with aggregation and accumulation leading to AD. It is unknown if this is the primary pathology in most forms of AD.
- Loss of cholinergic activity is the most prominent neurotransmitter deficit that correlates with AD severity. Cholinergic cell loss seems to be a consequence of AD pathology, not the cause.
- Other neurotransmitters involved include: (1) serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are lost; (2) monoamine oxidase type B activity is increased; (3) glutamate pathways of the cortex and limbic structures are abnormal; and (4) excitatory neurotransmitters, including glutamate, may be neurotoxic.

CLINICAL PRESENTATION

Early disease may be characterized by changes in learning and memory, planning organization, and mood. As the disease progresses, further declines in these domains, as well as changes in personality, judgment, speech, and spatial orientation are seen. In the late stages, functional decline may result in gait, swallowing, incontinence symptoms, and behavioral changes. Patients become increasingly unable to care for themselves.

Stages of Alzheimer Disease using Folstein Mini Mental State Examination (MMSE)

Mild (MMSE score 26–21)	Patient has difficulty remembering recent events. Ability to manage finances, prepare food, and carry out other household activities declines. May get lost while driving. Begins to withdraw from difficulttasks and to give up hobbies. May deny memory problems.
Moderate (MMSE score 20–10)	Patient requires assistance with activities of daily living. Frequently disoriented with regard to time (date, year, and season). Recent events recall is severely impaired. May forget some details of past lifeevents and names of family and friends. Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely. Agitation, paranoia, and delusions are common.
Severe (MMSE score 9–0)	Patient loses ability to speak, walk, and feed self. Incontinent ofurine and feces. Requires care 24 hours a day, 7 days a week.

DIAGNOSIS

- AD is a spectrum beginning with an asymptomatic preclinical phase progressing to the symptomatic preclinical phase and then to the dementia phase. AD is a clinical diagnosis, based largely on identified symptoms and difficulty with activities of daily living revealed by patient and caregiver interviews.
- Patients with suspected AD should have a history and physical examination with appropriate laboratory tests (ie, serum B_{12}, folate, thyroid panel, blood cell counts, serum electrolytes, and liver function tests).
- Structural imaging (ie, non-contrast enhanced CT or MRI) may be performed to identify structural abnormalities consistent with AD or other pathology, such as brain atrophy, vascular damage, or tumors. To exclude other diagnoses, cerebrospinal fluid analysis or an electroencephalogram can occasionally be justified. APOE genetic testing iscurrently not recommended.
- Obtain information on medication and substance use; family medical history; and history of trauma, depression, or head injury. Rule out medications (eg, anticholinergics, sedatives, hypnotics, opioids, antipsychotics, and anticonvulsants) as contributors to dementia symptoms or contribute to delirium (eg, digoxin, nonsteroidal anti-inflammatory drugs [NSAIDs], histamine 2 [H_2] receptor antagonists,amiodarone, antihypertensives, and corticosteroids).
- The Folstein Mini Mental State Examination (MMSE) can help establish a history of deficits in two or more areas of cognition at baseline against which to evaluate changein severity over time. The average expected decline in an untreated patient is 2–4 points per year.
- In the future, improved brain imaging and validated biomarkers of disease will enable sophisticated diagnosis with identified cognitive strengths and weaknesses and neuroanatomic localization of deficits.

TREATMENT

Goals of Treatment: To maintain cognitive functioning and activities of daily living as long as possible, with a secondary goal to treat the psychiatric and behavioral symptoms.

Non-pharmacologic Therapy

- Identify the possible causative factors for cognitive and noncognitive symptoms, andadapt the caregiving environment to remedy the situation.
- Sleep disturbances, wandering, urinary incontinence, agitation, and aggression should be managed with behavioral and environmental interventions whenever possible, for example, redirecting the patient's attention and removing stressors and triggers.
- On initial diagnosis, the patient and caregiver should be educated on the course of illness, available treatments, legal decisions, lifestyle changes that will become necessary, and other quality of life issues.
- Primary prevention includes smoking cessation, increasing physical activity, andreducing midlife obesity, hypertension, and diabetes. Adherence to the Mediterranean Diet or Dietary Approaches to Stop Hypertension (DASH) Diet may reduce the risk of cognitive impairment or decline.

Pharmacologic Therapy of Cognitive Symptoms

- Consider the anti-amyloid monoclonal antibody (mAb) aducanumab for mild cognitiveimpairment (MCI). Titrate to recommended maintenance dose as tolerated.
- In mild to moderate AD, consider a cholinesterase inhibitor (donepezil, rivastigmine, or galantamine) or aducanumab titrated to recommended maintenance dose astolerated.
- In moderate to severe AD, consider adding the anti-glutamatergic agent memantine titrated to recommended maintenance dose as tolerated; alternatively, consider memantine or cholinesterase inhibitor therapy alone.
- A reasonable response may be a slowed decline in abilities and delayed long term care placement.
- Simplify dosing regimens, taking patient and caregiver preferences into consideration medication adherence and persistence.
- Treatment gaps may be associated with a loss of benefits when medication is stopped but this is controversial.
- Behavioral symptoms may require additional pharmacologic approaches

Cholinesterase Inhibitors

- Table 2 summarizes cholinesterase inhibitor dosing. Donepezil, rivastigmine, and galantamine are indicated in mild to moderate AD; donepezil is also indicated forsevere AD. No trials have assessed the effectiveness of one agent over another.
- Successful treatment shows a MMSE score decline of less than 2 points per year withbenefit lasting 3–24 months.
- If rivastigmine or galantamine are interrupted for several days or longer, re-titrate starting at the lowest dose due to their short half-lives. Gradual dose titration over several months improves tolerability. When switching from one agent to another, a washout period is recommended.
- Abrupt discontinuation can cause worsening of cognition and behavior in some patients.
- Table below lists common medication adverse reactions and monitoring parameters.

Table 2: Adverse Medication Reaction Monitoring Reaction

Medication	Adverse Medication	Monitoring Parameters	Comments
Galantamine	Serious skin reactions (Stevens–Johnson syndrome and acute generalized exanthematous pustulosis)	Appearance of skin rash	Discontinue at first sign ofskin rash, unless clearly not related If signs/symptoms are suggestive of a serious reaction, consider alternative treatment and do not rechallenge
Rivastigmine	Allergic dermatitis	Reaction spread beyondpatch size, evidence of amore intense local reaction (increasing erythema, edema, papules, vesicles), and persistence of symptomsfor more than 48 hours after patch removal	Discontinue if evidence of disseminated allergic dermatitis appears Patients sensitized by patch exposure may not be able to take rivastigmine by mouth; allergy testing and close medical supervision recommended
Cholinesterase inhibitors	Dizziness, syncope, bradycardia, atrial arrhythmias, sinoatrial and atrioventricular block, myocardial infarction Nausea, vomiting, diarrhea, anorexia, weight loss Peptic ulcer disease, GI bleeding	Report of dizziness or falls, pulse, blood pressure, and postural blood pressure change Weight and GI complaints Signs or symptoms of active or occult GI bleeding	Dizziness is usually mild, transient, and not related to cardiovascular problems Routine pulse checks at baseline, monthly during titration, and every 6 months thereafter Take with food to reduce GI upset Usually transient, dose•related GI adverse effects seen with initiation, dosage titration, or medication switch Frail patients or those with low body weight may experience more GI effects and significant weight loss, particularly when rivastigmine is prescribed or when titrating to donepezil 23 mg GI effects less prominent with transdermal versus oral rivastigmine Increased concern for patients at increased risk of developing ulcers (eg, history of ulcer disease or concurrently taking NSAIDs)
Memantine	Headache, confusion, dizziness, hallucinations Constipation	Report of dizziness or falls, hallucinations GI complaints	Confusion may be observed during dose titration and is usually transient May mitigate GI effects associated with cholinesterase inhibitors

Aducanumab	ARIA Hypersensitivit y reactions	MRI at baseline, prior to 7th and 12th infusions, or if symptoms suggest ARIA, to identify brain edema, microhemorrhage, superficial siderosis Symptoms of headache, confusion, dizziness, visual disturbances, and nausea Angioedema and urticaria (rare)	Vigilance for ARIA and focal neurologic changes recommended especially during dose titration and the first eight doses

ARIA, Amyloid related imaging abnormalities; GI, gastrointestinal; NSAIDs, nonsteroidal anti inflammatory drugs.

N Methyl D Aspartate (NMDA) Receptor Antagonist

- Memantine is used as monotherapy and in combination with a cholinesterase inhibitor and is indicated for moderate to severe AD, but not for mild AD. It is not metabolized but requires dosing adjustments in patients with renal impairment. It is usually well tolerated.
- Combination therapy with cholinesterase inhibitors and memantine, individually or as Namzaric, is generally used for moderate to severe AD. It slows cognitive and functional decline compared to cholinesterase inhibitor monotherapy or no treatment. Memantine may help mitigate some of the GI effects seen with cholinesterase inhibitors.

Anti amyloid Monoclonal Antibody

- Four humanized, immunoglobulin G1 mAbs have been designated as AD breakthrough therapies by the FDA (ie, aducanumab, lecanemab, donanemab, and gantenerumab). Aducanumab was controversially approved for use in MCI due to AD and mild AD.
- Dosing for aducanumab, outlined in Tables 53•2 and 53•3, discusses its adverse effect monitoring.
- The potential degree and duration of clinical benefit of anti amyloid antibodies remains largely unclear.

Other Medications

- Use of estrogen, NSAIDS, prednisone, statins, or Ginkgo biloba is not recommended to prevent or treat dementia. Do not use Ginkgo biloba in individuals taking anticoagulants or antiplatelet medications, and use cautiously in those taking NSAIDs.
- Vitamin E is under investigation for AD prevention and is not recommended for treatment.
- There is currently insufficient evidence to recommend omega•3 fatty acids or medical foods such as Axona, Souvenaid, and Cerefolin NAC for treatment of AD.

Pharmacologic Therapy of Neuropsychiatric Symptoms

- No medication is FDA approved for the treatment of AD behavioral and psychological symptoms of dementia (BPSD) that are: (1) psychotic; (2) hyperactive (eg, inappropriate or disruptive behavior); (3) affective (eg, depression); and (4) apathy.
- General guidelines include: (1) reserve for situations where nonpharmacologic failed; (2) starting with reduced doses and titrating slowly; (3) monitoring closely; (4) periodically attempting to taper and discontinue medication; and (5) careful documentation.
- Cholinesterase inhibitors and memantine may be beneficial in treating BPSD but they do not reduce acute agitation. Avoid anticholinergic medications as they may worsen cognition.

Antidepressants

- Antidepressants may help manage anxiety, apathy, as well as agitation and aggression.
- A selective serotonin reuptake inhibitor (SSRI) can be used to treat depression with thebest evidence for sertraline and citalopram. Tricyclic antidepressants are usually avoided.

Antipsychotics

- Antipsychotic medications have traditionally been used for psychotic and but the risks and benefits must be carefully weighed.

- Second•generation antipsychotics (ie, aripiprazole, risperidone, olanzapine, and quetiapine) are more effective compared to placebo; however, the higher risk of adverseeffects and mortality offset this benefit. They should be restricted to patients with severesymptoms not responding to other measures. Taper treatment as early as possible andrarely used beyond 12 weeks.

✓ Common adverse medication reactions include somnolence, extrapyramidal symptoms, abnormal gait, worsening cognition, cerebrovascular events, and increased risk of death (black•box warning).

Miscellaneous Therapies

- Evidence for benzodiazepine use is lacking and is not advised due to significant AD reactions.
- Use of antiseizure medications (also known as mood stabilizers), carbamazepine, lamotrigine, pregabalin, and gabapentin, may be alternatives for agitation, but evidenceis conflicting.
- Use of valproic acid is no longer recommended due to severe adverse effects.

EVALUATION OF THERAPEUTIC OUTCOMES

- At baseline interview both patient and caregiver to identify target symptoms; define therapeutic goals; and document cognitive status, physical status, functional performance, mood, thought processes, and behavior.
- Use a validated scale to assess cognition, activities of daily living (eg, the Bristol Activities of Daily Living Scale), and behavioral disturbances (eg, Neuropsychiatric Inventory Questionnaire) to quantify symptom changes and functioning.
- Observe carefully for medication efficacy, need for dosage adjustments, adherence, potential adverse medication reactions, and document the method and frequency of monitoring.
- Medication changes and adjustments should occur at 2–4 and 8–12 weeks after initiation,with assessments being repeated every 3–6 months thereafter. Several months to 1year of treatment may be required to determine whether medications for cognition are beneficial.
- Medication deprescribing for people with AD is aided by the availability of depot therapy. When to stop treatment due to lack of efficacy, if ever, is controversial

ANXIETY DISORDERS

INTRODUCTION

Anxiety disorders (eg, generalized anxiety disorder [GAD] and panic disorder [PD]) have prominent features of anxiety and avoidance that are irrational or that impair functioning. In posttraumatic stress disorder (PTSD), there is previous exposure to trauma and the occurrence of intrusive, avoidant, and hyperarousal symptoms.

ETIOLOGY

Evaluation of anxiety requires a physical and mental status examination; complete psychiatric diagnostic exam; appropriate laboratory tests. Anxiety symptoms may be associated with medical illnesses or medications, and may be comorbid with other mental illnesses (eg, mood disorders, schizophrenia, and substance withdrawal).

Common Medical Illnesses Associated with Anxiety Symptoms

Cardiovascular: Angina, arrhythmias, cardiomyopathy, congestive heart failure, hypertension, ischemic heart disease, mitral valve prolapse, myocardial infarction
Endocrine and metabolic: Cushing disease, diabetes, hyperparathyroidism, hyperthyroidism, hypothyroidism, hypoglycemia, hyponatremia, hyperkalemia, pheochromocytoma, vitamin B12 or folate deficiencies
Gastrointestinal: Crohn's disease, irritable bowel syndrome, ulcerative colitis, peptic ulcer disease
Neurologic: Migraine, seizures, stroke, neoplasms, poor pain control
Respiratory system: Asthma, chronic obstructive pulmonary disease, pulmonary embolism, pneumonia
Others: Anemias, cancer, systemic lupus erythematosus, vestibular dysfunction

Medications and Substances Associated with Anxiety Symptoms

Antiseizure medications: carbamazepine, phenytoin
Antidepressants: bupropion, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors
Antihypertensives: clonidine, felodipine
Antibiotics: quinolones, isoniazid
Bronchodilators: albuterol, theophylline
Corticosteroids: prednisone
Dopamine agonists: amantadine, levodopa
Herbals: ma huang, ginseng, ephedra
Unhealthy substance use: ecstasy, cannabis
Nonsteroidal antiinflammatory drugs: ibuprofen, indomethacin
Stimulants: amphetamines, caffeine, cocaine, methylphenidate, nicotine
Sympathomimetics: pseudoephedrine, phenylephrine
Thyroid hormones: levothyroxine
Toxicity: anticholinergics, antihistamines, digoxin

PATHOPHYSIOLOGY

- The noradrenergic model suggests the autonomic nervous system is hypersensitive and overreacts to stimuli. The locus ceruleus (LC) activates norepinephrine release and stimulates the sympathetic and parasympathetic nervous systems. This downregulates α2 adrenoreceptors in patients with GAD and PTSD, while this receptor is hypersensitive in PD. Medications with anxiolytic or antipanic effects (eg, benzodiazepines and antidepressants) inhibit LC firing and decrease noradrenergic
- γ-Aminobutyric acid (GABA) receptor model. GABA is the major inhibitory neurotransmitter in the central nervous system (CNS). Benzodiazepines enhance GABA's inhibitory effects, which regulates or inhibits serotonin (5-hydroxytryptamine; 5-HT), norepinephrine, and dopamine activity. The number of GABAA receptors can change with environmental alterations, and hormones can alter subunit expression. Abnormal functioning of norepinephrine, GABA, glutamate, dopamine, and 5-HT may affect manifestations of anxiety disorders.
- 5-HT model suggests that greater 5-HT function facilitates avoidance behavior and that reducing 5-HT increases aggression. GAD symptoms may reflect excessive 5-HT transmission or overactivity of the stimulatory 5-HT pathways. The selective serotonin reuptake inhibitors (SSRIs) increase synaptic 5-HT and are effective in blocking manifestations of panic and anxiety.
- Cortisol reduces the stress response by tempering the sympathetic reaction. Patients with PTSD hypersecrete corticotropin-releasing factor but have subnormal levels of cortisol at the time of trauma and chronically. Dysregulation of the hypothalamic–pituitary– adrenal axis may be a risk factor for eventual development of PTSD.
- Neuroimaging studies support the role of the amygdala, anterior cingulate cortex, and insula in the pathophysiology of anxiety. In GAD, there is an abnormal increase in the brain's fear circuitry and activity in the prefrontal cortex. Patients with PD have midbrain structural abnormalities. In PTSD, the amygdala plays a role in the persistence of traumatic memory. Hypofunctioning in the ventromedial prefrontal cortex is theorized to prevent extinction in patients with PTSD and is inversely correlated with severity of symptoms.
- Glutamate signaling abnormalities may distort amygdala-dependent emotional process under stress, which may contribute to the dissociative and hypervigilant symptoms in PTSD.

GENERALIZED ANXIETY DISORDER: CLINICAL PRESENTATION AND DIAGNOSIS

- Psychological and cognitive symptoms of GAD include excessive anxiety, worries that are difficult to control, feeling keyed up or on edge, and trouble concentrating or mind going blank.
- Physical symptoms include restlessness, fatigue, muscle tension, sleep disturbance, and irritability.
- The diagnosis of GAD requires excessive anxiety and worry most days for at least 6 months with at least three physical symptoms present. Significant distress or impairment in functioning is present, and the disturbance is not caused by a substance or another medical condition.
- Females are twice as likely as males to have GAD. The illness has a gradual onset at an average age of 21 years. The course is chronic, with multiple exacerbations and remissions.

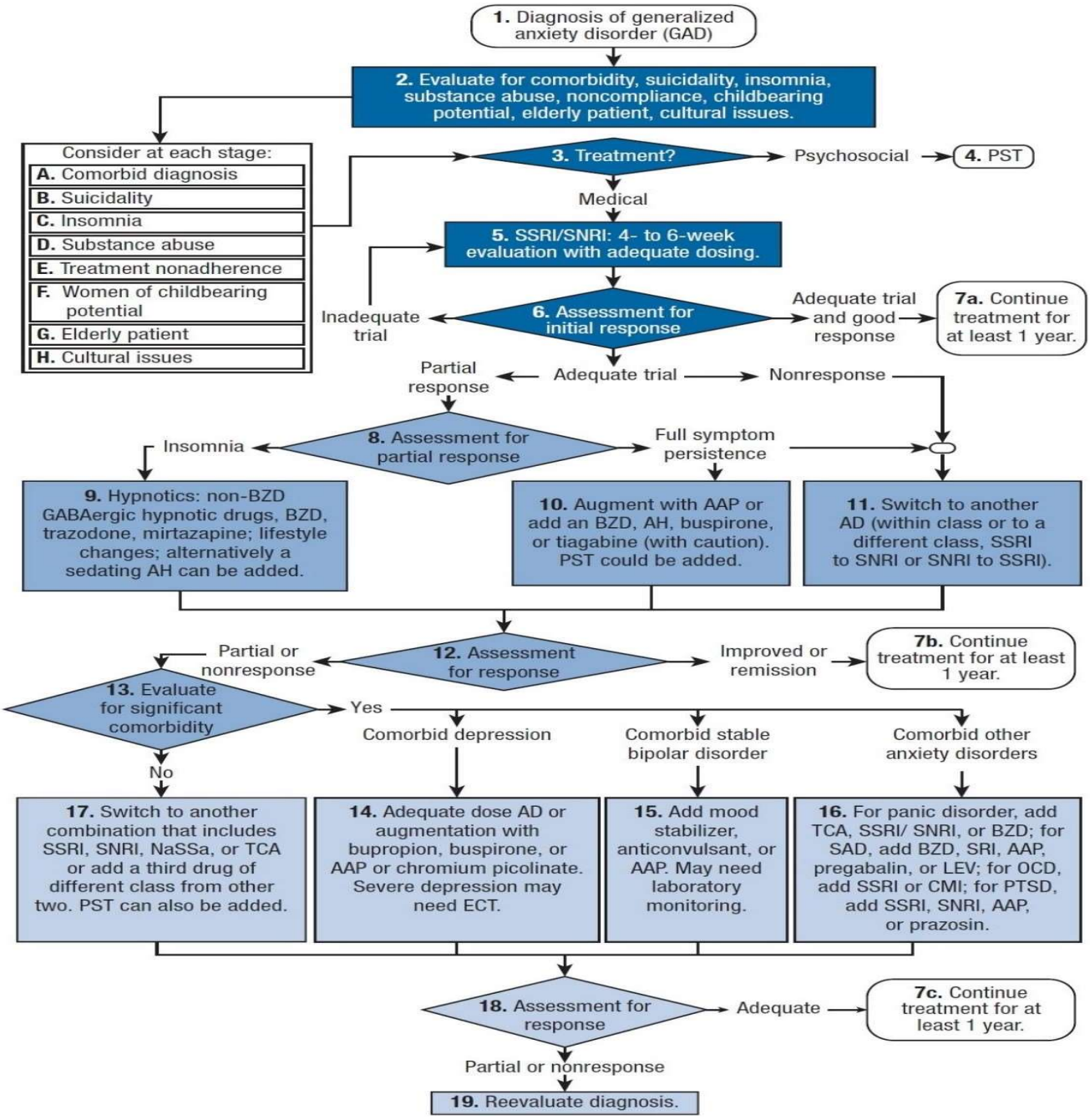
TREATMENT

Goals of Treatment: The goals are to reduce severity, duration, and frequency of symptoms and improve functioning. The long-term goal is minimal or no anxiety symptoms, no functional impairment, prevention of recurrence, and improved quality of life.

Nonpharmacologic Therapy

- Nonpharmacologic modalities include psychotherapy, short-term counseling, stress management, psychoeducation, meditation, and exercise. Ideally, patients with GAD should have psychological therapy, alone or in combination with antianxietymedications. Cognitive behavioral therapy (CBT), though not widely available, is the most effective psychological therapy. Patients should avoid caffeine, nicotine,stimulants, excessive alcohol, and diet pills.

- A treatment algorithm from the International Psychopharmacology Algorithm Project (IMAP) is shown below



Medications of Choice for Anxiety Disorders

Anxiety Disorder	First-Line Medications	Second-Line Medications	Alternatives
Generalized anxiety disorder	Duloxetine Escitalopram Paroxetine Sertraline Venlafaxine XR	Benzodiazepines Buspirone Imipramine Pregabalin	Hydroxyzine Quetiapine
Panic disorder	VenlafaxineXR	Alprazolam Citalopram Clomipramine Clonazepam Imipramine	Phenelzine

Nonbenzodiazepine Antianxiety Agents for Generalized Anxiety Disorder:

- Duloxetine, Escitalopram, Imipramine, Paroxetine, Sertraline, Venlafaxine XR, Vilazodone, Vortioxetine, Buspirone, Hydroxyzine, Pregabalin, Quetiapine XR
- Older patients are usually treated with approximately one-half of the dose exceptBuspirone.
- Paroxetine should be avoided in pregnancy
- Drug-drug interaction with concomitant use of Vilazodone with itraconazole, clarithromycin, voriconazole
- Pregabalin need dosage adjustment in patients with renal impairment.

Antidepressants

- Antidepressants are effective for acute and long-term management of GAD and are the treatment of choice, especially in the presence of depressive symptoms. An 8–12 weeks'trial with an SSRIs (eg, escitalopram, paroxetine, sertraline), or the serotonin- norepinephrine reuptake inhibitors (SNRIs) (eg, venlafaxine extended-release and duloxetine), results in response rates between 60% and 68%, and remission rates of ~30%.
- Venlafaxine, escitalopram, paroxetine, duloxetine, and quetiapine are more likely to achieve remission of GAD symptoms; however, sertraline may be the best tolerated.
- Patients may require small initial doses for the first week to limit the development of transient increased anxiety, also known as jitteriness syndrome.
- All antidepressants carry a black box warning regarding suicidal thinking and behaviorsin children, adolescents, and young adults less than 25 years and recommend specific monitoring parameters (consult the FDA-approved labeling or the FDA website).
- Clinical practice guidelines recommend fluoxetine, sertraline, or citalopram for pregnantpersons; however, jitteriness, myoclonus, and irritability in the neonate and premature infant have been reported and paroxetine should be avoided due to cardiovascularmalformation risk.

Monitoring of Adverse Medication Reactions for Anxiety Disorders

SSRIs	Jitteriness syndrome, Suicidality, Nausea, diarrhea, Headache, Weight gain (Paroxetine), Sexual dysfunction, Hyponatremia, Thrombocytopenia (Reported with citalopram), Teratogenicity (Avoid paroxetine), QT prolongation, Discontinuation syndrome (in all except fluoxetine)
SNRIs	Jitteriness syndrome, Suicidality, Nausea, diarrhea, Headache, Elevated blood pressure, Sexual dysfunction, Discontinuation syndrome.
TCAs	Jitteriness syndrome, Suicidality, Anticholinergic effects, Weight gain, Sexual dysfunction, Sedation, Arrhythmia, Orthostatic hypotension, Cholinergic rebound
Benzodiazepines	Drowsiness, fatigue, Anterograde amnesia and memory impairment (risk increase with concomitant intake of alcohol, medication abuse, Withdrawal symptoms, Respiratory depression (avoid use with CNS depressants (ie, opioids, alcohol), Psychomotor impairment, Paradoxical disinhibition.
Other Medications *Buspirone*	Nausea, abdominal pain, drowsiness, dizziness

Benzodiazepines

- All benzodiazepines possess anxiolytic properties, although only seven are FDA- approved for the treatment of GAD.
- Benzodiazepines are the most effective and frequently prescribed treatment for acute anxiety. About 65%–75% of patients with GAD have a marked to moderate response, with most improvement in the first 2 weeks. They are more effective for somatic and autonomic symptoms of GAD, whereas antidepressants are more effective for the psychicsymptoms (eg, apprehension and worry).
- The dose must be individualized. Older patients are more sensitive to benzodiazepines and may experience falls when taking them.
- Their most common adverse effect is CNS depression but tolerance usually develops. Others include disorientation, psychomotor impairment, confusion, aggression, excitement, ataxia, and anterograde amnesia.
- Start with low doses, and adjust weekly. Benzodiazepines should be used with a regular dosing regimen and not on an as needed basis when used for the treatment of an anxiety disorder.
- Treatment of acute anxiety generally should be 2–4 weeks. Manage persistent symptoms with antidepressants.
- Long half life benzodiazepines may be dosed once daily at bedtime, providing nighttime hypnotic and next day anxiolytic effects.
- Use low doses of short elimination half life agents in older patients.

- Diazepam and clorazepate have high lipophilicity and are rapidly absorbed and distributed into the CNS. They have rapid antianxiety effects, but a shorter duration of effect after a single dose than would be predicted based on half life, as they are rapidly distributed to the periphery.
- Lorazepam and oxazepam are less lipophilic, have a slower onset, but a longer duration of action. They are not recommended for immediate relief of anxiety.
- Avoid intramuscular (IM) diazepam and IM chlordiazepoxide because of variability in rate and extent of absorption. IM lorazepam provides rapid and complete absorption.
- Several benzodiazepines are converted to desmethyl diazepam, which has a long half life
- and can accumulate. Intermediateor short acting benzodiazepines are preferred for chronic use in older patients and those with liver disorders because of minimal accumulation and achievement Combining benzodiazepines with alcohol or other CNS depressants may be fatal.
- Addition of nefazodone, ritonavir, or ketoconazole (CYP3A4 inhibitors) can increase the blood levels of alprazolam and diazepam. Medications that induce cytochrome CYP3A4 (eg, carbamazepine, St. John's wort) can reduce benzodiazepine levels. Medications that inhibit or induce CYP2C19 (eg, fluoxetine, fluvoxamine, omeprazole) or N-acetyltransferase 2 activity can alter diazepam and clonazepam metabolism, respectively.
- Consult the medication interaction literature for more information on benzodiazepine interactions.
- Benzodiazepine use in pregnant persons has been associated with teratogenic effects (ie, cleft lip and palate, "floppy baby syndrome," and neonatal withdrawal). Antidepressants are preferred. If a benzodiazepine must be used, diazepam and chlordiazepoxide may be preferred. In infants receiving human milk from an individual receiving a benzodiazepine, sedation, lethargy, and weight loss may be seen.

Benzodiazepine Antianxiety Medications

Alprazolam, Chlordiazepoxide, Clonazepam, Clorazepate, Diazepam, Lorazepam,Oxazepam.

Benzodiazepine Discontinuation

- After benzodiazepines are abruptly discontinued, three events can occur: (1) rebound symptoms are an immediate but transient return of original symptoms with an increased intensity compared with baseline; (2) recurrence or relapse is the return of original symptoms at the same intensity as before treatment; or (3) withdrawal is the emergence of new symptoms and a worsening of preexisting symptoms.
- The onset of withdrawal symptoms is within 24–48 hours after discontinuation of short-elimination half-life benzodiazepines and 3–8 days after discontinuation of a long-elimination half-life medication.
- **Discontinuation strategies include:** A 25% per week reduction in dosage until 50% of the dose is reached, and then reduce by one-eighth every 4–7 days. If therapy duration exceeds 8 weeks, a taperover 2–3 weeks is recommended, but if duration of treatment is 6 months, a taperover 4–8 weeks is reasonable. Longer durations of treatment may require a 2–4-month taper.
- Adjunctive use of pregabalin can help to reduce withdrawal symptoms during the benzodiazepine taper.

Physical Dependence, Withdrawal, and Tolerance

- Benzodiazepine physical dependence is defined by appearance of a withdrawal syndrome(ie, anxiety, insomnia, agitation, muscle tension, irritability, nausea, diaphoresis, nightmares, depression, hyperreflexia, tinnitus, delusions, hallucinations, and seizures) upon abrupt discontinuation.
- Those with a history of a substance use disorder should not receive benzodiazepines, if possible. Those with GAD and PD are at high risk for unhealthy use and possibly physical dependence because of illness chronicity.

Buspirone

- Buspirone is a 5-HT$_{1A}$ partial agonist that lacks antiseizure, muscle relaxant, sedative-hypnotic, motor impairment, and dependence-producing properties.
- It is a second line agent for GAD because of inconsistent long-term efficacy, and delayed onset of effect. It is an option for patients who fail other anxiolytic therapies or patients with a history of unhealthy alcohol or substance use. It does not provide rapid or "as-needed" antianxiety effects.
- Buspirone can be titrated in increments of 5 mg/day every 2 or 3 days as needed.
- The onset of anxiolytic effects requires 2 weeks or more; maximum benefit may require 4–6 weeks. Improvement in psychic symptoms precedes improvement in somatic symptoms.
- It may be less effective in patients who have previously taken benzodiazepines. It has a mean $t_{1/2}$ of 2.5 hours, and it is dosed two to three times daily.
- Buspirone may elevate blood pressure in patients taking a monoamine oxidase inhibitor (MAOI).
- Verapamil, itraconazole, and fluvoxamine can increase buspirone levels through CYP3A4 inhibition, and rifampin reduces buspirone blood levels 10-fold.

Alternative Pharmacotherapy

- Hydroxyzine is considered a second-line agent.
- Pregabalin produced anxiolytic effects similar to lorazepam, alprazolam, and venlafaxinein acute trials. Sedation and dizziness are common adverse medication effects.
- Quetiapine extended release, 150 mg/day, was superior to placebo and as effective as paroxetine 20 mg/day and escitalopram 10 mg/day, but with earlier onset of action. Quetiapine is not FDA approved for GAD and the long-term risks are unknown.

Evaluation of Therapeutic Outcomes

- Initially, monitor every 2 weeks for symptom reduction, improvement in functioning, and medication adverse effects. The Hamilton Rating Scale for Anxiety (HAMA) or the Sheehan Disability Scale can help measure response.
- Treatment resistance may be diagnosed after poor, partial, or lack of response is seen with at least two antidepressants from different classes. For those not achieving an appropriate response with a first line agent, the dose may be increased. Other options include augmentation, or changing to a different agent. If treatment fails, assess for (a) symptoms (eg, psychotic symptoms) that need additional medications or (b) treatment nonadherence. Patients should also be assessed for concurrent substance use disorder, concurrent illnesses, and suicidal thoughts.

Depressive Disorders

Introduction

The essential feature of major depressive disorder (MDD) is a clinical course characterized by one or more major depressive episodes without a history of manic or hypomanic episodes.

Pathophysiology

- Monoamine hypothesis: Decreased brain levels of the neurotransmitters norepinephrine (NE), serotonin (5HT), and dopamine (DA) may cause depression.
- Postsynaptic changes in receptor sensitivity: Studies have demonstrated that desensitization or down- regulation of NE or 5HT1A receptors may relate to onset of antidepressant effects.
- Dysregulation hypothesis: Failure of homeostatic neurotransmitter regulation, rather than absolute increases or decreases in their activities.
- Inflammatory hypothesis: Chronic stress and inflammation may alter glutamatergic and GABA transmission. Brain-derived neurotrophic factor (BDNF) is a primary mediator of neuronal changes as well as synaptogenesis whose expression is reduced due to stress and may be associated with depression.
- Neuroactive steroids are a growing area of research for depression.

Clinical presentation

- Emotional symptoms: Diminished ability to experience pleasure, loss of interest in usual activities, sadness, pessimism, crying, hopelessness, anxiety, feelings of worthlessness or guilt, and psychotic features (eg, auditory hallucinations and delusions). Recurrent thoughts of death, suicidal ideation without a specific plan, suicide attempt, or a plan for committing suicide.
- Physical symptoms: Weight gain or loss, fatigue, pain (especially headache), sleep disturbance, decreased or increased appetite, loss of sexual interest, and gastrointestinal (GI) and cardiovascular complaints (especially palpitations).
- Cognitive symptoms: Decreased ability to concentrate, poor memory for recent events, confusion, and indecisiveness.
- Psychomotor disturbances: Psychomotor retardation (slowed physical movements, thought processes, and speech) or psychomotor agitation.

Diagnosis

- MDD is characterized by one or more major depressive episodes, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Five or more of the above symptoms must have been present nearly every day during the same 2week period and cause significant distress or impairment. Depressed mood or loss of interest or pleasure must be present in adults (or irritable mood in children and adolescents). Table 1 outlines a common acronym for MDD diagnostic criteria.
- The depressive episode must not be attributable to physiological effects of a substance or medical condition.
- There must not be a history of manic like or hypomanic like episodes unless they were induced by a substance or medical condition.
- Diagnosis requires a medication review, physical examination, mental status examination, a complete blood count with differential, thyroid function tests, and electrolyte determination.
- Many chronic illnesses (eg, stroke, Parkinson disease, traumatic brain injury, hypothyroidism) and substance use disorders are associated with depression. Medications associated with depressive symptoms include many antihypertensives, oral contraceptives, isotretinoin, interferonβ1a, and many others.
- Standardized rating scale should be used to diagnose depression and evaluate treatment.

Table 1: Diagnostic Criteria for Major Depressive Episode

S	Suicidal ideation with or without plan, suicide attempt; recurrent thoughts of death
I	Interest—loss of interest or pleasure in activities; anhedonia
G	Guilt—inappropriate or excessive in nature; feelings of worthlessness
E	Energy decreased
C	Concentration decreased; difficulty making decisions
A	Appetite changes; typically decreased; resulting in 5% change in weight from baseline
P	Psychomotor agitation or retardation
S	Sleep impairment; typically insomnia but may be hypersomnia

- At least five symptoms must be consistently present over a 2-week period.
- Symptoms must include depressed mood or anhedonia.
- Symptoms must cause substantial distress or impairment in functioning.
- Other medical conditions or substance use do not account for symptoms.

Treatment

Goals of Treatment: Resolution of current symptoms (ie, remission), prevention offurther episodes of depression (ie, relapse or recurrence), and prevention of suicide.

Nonpharmacologic Therapy

- Psychotherapy (eg, cognitive therapy, dialectical behavior therapy, or interpersonal psychotherapy) is recommended as primary treatment for mild tomoderately severe major depressive episode. For severe depression, it may be used in combination with medications as its effect is considered additive. Psychotherapy alone is not recommended for acute treatment of severe and/or psychotic MDD.
- Electroconvulsive therapy (ECT) may be considered when a rapid response is needed, risks of other treatments outweigh potential benefits, there is history of a poor response to medications, and the patient prefers ECT. A rapid therapeutic response (10–14 days) has been reported.
- Repetitive transcranial magnetic stimulation has demonstrated efficacy and does not require anesthesia as does ECT.
- Recent data suggest the benefit of physical activity in patients with MDD, and the American Psychiatry Association has endorsed inclusion of exercise into MDD treatment plans.

Pharmacologic TherapyGeneral Approach

- Antidepressants are considered first line and are equal in efficacy when administered in comparable doses. They are often classified by chemical structure and/or presumed mechanism.
- The initial choice of antidepressant is often made empirically and influenced by the patient's or family member's history of response, concurrent medical conditions, medications the patient is taking, presenting symptoms, potential for medication interactions, medication adverse effect profiles, patient preference, and medication cost.

- An individual's pharmacogenomics may be useful when choosing therapy as away to better predict antidepressant adverse effects or response. Dosing recommendations to aid in the interpretation of results are available through the Clinical Pharmacogenomics Implementation Consortium (CPIC) as well asthe FDA approved package inserts.
- About 50%–60% of patients with varying types of depression improve with pharmacologic treatment.
- At least a 6week trial of an antidepressant at maximum dosage is considered an adequate trial.
- The acute phase of treatment lasts 6–12 weeks, and the goal is remission (ie, absence of symptoms). The continuation phase (4–9 months after remission) seeks to eliminate residual symptoms or prevent relapse. The maintenance phase (12–36 months or more) seeks to prevent recurrence of a new episode ofdepression. Some guidelines recommend lifelong maintenance therapy for persons at greatest risk for recurrence (ie, younger than 40 years of age with two or more prior episodes or any age with three or more prior episodes).
- Give older patients one-half of the initial dose given to younger adults, and increase the dose more slowly. Older patients may require 6–12 weeks of treatment to achieve the desired antidepressant response.
- Early in treatment, all antidepressants can increase suicidal thinking and behavior in children, adolescents, and young adults less than 25 years of age. Suicide risk may also be elevated in the 30 days after discontinuation.
- Educate patients and their support systems about the delay in antidepressant response (typically 2–4 weeks) and the importance of adherence before starting therapy and throughout treatment.
- Occurrence of a withdrawal syndrome with some antidepressants may be reduced with a slow taper over weeks or months when the medication is being discontinued.
- The ability of any antidepressant to inhibit or induce the CYP450 enzymes canbe a significant factor determining its capability to cause pharmacokinetic interactions.

Selective Serotonin Reuptake Inhibitors

- The SSRIs inhibit the reuptake of 5HT into the presynaptic neuron. They are generally chosen as firstline antidepressants because of their relative safety in overdose and improved tolerability compared with earlier agents.
- Nonresponse to one SSRI does not predict nonresponse to an alternative SSRI.
- The SSRIs may have a nonlinear pattern of accumulation with chronic dosing. Hepatic impairment, renal impairment, and age can influence SSRI pharmacokinetics.
- Any antidepressant that enhances serotonergic activity can be associated with serotonin syndrome characterized by mental status changes, autonomic instability, and neuromuscular abnormalities. Combining an SSRI with another 5HT augmenting agent is also a risk.
- The primary adverse effects for SSRIs are nausea, vomiting, diarrhea, headache, insomnia, fatigue, and sexual dysfunction and have a reduced incidence of sedative, anticholinergic, and cardiovascular adverse effects or weight gain.
- A few patients have anxiety symptoms early in treatment which may be reduced by starting with lower doses and slowly titrating up.
- Citalopram and escitalopram may to an increase in QT interval at doses above 40 mg/day.
- Potentially fatal reactions may occur when any SSRI and MAOI are coadministered. A 5week washout after fluoxetine discontinuation is critical before starting an MAOI.
- If an SSRI is added to a regimen which includes interacting medications the SSRI starting dose should be low and slowly titrated.
- CYP2D6 and 3A4 are responsible for the metabolism of more than 80% of current medications.

Serotonin–Norepinephrine Reuptake Inhibitors

- Venlafaxine may have a slight efficacy advantage compared to other antidepressants.
- Common adverse effects may be doserelated and include nausea, sexual dysfunction, activation, and hyperhidrosis.
- Venlafaxine may cause a dose-related increase in diastolic blood pressure, which may require dosage reduction or discontinuation if sustained hypertension occurs. Nausea and vomiting may be worse with venlafaxine andthere may be higher adverse effect-related discontinuation rates withvenlafaxine and duloxetine than with the SSRIs.
- The most common adverse effects of duloxetine are nausea, dry mouth, constipation, decreased appetite, insomnia, and increased sweating.

Antidepressants with Mixed Serotonin Effects

- Mirtazapine enhances central noradrenergic and serotonergic activity by antagonizing central presynaptic α2adrenergic auto receptors and hetero- receptors. It also antagonizes 5HT2 and 5HT3 receptors and blocks histamine receptors. It may be an option for patients experiencing sexual dysfunction with other antidepressants. Mirtazapine's most common adverse effects are somnolence, and weight gain.
- Levomilnacipran is a single isomer, extended-release form of milnacipran (FDA approved to treat fibromyalgia). It inhibits NE reuptake more than 5HT reuptake and may increase blood pressure and heart rate. Its place in therapy for MDD is unknown.
- Trazodone and nefazodone antagonize the 5HT2 receptor and inhibit the reuptake of 5HT.
- They can also enhance 5HT1A neurotransmission. Trazodone blocks α1adrenergic and histaminergic receptors increasing dizziness and sedation.
- Trazodone cause minimal anticholinergic effects and sedation, dizziness, and cognitive slowing are the most frequent dose limiting adverse effects. Commonadverse effects with nefazodone are dizziness, orthostatic hypotension, and somnolence.
- Priapism occurs rarely with trazodone (1 in 6000 male patients). Surgical intervention may be required, and impotence may result.
- Nefazodone carries a black box warning for life threatening liver failure. Do not initiate nefazodone in individuals with active liver disease or elevated serum transaminases.
- Vilazodone and vortioxetine are antidepressants with mixed serotonin effects that are a combination SSRI and 5HT1A presynaptic receptor partial agonists. Vilazodone may be particularly useful for depressed patients with anxiety, andvortioxetine may be helpful for depressed patients with cognitive difficulties.
- Vilazodone is associated with nausea, diarrhea, dizziness, insomnia, and decreased libido, especially in males.
- Vortioxetine causes nausea and constipation and sexual dysfunction in malesat the highest dose (20 mg/day).

Bupropion

- Bupropion inhibits both the NE and DA reuptake making it one of the most activating antidepressants.
- The occurrence of seizures with bupropion is dose related and may be increased by predisposing factors (eg, history of head trauma or central nervous system [CNS] tumor). At the ceiling dose (450 mg/day), the incidenceof seizures is 0.4%.
- Other adverse effects are nausea, vomiting, tremor, insomnia, dry mouth, and skin reactions. It is contraindicated in patients with bulimia or anorexia nervosa, due to a higher risk for seizures. It causes less sexual dysfunction than SSRIs.

Tricyclic Antidepressants

- Tricyclic antidepressant (TCA) use has diminished given other equally effective therapies that are safer on overdose and better tolerated. They inhibit the reuptake of NE and 5HT and have affinity for adrenergic, cholinergic, and histaminergic receptors.
- TCAs cause anticholinergic effects (eg, dry mouth, blurred vision, constipation, urinary retention, tachycardia, memory impairment, and delirium) and sedation. Additional adverse effects include weight gain, orthostatic hypotension, cardiac conduction delay, and sexual dysfunction.
- Desipramine carries an increased risk of death in patients with a family history of sudden cardiac death, cardiac dysrhythmias, or cardiac conduction disturbances.
- Abrupt withdrawal of TCAs (especially high doses) may result in cholinergic rebound (eg, dizziness, nausea, diarrhea, insomnia, and restlessness).
- TCA metabolism appears to be linear within the usual dosage range. Dose- related kinetics cannot be ruled out in older patients. Factors reported to influence TCA plasma concentrations include renal or hepatic dysfunction, genetics, age, cigarette smoking, and concurrent medications.
- In acutely depressed patients, there is a correlation between antidepressant effect and plasma concentrations for some TCAs (eg, amitriptyline, nortriptyline, imipramine, and desipramine). The best-established therapeutic range is for nortriptyline, and data suggest a therapeutic window.
- Some indications for TCA plasma level monitoring include inadequate response or relapse; adverse effects; use of higher than standard doses; suspected nonadherence; pharmacokinetic interactions; older, pediatric, and adolescent patients; pregnant patients; pharmacogenomic indications; and cardiac disease. Obtain steady state plasma concentrations usually after aminimum of 1 week at constant dosage, during the elimination phase 12 hours after the last dose.
- TCAs may interact with other medications that modify hepatic cytochrome P450 (CYP450) enzyme activity or hepatic blood flow. TCAs also are involved in interactions through displacement from protein binding sites.
- Increased plasma concentrations of TCAs and symptoms of toxicity may occurwhen CYP2D6 inhibitors are added.

Monoamine Oxidase Inhibitors

- Isocarboxazide, phenelzine, and tranylcypromine increase the concentrations of NE, 5HT, and DA within the neuronal synapse through inhibition of monoamine oxidase (MAO). They are nonselective inhibitors of MAOA and MAOB. Selegiline, available as a transdermal patch for treatment of major depression, inhibits brain MAOA and MAOB but has reduced effects on MAOA in the gut.
- The most common medication adverse effect is postural hypotension (more likely with phenelzine than tranylcypromine), which can be minimized by divided dosing.
- Phenelzine is mildly to moderately sedating, but tranylcypromine is often stimulating, and the last dose of the day is administered in the early afternoon. Sexual dysfunction in both genders is common. Phenelzine has been associated with hepatocellular damage and weight gain.
- The potentially fatal hypertensive crisis can occur when MAOIs are taken concurrently with foods high in tyramine, and with certain medications.

  Symptoms include occipital headache, stiff neck, nausea, vomiting, sweating, and sharply elevated blood pressure. It can be treated with agents such as captopril. Education regarding dietary (e.g., aged cheese) and medication (e.g., Dextromethorphan, amphetamine, sympathomimetics, etc) restrictions are critical.
- Patients taking transdermal selegiline patch doses greater than 6 mg/24 hours must follow the dietary restrictions.
- Potentially fatal reactions may occur when any SSRI or TCA is co-administered with an MAOI. However, TCAs and MAOIs can be combined in refractory patients by experienced clinicians with careful monitoring.

Ketamine

- Ketamine modulates glutamate activity via extra synaptic N-methyl-D- aspartate (NMDA) receptor antagonism resulting in increased BDNF activity and synaptogenesis.
- It has rapid antidepressant effects when used in intravenous doses of 0.5mg/kg for treatment of treatment resistant depression (TRD).
- Esketamine is the single s-isomer of ketamine that has a higher affinity for the NMDA receptor than the R-isomer.
- Intranasal esketamine is FDA approved and requires supervised, in-clinic self administration (1–3 sprays in each nostril per session) followed by 2 hours of in- clinic observation. In trials, patients received doses twice weekly for 4 weeks and variable dosing thereafter.
- Medication adverse effects include transient psychotomimetic/dissociative effects and blood pressure elevation (10–20 mm Hg) with both agents. It has a mandatory Risk Evaluation and Mitigation Strategies (REMS).

Brexanolone

- Brexanolone (exogenous allopregnanolone) is thought to exert antidepressant effect by allosteric modulation of GABAA receptors, which may increase 5HTand NE transmission and is FDA approved for postpartum depression. Administration involves a 60 hour stepped dose, intravenous infusion which isvery costly.
- Common adverse effects are headache, dizziness, and somnolence. It also hasa REMS program with Elements to Ensure Safe Use (ETASU) due to the incidence of excessive sedation or loss of consciousness.

Alternative Pharmacotherapy

- St. John's wort, a herb containing hypericum, may be effective some with mild to moderate depression. It is associated with several medication interactions.
- Omega3 fatty acids, S-adenosyl-L-methionine (SAMe), and folate are additional pharmacotherapies that could be considered. Evidence regarding their use is conflicting or still emerging. All of these agents should be used with caution.

Special PopulationsOlder Patients

- In older patients, depressed mood may be less prominent than other symptoms, such as loss of appetite, cognitive impairment, sleeplessness, fatigue, physical complaints, and loss of interest in usual activities.
- The SSRIs are often considered first choice antidepressants for older patients. Bupropion, venlafaxine, and mirtazapine are also effective and well tolerated.
- Hyponatremia is more common in older patients.

Pediatric Patients

- Symptoms of depression in childhood include boredom, anxiety, failing adjustment, and sleep disturbance.
- Data supporting efficacy of antidepressants in children and adolescents are sparse. Fluoxetine and escitalopram are FDA approved for patients below 18 years of age.
- All antidepressants carry a black box warning for use in this population regarding increased risk for suicidal ideation and behavior. The FDA recommends specific monitoring parameters.
- Several cases of sudden death have been reported in children and adolescents taking desipramine and baseline electrocardiogram (ECG) is recommended.

Pregnancy and Lactation

- Individuals who discontinued antidepressant therapy during pregnancy were five times more likely to have a relapse during their pregnancy than those who continued treatment.
- The absolute risk of antidepressant use in pregnancy is unknown.

- Risks reported with SSRIs use in pregnancy include low birth weight,respiratory distress, and congenital heart defects.
- The risks and benefits of drug therapy during pregnancy must be weighed,including concerns about untreated depression.
- There is a great deal of uncertainty regarding long-term antidepressantexposure in infants exposed through human milk due to the lack of data.

Relative Resistance and Treatment Resistant Depression

- One in three patients who did not achieve remission with an antidepressant may become symptom free when an additional medication (eg, bupropion SR or buspirone) is added. One in four may achieve remission after switching to a different antidepressant (eg, venlafaxine XR or bupropion, or sertraline).
- The current antidepressant may also be augmented by addition of another agent (eg, lithium or triiodothyronine [T3]), or another antidepressant can be added. A second generation antipsychotic (eg, aripiprazole, quetiapine, brexpiprazole) can be used to augment antidepressant response. New medications such as ketamine and esketamine may be considered.
- The practice guideline of the American Psychiatric Association recommends that after 6–8 weeks of treatment, partial responders should consider changing the dose, augmenting the antidepressant, or adding psychotherapy or ECT. Forpatients with no response, options include changing to another antidepressant or the addition of psychotherapy or ECT.
- Before changing treatment, evaluate the adequacy of the medication dosage and adherence, as most "treatment resistant" depressed patients have received inadequate therapy.
- Issues to be addressed in assessing the patient who has not responded to treatment include asking: (1) Is the diagnosis correct?; (2) Does the patient have a psychotic depression?; (3) Is the dose and duration of treatment adequate?; (4) Do adverse medication reactions preclude adequate dosing?; (5)Is patient adherence appropriate?; (6) Was a stepwise approach to treatment used?; (7) Was treatment outcome adequately measured?; (8) Is there a coexisting or preexisting medical or psychiatric disorder?; (9) Are there other factors interfering with treatment?; (10) May pharmacogenomics be impactingtreatment?

Evaluation of therapeutic outcomes

- Several monitoring parameters, in addition to plasma concentrations, are useful. Monitor regularly for adverse effects, remission of target symptoms, and changes in social or occupational functioning. Assure regular monitoring for several months after discontinuation of antidepressants.
- Regularly monitor blood pressure of patients given serotonin–norepinephrine reuptake inhibitors.
- A pretreatment ECG is recommended before starting TCA therapy in children,adolescents, and patients over 40 years of age, and perform follow up ECGs periodically.
- Monitor for suicidal ideation after initiation of any antidepressant, especially in the first few weeks of treatment and up to 30 days after treatment discontinuation.
- In addition to the clinical interview, use psychometric rating instruments to rapidly and reliably measure the nature and severity of depressive and associated symptoms.

Schizophrenia

Definition

Schizophrenia is a chronic illness characterized by positive symptoms (eg, delusions and hallucinations); negative symptoms (eg, anhedonia and social isolation); and cognitive dysfunction (eg, impaired working memory, and executive function) all leading to impaired psychosocial functioning.

Pathophysiology

- Schizophrenia causation theories include genetics, obstetric complications with hypoxia, neurodevelopmental disorders, neurodegenerative theories, dopamine receptor defect, and regional brain abnormalities including hyperor hypoactivity of dopaminergic processes in specific brain regions. Increased ventricular size and decreased gray matter have been reported.
- Alterations in glutamatergic neurotransmission resulting in increased neuronal pruning have also been implicated in schizophrenia pathogenesis. Genes controlling N-methyl-D-aspartate (NMDA) receptor activity are hypothesized to be part of this process.
- There is now a plethora of diverse findings pointing to immune dysfunction in schizophrenia, as well as abnormalities of autoantibodies and cytokine functioning.
- Positive symptoms may associate with dopamine receptor hyperactivity in the mesocaudate, whereas negative and cognitive symptoms relate to dopamine receptor hypofunction in the prefrontal cortex.

Clinical presentation

- Symptoms may include positive symptoms: hallucinations (especially hearing voices); delusions (fixed false beliefs); ideas of influence (actions controlled by external influences); disconnected thought processes (loose associations); illogical conversation; ambivalence (contradictory thoughts); negative symptoms: alogia (poverty of speech), avolition, flat affect, anhedonia, and social isolation; and cognitive dysfunction (eg, impaired attention, working memory, and executive function). These may be accompanied by uncooperativeness, hostility, and verbal or physical aggression; impaired self- care skills; and disturbed sleep and appetite.
- After the acute psychotic episode has resolved, there may be residual features (eg, anxiety, suspiciousness, lack of motivation, poor insight, impaired judgment, social withdrawal, difficulty in learning from experience, and poor self-care skills).
- Comorbid psychiatric and medical disorders (eg depression, anxiety disorders, substance use, and general medical disorders such as respiratory disorders, cardiovascular disorders, and metabolic disturbances) can also occur. Medication nonadherence is also common.

Diagnosis

- The Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM5), specifies the following diagnostic criteria:
- Continuous symptoms persisting for ≥6 months with ≥1 month of active symptoms (Criterion A). May include prodromal or residual symptoms.

A. Criterion A: For ≥1 month, two of the following must be present for a significant time: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. At least one symptom must be delusions, hallucinations, or disorganized speech.
B. Criterion B: Significantly impaired functioning.

- Before treatment, perform a mental status and neurologic examination, a physical examination (vitals including height and weight), complete family and social history,

psychiatric diagnostic interview, and laboratory workup (complete blood count [CBC], electrolytes, hepatic function, renal function, electrocardiogram [ECG], fasting serum glucose, serum lipids, thyroid function, and urine toxicology screen).

Treatment

Goals of Treatment: The goal is to alleviate target symptoms, avoid medication adverse effects, improve psychosocial functioning and productivity, achieve compliance with the prescribed regimen, and prevent relapse. Involve the patient in treatment planning.

Non pharmacologic Therapy

- Psychosocial rehabilitation programs to improve adaptive functioning are the mainstay of non pharmacologic therapy for schizophrenia. Programs involving the family aimed at supportive employment and housing are considered "best practices" and decrease rehospitalization while improving functioning in the community.
- Clinical decision making should be a mutual process involving the patient and clinician.

Pharmacologic Therapy

- Both first generation antipsychotics (FGAs, also known as traditional) and second generation antipsychotics (SGAs, also known as atypical) treat schizophrenia symptoms.
- Available antipsychotics include: First generation (Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Perphenazine, Thioridazine, and Trifuroperazine); Second generation (Aripiprazole, Asenapine, Brexpiprazole, Cariprazine, Clozapine, Iloperidone, Lumateperone, Lurasidone, Olanzapine, Paliperidone, Quetiapine, Risperidone, and Ziprasidone).
- The antipsychotic's mechanism of action is unknown. FGAs have high D2 antagonism and low serotonin2 receptor [5HT2A] antagonism. SGAs exhibit moderate to high D2 antagonism and high 5HT2A antagonism, and clozapine shows low D2 antagonism and high 5HT2A antagonism.
- Base antipsychotic selection on: (1) avoidance of certain adverse medication effects, (2) concurrent medical or psychiatric disorders, and (3) patient or family history of response.
- Clozapine has superior efficacy for suicidal behavior.
- In first episode schizophrenia, initiate dosing at the lower end of the range. Use of SGAs during the first acute episode results in greater treatment retention and relapse prevention compared to FGAs. Aripiprazole, risperidone,or ziprasidone may be preferred first line.
- Risperidone injection is more effective than oral risperidone in preventing relapse over a 1year period for first episode schizophrenia. A long acting antipsychotic should be considered during stages 1A, 1B, and 2 as they have consistently demonstrated an advantage in reduced hospitalizations and relapse prevention in patients with schizophrenia.
- In Stage 3, clozapine monotherapy is recommended.
- For Stage 4, minimal evidence exists for any treatment option for patients withadequate symptom improvement with clozapine. Use of antipsychotic combinations is controversial, as limited evidence supports increased efficacy, despite this practice being somewhat common.
- Predictors of response include prior response to the medication, absence of alcohol or substance use, acute onset and short duration of illness, later age of onset, affective

symptoms, family history of affective illness, medication adherence, employment, and good premorbid adjustment. Negative symptoms are generally less responsive to antipsychotic therapy.

- An initial dysphoric response (eg, dislike of the medication or feeling worse, combined with anxiety or akathisia) portends a poor response, adverse effects, and non-adherence.
- The importance of developing a therapeutic alliance between the patient and the clinician cannot be overemphasized.
- Anticholinergic effects occur most commonly with low potency FGAs, clozapine, and olanzapine. These include impaired memory, dry mouth, constipation, tachycardia, blurred vision, inhibition of ejaculation, and urinary retention. Older patients are especially sensitive to these effects.
- Sedation can be reduced if most or the entire daily dose is taken at bedtime.
- Antipsychotics are highly lipophilic, bind highly to membranes and plasma proteins, have large volumes of distribution, and are largely metabolized by cytochrome P450 (CYP) pathways. Pharmacogenetics may impact their pharmacokinetics.
- Most antipsychotics, except quetiapine and ziprasidone, have elimination half lives ≥24 hours and can be dosed once daily.
- Antipsychotic pharmacokinetics can be significantly affected by concomitant enzyme inducers or inhibitors. Smoking induces hepatic enzymes and may increase antipsychotic clearance by as much as 50%. Asenapine, an inhibitorof CPY2D6, is the only antipsychotic that significantly affects the pharmacokinetics of other medications. Fluvoxamine, an inhibitor of CYP1A2, increases clozapine serum concentrations by two to threefold. Ketoconazole profoundly decreases lurasidone metabolism, and concomitant use is not recommended. Carbamazepine can decrease aripiprazole serumconcentrations. Reduce the iloperidone dose by 50% when used with CYP2D6 inhibitors such as fluoxetine or paroxetine.

Initial Therapy

- The goals for the first 7 days of treatment are decreased agitation, hostility, anxiety, and aggression and normalization of sleep and eating.
- Titrate the antipsychotic dose over the first few days to an effective dose in themiddle of the ranges. The starting dose for first episode psychosis is half ofthat used for chronically ill patients. Rapid titration is not recommended. If there is no improvement within 2 weeks at a therapeutic dose, then move to the next treatment stage.
- In partial responders who are tolerating the antipsychotic well, titration above the usual dose range for 2–4 weeks with close monitoring is appropriate.
- Intramuscular (IM) antipsychotic administration (eg, aripiprazole 5.25–9.75 mg, ziprasidone 10–20 mg, olanzapine 2.5–10 mg, or haloperidol 2–5 mg) canbe used for agitation. This approach does not improve the extent of response, time to remission, or length of hospitalization. IM lorazepam, 2 mg, as needed for agitation added to the maintenance antipsychotic is a rational alternative to an injectable antipsychotic. Combining IM lorazepam with olanzapine or clozapine is not recommended because of the risk of hypotension, central nervous system (CNS) depression, and respiratory depression.
- Inhaled loxapine powder, approved for acute agitation, can be administered only in a healthcare facility and through the FDA approved Risk Evaluation and Mitigation Strategy (REMS). Use is limited to one 10mg inhaled dose per 24 hours. Patients with any lung disease associated with bronchospasm (eg, asthma, chronic obstructive pulmonary disease) are excluded. It may offer no advantage over IM and oral products.

Stabilization Therapy

- During weeks 2 and 3, the goal is to improve socialization, self care, and mood. Dose titration may continue every 1–2 weeks as long as the patient has no adverse effects.
- If the patient begins to show an adequate response at a particular dose, then continue that dosage as long as symptoms continue to improve. Improvement in formal thought disorder may require an additional 6–8 weeks.

Maintenance Therapy

- The goal of maintenance therapy is relapse prevention. Continue medication for at least 12 months after remission of the first psychotic episode. Many experts recommend treatment for at least 5 years, and lifetime pharmacotherapy at the lowest effective dose is necessary in most patientswith schizophrenia.
- When switching from one antipsychotic to another, the first should be tapered and discontinued over at least 1–2 weeks while the second antipsychotic is initiated and tapered upward. Slow titration, especially FGAs and clozapine, can be done to avoid cholinergic rebound.

Management of Treatment-resistant Schizophrenia

- Only clozapine has shown superiority over other antipsychotics, with improvement occurring slowly. About 60% of patients improve if used for up to 6 months.
- Clozapine is usually titrated more slowly than other antipsychotics to reduce orthostatic hypotension. If a 12.5mg test dose does not produce hypotension, then 25 mg at bedtime is recommended. After 3 days, this is increased to 25 mg twice daily and then increased in 25–50 mg/day increments every 3 days until a dose of at least 300 mg/day is reached.
- A 12hour post-dose clozapine serum concentration of at least 350 ng/mL is associated with efficacy. Monitor serum concentrations before exceeding 600 mg daily, in patients with unusual or severe adverse effects, those concomitantly taking potentially interacting medications, those with age or pathophysiologic changes suggesting altered kinetics, and in those suspected of medication nonadherence.
- Mood stabilizers (eg, lithium, valproic acid, and carbamazepine) may improvelabile affect and agitation in patients with refectory schizophrenia. Selective serotonin reuptake inhibitors (SSRIs) may improve obsessive compulsive symptoms that worsen or arise during clozapine treatment.
- Little data supports or refutes combining anti psychotics, but this strategy is often employed. One of the medications should be discontinued if there is no improvement within 6–12 weeks.

Extrapyramidal Side Effects Dystonias

- Dystonias are prolonged tonic muscle contractions (occurring usually within 24–96 hours of dosage initiation or dosage increase); they may be life threatening (eg, pharyngeal–laryngeal dystonias). Other dystonias are trismus, glossospasm, tongue protrusion, blepharospasm, oculogyric crisis, torticollis, and retrocollis. Risk factors include younger (male) patients and use of FGA, high potency agents, and high dose.
- Treatment includes IM or IV anticholinergics (e.g., Benztropine) or benzodiazepines. Benztropine 2 mg, or diphenhydramine 50 mg, may be givenIM or IV, or diazepam, 5–10 mg by slow IV push, or lorazepam, 1–2 mg IM, may be given. Relief usually occurs within 15–20 minutes of IM injection or 5minutes of IV administration.

- Prophylactic anticholinergic medications are reasonable when using high potency FGAs (eg, haloperidol and fluphenazine) in young males or with a prior dystonia. Risk can be minimized by using lower initial doses or by using an SGA.

Akathisia

- Akathisia occurs in 20%–40% of patients treated with high potency FGAs and consists of subjective complaints (feelings of inner restlessness) and/or objective symptoms (pacing, shifting, shuffling, or tapping feet).
- Reduction in dose is the best intervention when feasible. Switching to an SGA is an option, although akathisia may still occur. Iloperidone, quetiapine, and clozapine appear to have the lowest risk. Benzodiazepines should be avoided in patients with a history of substance use. Propranolol (up to 160 mg/day) is reported to be effective. Emerging literature suggests that agents with antagonist activity at the 5HT2 receptor (cyproheptadine, mirtazapine, and trazodone) may be protective against akathisia.

Parkinsonism

- There are four cardinal symptoms: (1) akinesia, bradykinesia, or decreased motor activity, including masklike facial expression, micrographia; (2) tremor, primarily at rest; decreasing with movement; (3) cogwheel rigidity; limbs yield in jerky, ratchetlike fashion when moved passively by the examiner; (4) stooped, unstable posture and slow, shuffling, or festinating gait.
- Possible accessory symptoms include seborrhea, sialorrhea, hyperhidrosis, fatigue, weakness, dysphagia, and dysarthria.
- Risk factors include FGA use (especially in high dose), increasing age, and possibly female sex.
- Symptoms start 1–2 weeks after antipsychotic initiation or dose increase. Risk with SGAs is low except with risperidone in doses greater than 6 mg/day. Quetiapine, aripiprazole, brexpiprazole, iloperidone, asenapine, lumateperone, and clozapine are reasonable alternatives in a patient experiencing EPS with other SGAs.
- Benztropine has a half life that allows once to twice daily dosing. Typical dosing is 1–2 mg twice daily up to a maximum of 8 mg daily. Diphenhydramine produces more sedation. All of the anticholinergics have been misused for euphoriant effects. Amantadine is as effective as anticholinergics with less effect on memory.
- Attempt to taper and discontinue these agents 6 weeks to 3 months after symptoms resolve.

Tardive Dyskinesia

- Tardive dyskinesia (TD) is characterized by abnormal involuntary movements. The classic presentation is buccolingual-masticatory or orofacial movements interfering with chewing, wearing dentures, speech, respiration, or swallowing. Facial movements include frequent blinking, brow arching, grimacing, upward deviation of the eyes, and lip smacking. Restless choreiform and athetotic movements of the limbs occur in later stages. Movements may worsen with stress, decrease with sedation, and disappear with sleep.
- Screen at baseline using the Abnormal Involuntary Movement Scale (AIMS) and the Dyskinesia Identification System Condensed User Scale (DISCUS). Repeat monitoring every 6 months for those at high risk and every 12 months for all others.
- TD prevention includes: (1) use SGAs first line; (2) biyearly TD screening; and (3) discontinue antipsychotics or switch to SGAs at the earliest symptoms of TD, if possible.
- Risk factors for TD include duration of antipsychotic therapy, higher dose, possibly

cumulative dose, possibly female sex, increasing age, occurrence of acute extrapyramidal symptoms, poor antipsychotic response, diagnosis of organic mental disorder, diabetes mellitus, and mood disorders. With FGAs the prevalence of TD ranges from 20%–50%. With SGAs, the risk of TD is about 3.0% per year in younger adults compared to 7.7% per year for FGAs.

- Deutetrabenazine and valbenazine are vesicular monoamine transporter2 (VMAT2) inhibitors approved for TD treatment in adults. Warnings associatedwith their use include suicidality, depression, and QT interval prolongation.

Other Antipsychotic Adverse EffectsSeizures

- The highest risk is with chlorpromazine or clozapine and they are more likely with treatment initiation, higher doses, and rapid dose increases.
- Dosage reduction should occur for an isolated seizure, and antiseizure medication is usually not recommended.
- If a change in antipsychotic therapy is required, aripiprazole, risperidone, thioridazine, haloperidol, pimozide, trifluoperazine, and fluphenazine may be considered.

Thermoregulation

- Poikilothermia, the body temperature adjusting to the ambient temperature, can be a serious antipsychotic adverse effect. Hyperpyrexia, leading to heat stroke, may be dangerous in hot weather or during exercise. Hypothermia is also a risk, especially in older individuals. These problems are more common with the use of lowpotency FGAs and can occur with the more anticholinergic SGAs.

Neuroleptic Malignant Syndrome

- Neuroleptic malignant syndrome (NMS) occurs in <1% of patients with high potency FGAs having the greatest risk.
- Symptoms develop rapidly over 24–72 hours: body temperature exceeding 38°C [100.4°F]), altered level of consciousness, autonomic dysfunction (tachycardia, labile blood pressure, diaphoresis, and tachypnea), and rigidity.
- Myoglobinuria, leukocytosis, increases in creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) are common.
- Discontinue antipsychotics and provide supportive care. Dantrolene, bromocriptine, or amantadine may be useful in severe cases as all have reportsof reduced time to clinical improvement and reduction in mortality rates.
- Antipsychotic rechallenge with the lowest effective dose of an SGA or lowpotency FGA may be considered after at least 2 weeks without antipsychotics. Monitor carefully and titrate the dose slowly.

Endocrine Effects

- Prolactin elevations are associated with galactorrhea, gynecomastia, decreasedlibido, and menstrual irregularities. They are common and are likely with FGAs, risperidone, and paliperidone. Possible management strategies include switching to an agent with lower risk (eg, aripiprazole, asenapine, iloperidone, lurasidone, brexpiprazole, lumateperone, and cariprazine). Dopamine agonists are not recommended due to potential psychosis exacerbation.

- Weight gain with antipsychotic therapy may be most likely with olanzapine, clozapine, risperidone, quetiapine, and iloperidone. Ziprasidone, aripiprazole, lumateperone, lurasidone, brexpiprizole, and cariprazine appear to cause minimal weight gain.
- Patients with schizophrenia have a high prevalence of type 2 diabetes, which antipsychotics can worsen. Olanzapine and clozapine have the highest risk of causing new onset diabetes, followed by risperidone and quetiapine. The risk with aripiprazole and ziprasidone is likely less than with other SGAs. Asenapine, iloperidone, lurasidone, brexpiprazole, cariprazine, and lumateperone also appear to have a lower risk, but more data is needed.
- Genetic variation within the dopamine, serotonin, melanocortin4, and alpha 2 receptors have been associated with antipsychotic weight gain. However, it is most likely polygenic and impacted by the environment.

Cardiovascular Effects

- Orthostatic hypotension (defined as >20 mm Hg drop in systolic blood pressure upon standing) is greatest with lowpotency FGAs, clozapine, iloperidone, quetiapine, and combination antipsychotics. Older patients and those with diabetes and cardiovascular disease are predisposed. Dose reduction or changing to an antipsychotic with less α adrenergic blockade mayhelp, and tolerance may develop within 2–3 months.
- The low potency piperidine phenothiazines (thioridazine), clozapine, iloperidone, and ziprasidone are the most likely to cause ECG changes, including increased heart rate, flattened T waves, STsegment depression, and prolongation of QT and PR intervals. Thioridazine prolongs the QTc on average about 20 milliseconds longer than haloperidol, risperidone, olanzapine, or quetiapine. For thioridazine, the effect is dose related, and the medication's labeling carries a boxed warning for torsades de pointes and sudden death.
- Iloperidone pharmacogenomic metabolism may increase the risk of QTc prolongation in CYP2D6 poor metabolizers. High IV doses of haloperidol alsocan prolong the QTc, and it also carries a boxed warning.
- Medication discontinuation should occur with QTc prolongation consistently exceeding 500 milliseconds. Torsades rarely happens in the absence of additional risk factors (eg, age greater than 60, female sex, preexisting cardiac or cerebrovascular disease, hepatic impairment, hypokalemia, hypomagnesemia, additional medications that prolong the QTc interval, metabolic inhibition by another medication, or preexisting QTc prolongation).
- In patients older than 50 years, pretreatment ECG and serum potassium and magnesium levels are recommended.
- Myocarditis is an infrequent and dose independent adverse effect that is most likely to occur with clozapine but has been reported with quetiapine, and possibly with olanzapine. Recommended laboratory monitoring has been proposed with baseline and weekly monitoring of Creactive protein (CRP) for the first 4 weeks, while troponin (I or T) and B type natriuretic peptide monitoring has also been suggested. Cardiomyopathy, a potentially life threatening adverse effect, can also be seen with clozapine, which typically presents later in the course of treatment than myocarditis, with an average timeof onset of 14 months. Clozapine rechallenge after myocarditis is debated, andnot recommended after cardiomyopathy.
- Those taking FGAs or SGAs have twice the risk of sudden cardiac death than nonusers. Antipsychotics are associated with a 1.53fold increase in ventriculararrhythmia or sudden cardiac death.

- Compared to the general population, the risk of venous thromboembolism (VTE) is twofold higher in individuals with schizophrenia treated with an antipsychotic. Although the mechanism of this risk is unknown, increased sedative adverse effects, metabolic effects, antipsychotic effect on platelet aggregation, and hyperprolactinemia indirectly increasing venous stasis have been proposed.

Lipid Effects

- Some SGAs and phenothiazines cause serum triglycerides and cholesterol elevations. Olanzapine, clozapine, and quetiapine have the highest risk for dyslipidemia.
- Weight gain, diabetes, and lipid abnormalities during antipsychotic therapy areconsistent with development of metabolic syndrome (consisting of raised triglycerides, ≥150 mg/dL [1.70 mmol/L]), low high density lipoprotein cholesterol (≤40 mg/dL [1.03 mmol/L] for males, ≤50 mg/dL [1.29 mmol/L] for females), elevated fasting glucose (≥100 mg/dL [5.6 mmol/L]), blood pressure elevation (≥130/85 mm Hg), and weight gain (abdominal circumference >102 cm for males, >89 cm for females).

Psychiatric Effects

- Aripiprazole is associated with impulse control disorders such as pathological gambling, uncontrolled sexual urges, uncontrolled spending, binge or compulsive eating, and other intense urges.

Ophthalmologic Effects

- Exacerbation of narrow angle glaucoma can occur with antipsychotics and/or anticholinergic use.
- Opaque deposits in the cornea and lens may occur with chronic phenothiazine treatment, especially chlorpromazine. Although visual acuity is not usually affected, periodic slit lamp examinations are recommended with long-term phenothiazine use. Baseline and periodic slit-lamp examinations are also recommended for quetiapine treated patients because of cataract development in animal studies.
- Thioridazine doses greater than 800 mg daily (the recommended maximum dose) can cause retinitis pigmentosa with permanent visual impairment or blindness.

Genitourinary System

- Urinary hesitancy and retention are common, especially with low potency FGAs and clozapine, and males with benign prostatic hyperplasia.
- Urinary incontinence resulting from α blockade, by the SGAs, is especially problematic with clozapine.
- Risperidone and paliperidone produce as much sexual dysfunction as FGAs, but other SGAs with weaker prolactin effects pose less risk. Priapism, an unprovoked painful erection that persists for longer than an hour, is increasingly reported with antipsychotic use.

Hematologic System

- Antipsychotics can cause transient leukopenia that usually does not progress to clinical significance. Clozapine, chlorpromazine, and olanzapine have the highest risk for neutropenia.
- The risk of developing neutropenia or agranulocytosis with clozapine is approximately 3% and 0.8%, respectively. Increasing age and female sex increase risk. The greatest risk is between 1 and 6 months of initiating treatment. The baseline absolute neutrophil count (ANC) must be ≥ 1500/μL (1.5 × 109/L) to start clozapine. Weekly ANC monitoring for the first 6 months is FDA mandated. After this time, if it remains >1500/μL (1.5 × 109/L), ANC monitoring can be decreased to every 2 weeks for the next 6 months. Subsequently, if all ANCs remain >1500/μL (1.5 × 109/L) monitoringcan be decreased to monthly. If at any time the ANC drops to <500/μL

(0.5 × 109/L), discontinue clozapine and monitor the ANC daily until it is >1500/μL (1.5 × 109/L). Refer to the product labeling for more detailed information, including monitoring for mild and moderate leukopenia.

- Agranulocytosis also occurs in 0.01% of patients receiving FGAs, and it may occur more frequently with chlorpromazine and thioridazine. The onset is usually within the first 8 weeks of therapy and can manifest as sore throat, leukoplakia, erythema, and ulcerated pharynx. Patients with these symptoms and a ANC <500/μL (0.5 × 109/L), should discontinue the antipsychotic with close monitoring for secondary infection.

Dermatologic System

- Allergic reactions are rare and usually occur within 8 weeks of initiating therapy. They manifest as maculopapular, erythematous, or pruritic rashes.
- Contact dermatitis, on the skin or oral mucosa, may occur. Swallowing of the FGA oral concentrates quickly may decrease rashes on the oral mucosa.
- Ziprasidone carries a warning about a rare but fatal skin reaction called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Both FGAs and SGAs can cause photosensitivity with severe sunburns. Patients should use maximal blocking sunscreens, hats, protective clothing,and sunglasses when in the sun.
- Blue-gray or purplish discoloration of skin exposed to sunlight may occur withhigher doses of low-potency phenothiazines (especially chlorpromazine) givenlong term. This may occur with concurrent corneal or lens pigmentation.

Use in Pregnancy and Lactation

- Haloperidol is the best studied FGA with approximately 400 reported exposures. A small study found a twofold elevated risk of preterm birth in pregnant persons with schizophrenia taking FGAs as compared with those not taking antipsychotics. Risk of neonatal EPS is increased with inutero exposureto FGAs, with effects in the infant lasting for 3–12 months after birth.
- All SGAs cross the blood–placental barrier to varying degrees. A meta- analysis found a greater risk of birth defects and preterm births with first trimester exposure to SGA, but no specific abnormality was identified. Other larger studies also suggest that aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone collectively do not increase the risk of congenital malformations or cardiac malformation. Large, well controlled studies are needed to clarify the safety of SGAs during pregnancy.
- For all of the FGAs, the overall relative infant doses (RID) obtained through human milk is thought to be less than 10%, which is a common threshold indicating safe use. Olanzapine and quetiapine have reported RIDs of <4%. Risperidone and aripiprazole have higher RIDs up to ~9%. Nursing while on clozapine is not recommended due to the risk of severe neutropenia and seizures in the infant.

Evaluation of therapeutic outcomes

The four item Positive Symptom Rating Scale and the Brief Negative Symptom Assessment are brief enough to be useful in the outpatient setting to measure changes in symptomatology. Patient-rated self-assessments can also be useful, as they engage the patient in treatment and can open the door for patient education and addressing misconceptions. Clinicians should be assertive in attempting to achieve symptom remission.

Insomnia

Clinical presentation

- Insomnia is subjectively characterized as trouble initiating or maintaining sleep or waking up early with the inability to fall back asleep. The consequence of this disrupted sleep is daytime sleepiness.
- Transient (two or three nights) and short term (less than 3 months) insomnia iscommon. Chronic insomnia (more than 3 months duration) occurs in 9%–12%of adults and in up to 20% of older individuals.
- Causes of insomnia include stress; jet lag or shift work; pain or other medical problems; mood or anxiety disorders; substance withdrawal; stimulants, steroids, or other medications.

Treatment

Goals of Treatment: To correct the underlying sleep complaint, improve daytimefunctioning, and avoid adverse medication effects.

Nonpharmacologic Therapy

- Behavioral and educational interventions that may help include short-term cognitive behavioral therapy, relaxation therapy, stimulus control therapy, cognitive therapy, sleep restriction, paradoxical intention, and sleep hygiene education.

Stimulus control procedures

1. Establish regular time to wake up and to go to sleep (including weekends).
2. Sleep only as much as necessary to feel rested.
3. Go to bed only when sleepy. Avoid long periods of wakefulness in bed. Use the bed only for sleep or intimacy; do not read or watch television in bed.
4. Avoid trying to force sleep; if you do not fall asleep within 20–30 minutes, leave the bed and perform a relaxing activity (eg, read, listen to music) until drowsy. Repeat this as often as necessary.
5. Avoid blue spectrum light from television, smart phones, tablets, and other mobile devices.
6. Avoid daytime naps.
7. Schedule worry time during the day. Do not take your troubles to bed.

Sleep hygiene recommendations

1. Exercise routinely (three to four times weekly) but not close to bedtimebecause this can increase wakefulness.
2. Create a comfortable sleep environment by avoiding temperatureextremes, loud noises, and illuminated clocks in the bedroom.
3. Discontinue or reduce the use of alcohol, caffeine, and nicotine.
4. Avoid drinking large quantities of liquids in the evening to preventnighttime trips to the restroom.
5. Do something relaxing and enjoyable before bedtime.

- Management includes identifying and correcting the cause of insomnia, educating about sleep hygiene, managing stress, monitoring for mood symptoms, and eliminating unnecessary pharmacotherapy.
- In patients aged 55 years and older, cognitive behavioral therapy may be more effective than pharmacologic therapy at improving certain measures of insomnia.
- Transient and short-term insomnia should be treated with good sleep hygiene and careful use of sedative–hypnotics if necessary. Chronic insomnia calls for careful assessment for a medical cause, non-pharmacologic treatment, and careful use of sedative–hypnotics if necessary.

Pharmacologic Therapy Antidepressants

- Antihistamines (eg, diphenhydramine, doxylamine, and pyrilamine) are available without a prescription. Their anticholinergic adverse effects may be problematic, especially in older individuals.
- Antidepressants are good alternatives for patients who should not receive benzodiazepines, especially those with depression, pain, or a history of substance use disorder or unhealthy substance use.
- Amitriptyline, doxepin, and nortriptyline are effective, but medication adverse effects include sedation, anticholinergic effects, adrenergic blockade effects, and cardiac conduction prolongation.
- Low dose doxepin is approved for sleep maintenance insomnia.
- Mirtazapine may improve sleep, but may cause daytime sedation and weight gain.
- Trazodone, 25–100 mg at bedtime, is often used for insomnia induced by selective serotonin reuptake inhibitors or bupropion and in patients prone to unhealthy substance use. Medication adverse effects include risk for serotonin syndrome (when used with other serotonergic drugs), over sedation, α adrenergic blockade, dizziness, and rarely, priapism.

Miscellaneous Agents

- Suvorexant and lemborexant are dual orexin A and orexin B receptor antagonists (DORA). Instead of inducing sleepiness, they turn off wake signaling. Suvorexant doses of 10–20 mg or lemborexant doses of 5–10 mg at bedtime are indicated for difficulty initiating or maintaining sleep. Adverse effects include sedation and rarely narcolepsy-like symptoms. Use caution in patients with depression because they can worsen depression and trigger suicidal thinking in a dose dependent manner.
- Ramelteon is a melatonin receptor agonist selective for the MT1 and MT2 receptors. The dose is 8 mg at bedtime. It is well tolerated, but adverse effects include headache, dizziness, and somnolence. It is not a controlled substance, and does not cause acute drowsiness similar to other insomnia agents. It is effective for patients with chronic obstructive pulmonary disease and sleep apnea.
- Valerian, an herbal product, is available without a prescription. The recommended dose is 300–600 mg. Data supporting its efficacy are lacking.

Benzodiazepine Hypnotics

- The benzodiazepine receptor agonists (BZDRAs) are the most commonly used drugs for insomnia. They include the newer non-benzodiazepine γ- aminobutyric acid A (GABAA) agonists and the traditional benzodiazepines, which also bind to GABAA. The United States Food and Drug Administration(FDA) requires labeling regarding anaphylaxis, facial angioedema, complex sleep behaviors (eg, sleep driving, phone calls, and sleep eating).
- BZDRAs include Estazolam, Flurazepam, Quazepam, Temazepam, and Triazolam. Other BZDRAs are often used off label for the treatment of insomnia.
- Benzodiazepines have sedative, anxiolytic, muscle relaxant, and anticonvulsant properties. They increase stage 2 sleep and decrease REM and delta sleep.
- Overdose fatalities are rare unless benzodiazepines are taken with other central nervous system (CNS) depressants.
- Triazolam is distributed quickly because of its high lipophilicity, and it has a short duration of effect. Erythromycin, nefazodone, fluvoxamine, and ketoconazole reduce the clearance of triazolam and increase plasma concentrations.
- The effects of flurazepam and quazepam are long because of active metabolites and therefore they should not be used as first-line agents.
- Adverse effects include drowsiness, psychomotor incoordination, decreased concentration, cognitive deficits, and anterograde amnesia, which are minimized by using the lowest dose possible.

- Tolerance to daytime CNS effects (eg, drowsiness, decreased concentration) may develop in some individuals.
- Rebound insomnia is minimized by using the lowest effective dose and tapering the dose upon discontinuation.
- Long elimination half life benzodiazepines are associated with falls and hip fractures; thus, flurazepam and quazepam should be avoided in older individuals. Lorazepam, oxazepam, and temazepam are the three BZDRAs often suggested to be used for older patients as they are primarily broken down by conjugation. Not all of these agents are FDA approved for insomnia.

Nonbenzodiazepine GABAA Agonists

- In general, the nonbenzodiazepine hypnotics (Eszopiclone, Zolpidem , and Zaleplon) do not have significant active metabolites, and they are associated with less physical withdrawal, tolerance, and rebound insomnia than the benzodiazepines.
- Zolpidem is comparable in effectiveness to benzodiazepine hypnotics, and it has little effect on sleep stages. Its duration is approximately 6–8 hours. Common adverse effects are drowsiness, amnesia, dizziness, headache, and gastrointestinal (GI) complaints. It appears to have minimal effects on next- day psychomotor performance. The usual dose is 5 mg in females, older persons, and those with liver impairment, and 5–10 mg in males. Sleep eating has been reported. It should be taken on an empty stomach.
- Zaleplon has a rapid onset, a half life of ~1 hour, and no active metabolites. It decreases time to sleep onset, but does not reduce nighttime awakenings or increase the total sleep time. It does not appear to cause nextday psychomotor impairment. The most common adverse effects are dizziness, headache, and somnolence. The recommended dose is 10 mg (5 mg in older patients).
- Eszopiclone has a rapid onset and duration of action of up to 6 hours. The most common adverse effects are somnolence, unpleasant taste, headache, anddry mouth. It may be taken nightly for up to 6 months.

Evaluation of therapeutic outcomes

Assess patients with short-term or chronic insomnia after 1 week of therapy for drug effectiveness, adverse events, and adherence to non-pharmacologic recommendations. Patients should maintain a daily recording of awakenings, medications taken, naps, and an index of sleep quality.

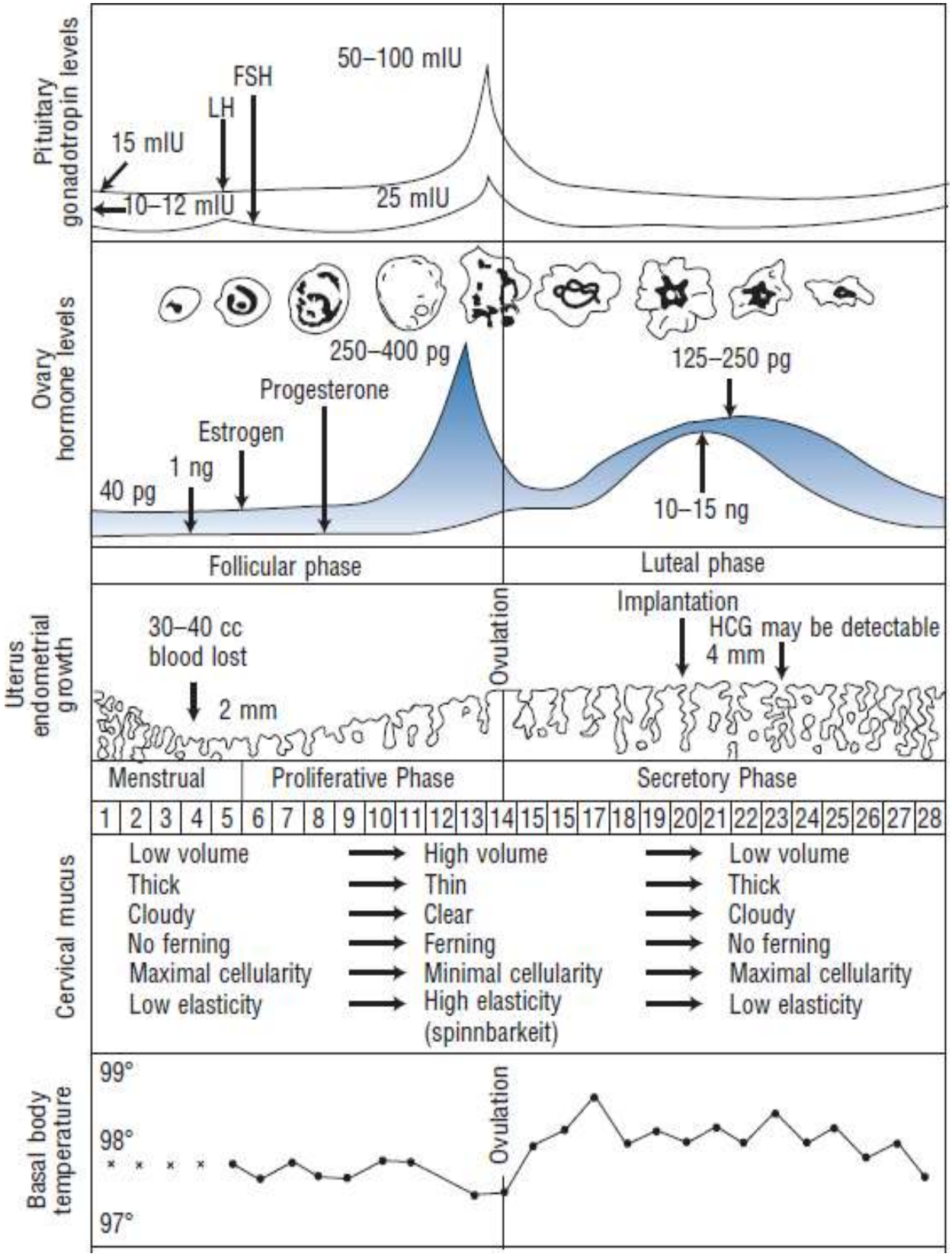
Contraception

INTRODUCTION

- Contraception is the prevention of pregnancy by inhibiting sperm from reaching a mature ovum or by preventing a fertilized ovum from implanting in the endometrium.
- While cis-women are the primary use of hormonal contraception, these agents are also used by transgender individuals and this chapter has been written to reflect this.

MENSTRUAL CYCLE PATHOPHYSIOLOGY

- The median menstrual cycle length is 28 days (range 21–40 days). Day 1 is the first day of menasneds marks the beginning of the follicular phase. Ovulation usually occurs on day 14, followed by the luteal phase that lasts until the beginning of the next cycle.
- The hypothalamus secretes gonadotropin releasing hormone, which stimulates the anteriorpituitary to secrete the gonadotropins follicle• stimulating hormone (FSH) and luteinizing hormone (LH).
- In the follicular phase, FSH levels increase and cause recruitment of a small group of follicles continued growth. Between days 5 and 7, one of these becomes the dominant follicle, which later ruptures to release the oocyte. The dominant follicle develops increasing amounts of estradiol and inhibin, providing negative feedback on the secretion of gonadotropin• releasing hormone and FSH.
- The dominant follicle continues to grow and synthesizes estradiol, progesterone, and androgen. Estradiol stops the menstrual flow from the previous cycle, thickens the endometrial lining, and produces thin, watery cervical mucus. FSH regulates aromatase enzymes that induce conversion of androgens to estrogens in the follicle.
- The pituitary releases a midcycle LH surge that stimulates the final stages of follicular maturation and ovulation. Ovulation occurs 24–36 hours after the estradiol peak and 10–16 hours after the LH peak.
- The LH surge is the most clinically useful predictor of approaching ovulation. Conception is most successful when intercourse takes place from 2 days before ovulation to the day of ovulation.
- After ovulation, the remaining luteinized follicles become the corpus luteum, which synthesize androgen, estrogen, and progesterone.
- If pregnancy occurs, human chorionic gonadotropin prevents regression of the corpus luteum and stimulates continued production of estrogen and progesterone. If pregnancy does not occur, the corpus luteum degenerates, progesterone declines, and menstruation occurs.


Pituitary gonadotropin levels
50–100 mIU
FSH
LH
15 mIU
10–12 mIU
25 mIU
Ovary hormone levels
250–400 pg
125–250 pg
Progesterone
Estrogen
1 ng
40 pg
10–15 ng
Follicular phase
Luteal phase
Uterus endometrial growth
30–40 cc blood lost
2 mm
Ovulation
Implantation
HCG may be detectable
4 mm
Menstrual
Proliferative Phase
Secretory Phase
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 15 17 18 19 20 21 22 23 24 25 26 27 28
Cervical mucus
Low volume → High volume → Low volume
Thick → Thin → Thick
Cloudy → Clear → Cloudy
No ferning → Ferning → No ferning
Maximal cellularity → Minimal cellularity → Maximal cellularity
Low elasticity → High elasticity (spinnbarkeit) → Low elasticity
Basal body temperature
99°
98°
97°
Ovulation

TREATMENT

- Goal of Treatment: The prevention of pregnancy from sexual intercourse. Additional benefitsinclude prevention of sexually transmitted infections [STIs] and menstrual cycle regulation.

Non-pharmacologic Therapy

- The fertility awareness based method includes avoiding intercourse when contraception islikely to occur. It is associated with relatively high pregnancy test.
- Diaphragms and the cervical cap are effective barriers that should be used with spermicide and inserted up to 6 hours before intercourse. They must be left in place for at least 6 hoursafter. A diaphragm should not be left in place for more than 24 hours due to the risk of toxicshock syndrome (TSS), while the cervical cap should not remain in place for longer than 48hours to reduce TSS risk. These do not protect against STIs including humanimmunodeficiency virus (HIV).
- Most external condoms (also known as male condoms) are made from latex, which is impermeable to viruses. A small percentage are made from lamb intestine, which are notimpermeable to viruses. Water soluble lubricants (ie, Astroglide and K•Y Jelly) are preferredto prevent condom breakdown. Condoms with spermicides are not recommended, as theyprovide no additional protection against pregnancy or STIs, and may increase vulnerability toHIV.
- The internal condom (also known as the female condom) covers the labia and the cervix.Its pregnancy rate is higher than with external condoms, but it protects against many viruses, including HIV. Do not use external and internal condoms together.
- Most spermicides contain nonoxynol•9, a surfactant that destroys sperm cell walls and blocks entry into the cervical os. They offer no protection against STIs, and when used morethan twice daily, nonoxynol•9 may increase HIV transmission.
- Phexxi is a prescription non•oxynol•9•free spermicide. It should be used within 1 hour beforeeach act of intercourse. It reduces vaginal pH to reduce sperm motility but carries a riskof cystitis.
- The vaginal contraceptive sponge is available over the counter and contains nonoxynol•9 and provides protection for 24 hours. After intercourse, it must be left in place for at least 6hours but no more than 24–30 hours to reduce the risk of TSS. It should not be reused afterremoval.

Comparison of Methods of Nonhormonal Contraception

Method	Absolute Contraindications	Advantages	Disadvantages	Pregnancy Risk With Use[a]	
Perfect Use	Typical Use				
Internal condoms, male	Allergy to latex or rubber	Inexpensive STI/STD protection, including HIV (latex only)	High failure rate Poor acceptance Possibility of breakage Efficacy decreased by oil•based lubricants Possible allergic reactions to latex in either partner	2	13
External condoms, female	Allergy to polyurethane History of TSS	Inserted just before intercourse or ahead of time STI/STD protection, including HIV	High failure rate Dislike ring hanging outside vagina Cumbersome	5	21
Diaphragm with spermicide	Allergy to latex, rubber, or spermicide Recurrent UTIs History of TSS	Low cost Decreased incidence of cervical neoplasia Some protection against	High failure rate Decreased efficacy with increased intercourse frequency Increased incidence of vaginal	16	17
	Abnormal gynecologic anatomy	STIs/STDs	yeast UTIs, TSS Efficacy decreased by oil•based lubricants Cervical irritation		
Cervical cap (FemCap)	Allergy to spermicide History of TSS Abnormal gynecologic anatomy Abnormal papanicolaou smear	Low cost Latex•free Some protection against STIs/STDs Reusable for up to 1 years	High failure rate Decreased efficacy with parity Cannot be used during menses	13.5	4–29[b]

Spermicides alone (Phexxi)	Allergy to spermicide	Inexpensive	High failure rate Must be reapplied before each act of intercourse May enhance HIV transmission No protection against STI/STDs Risk of cystitis	16	21–28[c]
Sponge (Today) spermicide Recurrent UTIs History of TSS Abnormal gynecologic	Allergy to	Inexpensive	High user failure rate Decreased efficacy with parity Cannot be used during menses No protection against STIs/STDs	9[d]	14[e]

Pharmacologic Therapy

Hormonal Contraceptives

- Hormonal contraceptives contain a combination of estrogen and progestin or progestin alone. They may be administered as oral contraception (OC), transdermal patch, vaginal ring, long•acting injection, subdermal implant, and intrauterine device (IUD).
- Combined Hormonal Contraceptive (CHC) contain both estrogen and progestin and workprimarily before fertilization to prevent conception.
- Estrogens suppress FSH release (contributing to blocking the LH surge) and also stabilize the endometrial lining and provide cycle control. Ethinyl estradiol (EE) is the most common synthetic estrogen; however, estetrol (E4) and estradiol valerate are also used.
- Progestins thicken cervical mucus, delay sperm transport, and induce endometrial atrophy, while also blocking the LH surge and inhibiting ovulation. They vary in their pro-gestational activity and differ in their inherent estrogenic, antiestrogenic, and androgenic effects. Androgenic activity depends on the presence of sex hormone (testosterone)–binding globulin and the androgen to progesterone activity ratio. If sex hormone–binding globulin decreases, free testosterone levels increase, and androgenic adverse effects are more prominent.
- With perfect use, CHC efficacy is more than 99%, but with typical use, up to 7% of indievxidpuearile'snce unintended pregnancy.
- Monophasic CHCs contain a constant amount of estrogen and progestin for 21 days, while biphasic and triphasic pills contain variable amounts of estrogen and progestin for 21 days. All are followed by a 7• day placebo phase.
- Extended•cycle pills and continuous combination regimens may reduce adverse effectsandare more convenient as the number of hormone•containing pills increases from 21 to 84 days, followed by a 7• day placebo phase, resulting in four menstrual cycles per year.

- The progestin only "minipills" are less effective than CHCs and are associated with irregularand unpredictable menstrual bleeding. They must be taken every day at approximately the same time of day to maintain efficacy and are associated with more ectopic pregnancies than other hormonal contraceptives.
- The first day start method starts on the first day of the menstrual cycle. The Sunday start method starts on the first Sunday after the menstrual cycle starts.
- The quick start method starts the day of the office visit. A second contraceptive method should be used for 7–30 days after CHC initiation and hormonal contraception should resume no sooner than 5 days after the use of emergency contraception (ie, ulipristal acetate).
- Provided guidance about what to do if a pill is missed or if vomiting and diarrhea occur.
- CHCs lack protection against STIs, and condoms should be used.
- The choice of an initial CHC is based on hormonal content and dose, preferred formulation, and coexisting medical conditions.
- A complete medical examination and papanicolaou (Pap) smear are not necessary before a CHC is prescribed. Obtain a medical history and blood pressure measurement, and discuss the risks, benefits, and adverse medication effects before prescribing a CHC.
- Non-contraceptive benefits of CHCs include decreased menstrual cramps and ovulatory pain; decreased menstrual blood loss; improved menstrual regularity; decreased iron deficiency anemia; reduced risk of ovarian and endometrial cancer; and reduced risk of ovarian cysts, ectopic pregnancy, pelvic inflammatory disease, endometriosis, uterine fibroids, and benign breast disease.

✓ Adverse medication effects occurring in the first cycle of CHC use (eg, breakthrough bleeding, nausea, and bloating) improve by the third cycle of use.

✓ Immediately discontinue if any warning signs referred to by the mnemonic ACHES (Abdominal pain, Chest pain, Headaches, Eye problems, and Severe leg pain) occur.

Serious or Potentially Serious Symptoms Associated with Combined Hormonal Contraception

SERIOUS: Stop immediately	
Loss of vision, proptosis, diplopia, papilledema Unilateral numbness, weakness, or tingling Severe pain in chest, left arm, or neck	Hemoptysis Severe pain, tenderness or swelling, warmth or palpable cord in legs Hepatic mass or tenderness
	Slurring of speech
POTENTIALLY SERIOUS: May continue with caution while being evaluated	
Absence of menses Spotting or breakthrough bleeding Breast mass, pain, or swelling Right upper-quadrant pain Mid-epigastric pain	Severe nonvascular headache Galactorrhea Jaundice, pruritus Depression, sleepiness Uterine size increase

Monitoring for Hormonal Contraception

Adverse Medication Effect	Monitoring Parameter	Comments
Combined hormonal Contraception		
Nausea/vomiting Breast tenderness Weight gain	Patient symptoms and Weight	Typically improves after two to three cycles; consider changing to lower estrogenic
Acne, oily skin	Visual inspection	Consider changing to lower androgenic
Depression, fatigue	Depression screening	Data are limited and conflicting
Breakthrough bleeding/spotting	Menstrual symptoms	Consider changing to higher estrogenic
Application site reaction (transdermal)	Visual inspection	
Vaginal irritation (vaginal ring)	Patient symptoms	
D epot medroxyprogesterone acetate		
Menstrual irregularities[a]	Menstrual symptoms	Typically improves after 6 months
Weight gain Acne Hirsutism Depression	Weight, Visual inspection, and Depression Screening	Data are limited and conflicting
Decreased bone density	BMD	Do not routinely screen with DXA
Levonorgestrel I U D		
Menstrual irregularities[a]	Menstrual symptoms	Typically spotting, amenorrhea Typically heavier menses with copper IUD
Insertion related complications	Cramping, pain	Prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) or local anesthetic may reduce occurrence

Expulsion	Cramping, pain, spotting, dyspareunia, missing strings	IUD strings should be checked regularly to ensure IUD properly placed
Pelvic inflammatory disease	er abdominal pain, unusual vaginal discharge, fever	Overall risk of developing is rare, but counseling on STI prevention is important
Progestin only implant		
Menstrual irregularities[a]	Menstrual symptoms	Typically well tolerated and resolve without treatment; infection is rare

Transdermal Contraceptives

- Two combination contraceptives are available as a transdermal patch. Xulane delivers 35 mcgEE and 150 mcg norgestimate daily. Twirla provides 120 mcg of levonorgestrel and 30 mcg

of EE daily. They are effective as CHCs in individuals weighing less than 90 kg (198 lb) or having a BMI less than 30 kg/m2 with failure rates between 3% and 7%.

✓ Apply patch to the abdomen, buttocks, upper torso, or upper arm at the beginning of the menstrual cycle and replace every week for 3 weeks. The fourth week is patch•free. Individuals should be counseled on the steps to follow should the patch detach or is forgotten.

✓ Approved labeling includes a warning regarding VTE risk.

Vaginal Rings

- There are two vaginal rings available. Over a 3•week period NuvaRing releases ~15 mcg/day of EE and 120 mcg/day of etonogestrel and Annovera releases 13 mcg of EE and 150 mcgof segesterone acetate. On first use, the ring should be inserted on or prior to the fifth day ofthe cycle, remain in place for 3 weeks, and then be removed. One week should lapse beforethe new ring is inserted on the same day of the week as it was for the last cycle. A secondform of contraception should be used for the first 7 days of ring use or if the ring has beenexpelled for more than 3 hours for NuvaRing or 2 hours for Annovera.
  - If the Annovera is not removed after 4 weeks, no backup contraception is needed, but 1weeskhould lapse before a new ring is inserted.
  - If the NuvaRing is left in place for 4 weeks, a pregnancy test should be taken, followed by new ring insertion with 7 days of nonhormonal contraception.

Injectable Progestins

- Individuals who particularly benefit from progestin only methods, including minipills, are those who are lactating, intolerant of estrogens, and those with concomitant medical conditions in which estrogen is not recommended.
- Injectable and implantable contraceptives are also beneficial for individuals with a history of failure rates are lower than with CHC.
- Depot medroxyprogesterone acetate (DMPA) 150 mg is administered by deep intramuscular injection in the gluteal or deltoid muscle within 5 days of onset of menstrual bleeding, and repeated every 12 weeks. Another formulation contains 104 mg of DMPA (Depo•SubQ Provera 104), which is injected subcutaneously into the thigh or abdomen. Exclude pregnancy if more than 1 week late for repeat injection of the intramuscular formulation or 2 weeks late for repeat injection of the subcutaneous formulation. Return of fertility may be delayed after discontinuation.
- DMPA can be given immediately postpartum in individuals not breastfeeding, and at 6 weeks postpartum if breastfeeding. The median time to conception from the first omitted dose is 10 months.

✓ DMPA is contraindicated with a current breast cancer diagnosis and used cautiously with a history of breast cancer, cardiovascular disease, or lupus.

✓ The most frequent adverse medication effect is menstrual irregularity, which decreases after the first year. Breast tenderness, weight gain, and depression occur less frequently.

✓ DMPA has a black box warning for reduced bone mineral density (BMD) but not increased fracture risk. BMD loss seems to be greater with increasing duration of use, and for the majority it is reversible. DMPA should not be continued beyond 2 years unless other contraceptive methods are inadequate.

Subdermal Progestin Implants

- Etonogestrel implant (Nexplanon) is a radiopaque, 4•cm implant containing 68 mg of etonogestrel that is placed under the skin of the upper arm. It releases 60 mcg daily for the first month, decreasing gradually to 30 mcg/day at the end of the 3 years of recommended use. Efficacy exceeds 99%, but it may be less in individuals who weigh more than 130% of their ideal body weight.
- Its contraceptive effects are quickly reversible upon removal.
- Need for backup contraception varies based on prior contraceptive use and where in the menstrual cycle the implant is inserted. Fertility returns
- 30 days after removal.

✓ Irregular menstrual bleeding is common followed by headache, vaginitis, weight gain, acne, and breast and abdominal pain. It does not appear to decrease BMD. Fertility returns within 30 days of removal.

✓ There is potential for interactions in the presence of potent CYP450 inducers (eg, rifampin, phenytoin, and carbamazepine).

Intrauterine Devices (IUDs)

- The contraceptive activity occurs before implantation. Endometrial suppression is caused by progestin•releasing IUDs. Efficacy rates are greater than 99% and their contraceptive effects are reversible upon removal.

- Consideration of an IUD is appropriate in nulliparous and adolescent individuals, given high efficacy and low complication rates. Need for backup contraception varies based on prior contraceptive use and when in the menstrual cycle the implant is inserted.

- The risk of pelvic inflammatory disease among users is low with no long•term effects on fertility.
- ParaGard (copper) can be left in place for 10 years. Mirena, Liletta, Skyla, and Kyleena release levonorgestrel and must be replaced after 6 years
- (Mirena, Liletta, and Kyleena) and 3 years (Skyla).

✓ Major adverse medication effects include increased menstrual blood flow and dysmenorrheawith ParaGard, while levonorgestrel IUDs are associated with reduced menstrual blood loss and possible amenorrhea.

Special Consideration for Contraceptive Use:
Over 35 Years of Age

- Use of CHCs containing less than 50•mcg estrogen may be considered in healthy nonsmokingindividuals older than 35 years.
- CHCs are not recommended for individuals older than 35 years with migraine, uncontrolledhypertension, smoking, or diabetes with vascular disease.
- Studies have not demonstrated an increased risk of cardiovascular disease with low•dose CHCsin healthy, nonobese individuals.
- Smoking 15 or more cigarettes per day by individuals over 35 years is a contraindication to theuse of CHCs, and progestin•only methods should be considered.

Smoking
Use of a CHC with less than 50•mcg EE should be used in individuals younger than 35 whosmoke to reduce the risk of myocardial infarction (MI).

Hypertension
- CHCs, regardless of estrogen dose, can cause small increases in blood pressure (6–8 mm Hg).Use of low•dose CHCs is acceptable in those younger than 35 years with well•controlled and monitored hypertension to reduce the risk of MI and stroke
- Individuals with a systolic blood pressure of 140−159 or a diastolic blood pressure of 90−99 mm Hg should avoid CHCs. Their use is contraindicated with blood pressures ≥160/100 mm Hg.
- Monitor potassium with potassium•sparing diuretics, angiotensin•converting enzyme inhibitors, angiotensin•receptor blockers, or aldosterone antagonists if also using a product containing drospirenone.

Diabetes
Nonsmoking individuals younger than 35 years with diabetes but no vascular disease can safelyuse CHCs. Individuals with diabetes for >20 years or with vascular disease should not use CHCs.

Dyslipidemia

- Generally, synthetic progestins decrease high density lipoprotein (HDL) and increase low density lipoprotein (LDL). Estrogens decrease LDL but increase HDL and may moderately increase triglycerides. Most low dose CHCs have no significant impact on HDL, LDL, triglycerides, or total cholesterol.
- The mechanism for the increased cardiovascular disease in CHC users is believed to be thromboembolic and thrombotic changes, not atherosclerosis.
- CHCs use in individuals with dyslipidemia as a single cardiovascular risk factor is generally acceptable. An alternative method of contraception is recommended in individuals with dyslipidemia and other cardiovascular risk factors.

Thromboembolism

- The risk of venous thromboembolism (VTE) in individuals using combined oral contraceptives (COCs) is three times that of nonusers, but is less than the risk of thromboembolic events during pregnancy.
- Estrogens increase hepatic production of factors involved in the coagulation cascade. Risk forthromboembolic events is increased in those with underlying hypercoagulable states or with acquired conditions (eg, obesity, pregnancy, immobility, trauma, surgery, and certain malignancies) that predispose to coagulation abnormalities.
- COCs containing the newer progestins (eg, drospirenone, desogestrel, norgestimate) carry a slightly increased risk of thrombosis compared to other progestins due to unknown mechanisms.
- The transdermal patch and vaginal ring provide continuous higher exposure to estrogen and have an increased thromboembolic risk.
- For individuals at increased risk of thromboembolism (older than 35 years, obesity, smoking, personal or family history of venous thrombosis, prolonged immobilization), consider low•dose oral estrogen contraceptives containing older progestins or progestin•only methods.

Obesity

- COCs have lower efficacy in obesity, and low•dose COCs may be especially problematic. IUDs, implants, and DMPA have very low failure rates, and progestin•only contraceptives areconsidered safe in obese individuals.
- Obese individuals have increased VTE risk, and progestin•only contraception may be better for those over 35 years.

Migraine Headache

- CHCs may decrease or increase migraine frequency.
- C HCs may be considered for healthy, nonsmoking individuals (less than 35 years old) with migraines without aura. Discuss continued use of CHC risks and benefits with individuals developing migraines without aura.
- individuals of any age who have migraine with aura should not use CHCs due to the risk of stroke. individuals who develop migraines with aura while receiving CHCs should discontinuetheir use and consider a progestin•only option

Breast Cancer

- There is a small increase in the relative risk of having breast cancer while CHCs are taken andfor up to 10 years following discontinuation.
- For individuals over the age of 40 or those with elevated breast cancer risk due to family historyor other factors, alternatives may be considered.
- The choice to use CHCs should not be influenced by the presence of benign breast disease or a family history of breast cancer. For individuals with either BRCA1 or BRCA2 mutation, CHC use is controversial, and individuals with a current or past history of breast cancer should not use CHCs.

Systemic Lupus Erythematosus (SLE)

- COCs with less than 50•mcg EE do not increase the risk of flare in those with stable SLE and without antiphospholipid/anticardiolipin antibodies.
- CHCs and progestin•only products should be avoided in individuals with SLE and antiphospholipid antibodies or vascular complications. The copper IUD may be the best.
- For those with SLE without antiphospholipid antibodies or vascular complications, progestin•only contraceptives or the copper IUD may be an alternative.
- A copper IUD and DMPA injection should be avoided in those with SLE and severe thrombocytopenia.

Postpartum

- In the first 21 days postpartum (when the risk of thrombosis is higher), estrogen containing hormonal contraceptives should be avoided due to increased VTE risk. Progestin only methodsshould be used if contraception is necessary.
- CHC should be avoided in the first 42 days postpartum in individuals with VTE risk factors and for 30 days for those without VTE risk factors who are breastfeeding.

Medication Interactions

- Tell patients to use an alternative method of contraception if a possible medication interactionmay compromise OC efficacy.
- There is a small interaction risk with antimicrobials, and additional nonhormonal contraceptives should be considered, especially when receiving an antimicrobial for more than2 months.
- Rifampin reduces the efficacy of CHCs. Additional nonhormonal contraception should be used for at least 7–28 days after rifampin therapy.
- Phenobarbital, carbamazepine, and phenytoin potentially reduce the efficacy of CHCs, and many anticonvulsants are known teratogens. IUDs, injectable medroxyprogesterone, or nonhormonal options should be used instead.
- CHCs may decrease the efficacy of lamotrigine and increase seizure risk.
- Certain antiretroviral therapies and St. John's Wort may decrease the efficacy of CHCs.
- Monitor potassium in patients taking drospirenone and concomitant medications that increasepotassium levels or those taking strong CYP3A4 inhibitors.

Return of Fertility After Discontinuation

- There is no evidence that hormonal contraception use decreases subsequent fertility and there is no greater chance of miscarriage or a birth defect in the first month after discontinuation Emergency Contraception (EC).
- EC is used to prevent unintended pregnancy after unprotected or inadequately protected sexual intercourse.
- FDA approved progestin only and progesterone receptor modulator products are recommended as first line EC options. They will not disrupt the fertilized egg if implantation has already occurred.
- Progestin only EC formulations containing one 1.5•mg tablet of levonorgestrel are availablewithout a prescription in the United States. They may be less effective in individuals weighinggreater than 75 kg.
- Ulipristal (Ella) is a prescription selective progesterone receptor modulator. It is taken as a single dose of 30 mg within 120 hours (5 days) of unprotected intercourse. It is considered noninferior to levonorgestrel containing ECs and is not recommended in breastfeeding individuals.
- Common adverse medication effects of EC include nausea, vomiting, and irregular bleeding.
- Insertion of a copper IUD or prescribing higher doses of CHCs (Yuzpe method) are other ECoptions.
- EC should be given within 72 hours (3 days) of unprotected intercourse, but the sooner it is taken, the greater the efficacy. There is some evidence that it may be effective for up to 5 days after unprotected intercourse, but in this situation ulipristal or a copper IUD may be a better option.
- Backup nonhormonal contraceptive methods should be used after EC for at least 7 days.

Pregnancy Termination

- Medications used in early pregnancy (≤70 days) termination include mifepristone and misoprostol. Misoprostol can be used alone or more effectively in combination with mifepristone.
- The FDA has approved mifepristone 200 mg orally on day 1 and then misoprostol 800 mcg buccally 24–48 hours after the mifepristone dose. This regimen has a 98% efficacy in pregnancies up to 49 days.
- Mifepristone binds progesterone receptors to block progesterone, resulting in cervical softening and an increase in prostaglandin sensitivity, leading to contraction stimulation. Mifepristone is usually administered orally, and prescribing is limited to trained prescribers who also dispense the medication. It is contraindicated in patients with bleeding disorders or those on anticoagulants. It is a major substrate for CYP3A4, so medication interactionsneed to be considered.
- Misoprostol is a prostaglandin 1 analog that has good absorption when given vagibnuaclIcya,lly, or sublingually resulting in cervical ripening and contractions. Oral administration is not recommended.

✓ Adverse medication effects of misoprostol include stomach upset, diarrhea, headache, dizziness, and fever. Mifepristone has a boxed warning regarding infection and excessive bleeding may occur and could be a sign of incomplete termination or other complications and needs prompt medical attention.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor blood pressure annually in all CHCusers.
- Monitor glucose levels closely when CHCs are started or stopped in individuals with a histofyglucose intolerance or diabetes mellitus.
- Contraceptive users should have an annual exam that may include cytologic screening, andpelvic and breast examination. Regularly evaluate for problems that may relate to the CHCs (eg, breakthrough bleeding, amenorrhea, weight gain, and acne). These screenings do nothae to occur before prescribing hormonal contraceptives.
- Monitor Nexplanon users annually for menstrual cycle disturbances, weight gain, local inflammation or infection at the implant site, acne, breast tenderness, headaches, and hair loss
- Evaluate individuals using DMPA every 3 months for weight gain, menstrualcycle disturbances and fractures.
- Monitor IUD users at 1• to 3•month intervals for proper IUD positioning, changesin menstrual bleeding patterns, and upper genital tract infection.
- Clinicians should monitor and when indicated screen for HIV and STIs. Counsel about healthy sexual practices, including the use of condoms to prevent transmission of STIs when necessary.

Hormone Replacement Therapy

INTRODUCTION

Perimenopause begins with the onset of menstrual irregularity and ends 12 months after the last menstrual period, which marks the beginning of menopause. **Menopause is the permanent cessation of menses caused by the loss of ovarian follicular activity. Females spend about 40% of their lives in postmenopause.**

PATHOPHYSIOLOGY

- The hypothalamic–pituitary–ovarian axis controls reproductive physiology. Follicle stimulating hormone (FSH) and luteinizing hormone (LH), produced by the pituitary in response to gonadotropin releasing hormone from the hypothalamus, regulate ovarian function.
- Gonadotropins are also influenced by negative feedback from the sex steroids estradiol (produced by the dominant follicle) and progesterone (produced by the corpus luteum). Other sex steroids are androgens, primarily testosterone and androstenedione, secreted by the ovarian stroma.
- As females age, circulating FSH progressively rises, and ovarian (inhibin-B) and anti-Mullerian hormone decline. In menopause, there is a 10-to-15-fold increase in circulating FSH, a 4-to-5-fold increase in LH, and a greater than 90% decrease in circulating estradiol concentrations.

CLINICAL PRESENTATION

- Vasomotor symptoms (hot flushes and night sweats), sleep disturbances, depression, anxiety, poor concentration and memory, vaginal dryness and dyspareunia, headache, sexual dysfunction, and arthralgia. Individuals of different races/ethnicity experience vasomotor symptoms differently.
- Signs include urogenital atrophy in menopause and dysfunctional uterine bleeding in perimenopause. Additionally, loss of estrogen production results in metabolic changes; increase in central abdominal fat; and effects on lipids, vascular function, and bone metabolism.

DIAGNOSIS

- Menopause is determined retrospectively after 12 consecutive months of amenorrhea. FSH on day 2 or 3 of the menstrual cycle greater than 10–12 IU/L indicates diminished ovarian reserve.
- The diagnosis should include a comprehensive medical history and physical examination, complete blood count, and measurement of serum FSH. Altered thyroid function and pregnancy must be excluded.

TREATMENT

The goals are to relieve symptoms, improve quality of life, and minimize medication adverse effects.

NONPHARMACOLOGIC THERAPY

- Mild vasomotor and/or vaginal symptoms can often be alleviated by lowering the room temperature; decreasing intake of caffeine, spicy foods, and hot beverages; smoking cessation; exercise; and a healthy diet.
- Mild vulvovaginal symptoms may be adequately managed with nonhormonal lubricants and moisturizers.

PHARMACOLOGIC THERAPY

- FDA approved indications and contraindications for **menopausal hormone therapy** (MHT) are shown in Table 1.
- The decision to use MHT and the type of formulation used must be individualized based on several factors, including personal preference, age, menopause onset, the severity of menopausal symptoms, and MHT associated risks.
- MHT remains the most effective treatment for moderate and severe vasomotor symptoms, impaired sleep quality, and vulvovaginal symptoms of menopause.
- When urogenital symptoms, such as vaginal dryness and dyspareunia, are the only menopausal complaint, intravaginal estrogen cream, tablet, or ring should be considered before oral therapy.
- Intravaginal estrogen minimizes systemic absorption and is more effective for vaginal symptoms than oral therapy. Intravaginal estrogen reduces the risk of recurrent urinary tract infections and may improve urge incontinence and overactive bladder.
- Ospemifene, a selective estrogen receptor modulator, is another option.
- MHT is the most effective treatment for moderate to severe vasomotor symptoms, and impaired sleep quality. Estrogen only therapy may decrease heart disease and all-cause mortality in 50- to 59-year-old females with a history of hysterectomy.
- MHT is effective and appropriate for prevention of osteoporosis related fractures in recently menopausal individuals at risk.
- In patients with an intact uterus, MHT consists of an estrogen plus a progestogen or estrogen agonist/antagonist (e.g. bazedoxifene).
- In patients who have undergone hysterectomy, estrogen therapy is given unopposed by a progestogen. Concomitant progestogen therapy is unnecessary when low dose vaginal estrogen is used.
- Individuals with vasomotor symptoms taking MHT have better mental health and fewer depressive symptoms compared with those receiving placebo, but MHT may worsen the quality of life in individuals without vasomotor symptoms.

Table 1: FDA Approved Indications and Contraindications for Menopausal Hormone Therapy with Estrogens and Progestins

Indications	
For systemic use	Treatment of moderate to severe vasomotor symptoms (ie, moderate to severe hot flashes)
For intravaginal use (low systemic exposure)	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (ie, moderate to severe vaginal dryness, dyspareunia, and atrophic vaginitis)
Contraindications	
Absolute contraindications	▪ Undiagnosed abnormal genital bleeding ▪ Known, suspected, or history of cancer of the breast ▪ Known or suspected estrogen or progesterone dependent neoplasia ▪ Active deep vein thrombosis, pulmonary embolism, or a history of these conditions ▪ Active or recent (eg, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction)

	▪ Liver dysfunction or disease
Relative contraindications	▪ Elevated blood pressure ▪ Hypertriglyceridemia ▪ Impaired liver function and past history of cholestatic jaundice ▪ Hypothyroidism ▪ Fluid retention ▪ Severe hypocalcemia ▪ Ovarian cancer ▪ Exacerbation of endometriosis ▪ Exacerbation of asthma, diabetes mellitus, migraine, systemic lupus erythematosus, epilepsy, porphyria, and ▪ hepatic hemangioma

Estrogens

- The oral and transdermal routes are used most frequently and are considered equally effective.
- Conjugated equine estrogens are composed of estrone sulfate (50%–60%) and other estrogens such as equilin and 17α-dihydroequilin.
- Estradiol is the predominant and most active form of endogenous estrogens. Given orally, it is metabolized by the intestinal mucosa and liver, and resultant estrone concentrations are three to six times those of estradiol.
- Ethinyl estradiol is a semisynthetic estrogen that has similar activity following oral or parenteral administration.
- Nonoral estrogens, including transdermal, intranasal, and vaginal products, to avoid first pass metabolism and result in a more physiologic estradiol : estrone ratio. Transdermal estrogen is also less likely to increase sex hormone–binding globulin, triglycerides, blood pressure, or C-reactive protein levels. Transdermal dosage forms may also have a lower risk for deep vein thrombosis, stroke, and myocardial infarction.
- Variability in absorption is common with percutaneous preparations (ie, gels, creams, and emulsions).
- Vaginal creams, tablets, and rings are used for treatment of urogenital atrophy. Most tablets and rings provide local estrogen, but Femring is designed to achieve systemic estrogen concentrations and is indicated for moderate to severe vasomotor symptoms.
- New evidence indicates that lower doses of estrogens are effective in controlling postmenopausal symptoms and reducing bone loss. Topical gels, creams, and sprays are also available in low doses. The lowest effective dose should be used.

✓ Adverse effects of estrogen include nausea, headache, breast tenderness, and heavy bleeding. More serious adverse effects include increased risk for stroke, venous thromboembolism (VTE), and gallbladder disease. Transdermal estrogen is less likely to cause breast tenderness, gallbladder disease, and deep vein thrombosis.

✓ Risk of VTE and stroke increases with oral MHT containing estrogen, but the absolute risk is low below 60 years of age. Transdermal MHT and low dose oral estrogen therapy appear to have a lower risk of VTE and stroke compared to standard dose oral estrogen regimens.

✓ MHT is contraindicated in individuals with a personal history of breast cancer. The risk of MHT related

breast cancer appears to be associated with the addition of progestogen to estrogen after 3 years of combined use.

✓ Combined oral MHT does not increase endometrial cancer risk compared with placebo, but estrogen alone given to individuals with an intact uterus significantly increases uterine cancer risk.

✓ Postmenopausal individuals 65 years or older taking estrogen plus progestogen therapy had twice the rate of dementia, including Alzheimer disease, than those taking placebo. Combined therapy did not prevent mild cognitive impairment. The estrogen alone arm showed similar findings.

Progestogens

In individuals who have not undergone hysterectomy, a progestogen or tissue selective estrogen complex (estrogen/bazedoxifene) should be added for endometrial protection. Medroxyprogesterone acetate, Micronized progesterone and Norethindrone acetate are progestogens approved for menopausal symptom treatment.

✓ Adverse effects of progestogens include irritability, headache, mood swings, fluid retention, and sleep disturbance.

Methods of administration include the following:

- Cyclic (Sequential) estrogen progestogen results in scheduled vaginal withdrawal bleeding in approximately 80%–90% of patients. The progestogen is administered 12–14 days of the 28day cycle.
- Continuous combined estrogen progestogen causes endometrial atrophy but prevents monthly bleeding, which is preferable, although it may initially cause unpredictable spotting or bleeding. Use of conjugated estrogens (0.625 mg/day) plus medroxyprogesterone acetate (2.5 mg/day) lead to a decreased risk of endometrial cancer.
- Intermittent combined estrogen progestogen (continuous pulsed) consists of 3 days of estrogen therapy alone, followed by 3 days of combined estrogen and progestogen, repeated without interruption. It causes fewer adverse effects than regimens with higher progestogen doses and lowers the incidence of uterine bleeding.

Compounded Bioidentical Hormone Therapy (CBHT)

- CBHTs are hormone therapy formulations custom prepared (ie, compounded) for individual patients, often involving the use of measuring and monitoring hormone levels in blood and/or other body fluids such as saliva.
- Hormones commonly used in CBHT include estrone, estradiol, estriol, progesterone, testosterone, DHEA, and thyroid hormone. Bioidentical hormones appear to carry the same risks as traditional hormone therapy products. Use is only recommended only when there is a medical need for an unusual dosing regimen or ingredients or when patients have allergies to FDA approved therapies.

Estrogen Alternatives for the Treatment of Hot Flashes

- Some clinicians consider selective serotonin reuptake inhibitors (eg, paroxetine, fluoxetine, citalopram, escitalopram) or serotonin norepinephrine reuptake inhibitors (eg, venlafaxine and desvenlafaxine) to be first line agents.

- Clonidine can be effective, but adverse effects are often problematic (eg, sedation, dry mouth, hypotension). Gabapentin has beneficial effects for reducing the frequency and severity of vasomotor symptoms but adverse effects may limit dosing. It may be a reasonable option for those with disrupted sleep and hot flashes when administered in the evening.

Androgens

- Testosterone use is controversial, but use with or without estrogen, may improve the quality of the sexual experience in postmenopausal individuals.
- Absolute contraindications to androgen therapy include pregnancy or lactation and known or suspected androgen dependent neoplasia.
- Adverse effects include virilization, fluid retention, and adverse lipoprotein lipid effects, which are more likely with oral administration. Evidence on the efficacy and safety of testosterone in females is lacking.
- Dehydroepiandrosterone (DHEA) is a precursor hormone in the synthesis of estrone, estradiol, and testosterone. Intravaginal DHEA (Prasterone) has FDA approval for the treatment of moderate to severe dyspareunia.

Selective Estrogen Receptor Modulators (SERMs)

- SERMs are nonsteroidal compounds that act as estrogen agonists in some tissues such as bone and as estrogen antagonists in other tissues such as breast through high affinity binding to the estrogen receptor.
- Tamoxifen is an antagonist in breast tissue and an agonist on the bone and endometrium.
- Raloxifene is approved for prevention and treatment of postmenopausal osteoporosis and reduction in risk of invasive breast cancer.
- The third generation SERM, bazedoxifene, is used in conjunction with conjugated estrogen, and is FDA approved for moderate to severe vasomotor symptoms and prevention of osteoporosis.
- Ospemifene is approved for dyspareunia from menopausal vulvar and vaginal atrophy. It has a boxed warning for increased risk of endometrial cancer in patients with a uterus who use ospemifene without a progestogen to reduce endometrial hyperplasia.

✓ Depending on tissue selectively, the SERMs are associated with hot flashes and leg cramps. They can also increase the risk of VTE and stroke similar to oral estrogen, but the degree of risk is agent specific. Additional adverse effects of bazedoxifene include muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain.

Complementary and Alternative Agents

- Phytoestrogens are plant compounds with estrogen like biologic activity and relatively weak estrogen receptor binding properties, resulting in physiologic effects in humans.
- Although clarity regarding, dosing, biological activity, safety, and efficacy is needed before they can be considered as an alternative to MHT.
- Other herbals and alternative treatments that may be used include black cohosh, dong quai, red clover leaf (contains phytoestrogens), and ginseng.

EVALUATION OF THERAPEUTIC OUTCOMES

- In order to adequately assess treatment effect, individuals should be encouraged to continue their MHT regimen for at least 1 month with dosages being modified to balance adverse effects and efficacy. Those receiving MHT should be seen annually for monitoring.

Menstruation Related Disorders

Introduction

Menstrual cycle disorders are common amongst women of reproductive age. The most common include dysmenorrhea, amenorrhea, anovulatory bleeding, and heavy menstrual bleeding. Menstruation-related disorders can negatively affect quality of life (QOL), reproductive health, and productivity and may also lead to long-term health consequences. As menstruation begins to cease, the perimenopause and menopause phases begin. During this time, irregular menses, vaginaldryness, dyspareunia, hot flashes, and mood swings may occur.

Dysmenorrhea

Dysmenorrhea is pelvic pain, generally described as painful cramping, occurring during orjust prior to menstruation. Primary dysmenorrhea occurs with normal pelvic anatomy and physiology, whereas secondary dysmenorrhea is associated with underlying pelvic pathology.

Epidemiology and Etiology

Dysmenorrhea is the most commonly reported menstrual complaint, with over 50% of menstruating women reporting pain for at least 1 or 2 days each month. Of adolescents with dysmenorrhea, up to 12% report missing work or school each month due to pain. Risk factors include irregular or heavy menses, age less than 30, menarche prior to age 12, body mass index less than 20 kg/m2, history of sterilization or sexual abuse, and smoking. Causes of secondary dysmenorrhea may include endometriosis, pelvic inflammatory disease (PID), uterine or cervical polyps, and uterine fibroids.

Pathophysiology

In primary dysmenorrhea, elevated arachidonic acid levels in the menstrual fluid lead to increased concentrations of prostaglandins and leukotrienes in the uterus. This induces uterine contractions, stimulates pain fibers, reduces uterine blood flow, and causes uterine hypoxia.

Treatment

▶ **Desired Outcomes:** Desired treatment outcomes (Figure 50–1) are reduction of pelvic pain, improved QOL, and fewer missed days from school and work.

▶ **Nonpharmacologic Therapy:** Dysmenorrhea intensity has shown to be decreased by exercise, applying topical heat therapy, acupuncture, and consuming a low-fat vegetarian diet.

▶ **Pharmacologic Therapy:**

1. **Nonsteroidal Anti-inflammatory Drugs:** Nonsteroidal anti-inflammatory drugs (NSAIDs)are first-line therapy for dysmenorrhea and are effective in up to 80% of patients. NSAIDs inhibit prostaglandin production, exert analgesic properties, decrease uterine contractions, andreduce menstrual blood flow. Choice of agent is based on effectiveness, tolerability, and patientpreference, with the most commonly utilized agents being naproxen and ibuprofen. Of note, aspirin is not recommended as it is not potent enough in usual dosages. NSAID treatment should begin 1 to 2 days prior to menses, or at dysmenorrhea onset, and continued for 2 to 3 days or until pain resolves. A loading dose (twice the usual single dose) is recommended, followed by the usual recommended dose. For patients with limited response or with contraindications to NSAID therapy, combination hormonal contraceptives (CHCs) should beconsidered.
2. **Combination Hormonal Contraceptives**: CHCs improve dysmenorrhea by decreasing

endometrial lining and inhibiting ovulation, which decreases the formation of prostaglandins and leukotrienes contributing to menstrual pain. Precisely, 2 to 3 months of therapy are often required to achieve full effects, and can take up to 6 months.4 Both cyclic(28-day) and extended cycle (91-day) therapies have been used effectively. Continuous CHC may provide more rapid pain relief when compared to cyclic therapy; however, both effects are similar when evaluated at 6 months. For dysmenorrhea secondary to endometriosis, CHCs, specifically extended cycle regimens, are considered first-line. If no response with any agent occurs after 3 to 6 months, the patient should be reevaluated.

3. **Progestin-Only Hormonal Contraceptives**: Long-acting progestins are often utilized for dysmenorrhea treatment and work by reducing or eliminating menses over 6 to 12 months of use, thus eliminating prostaglandin release. Three long-acting reversible contraceptive agents are available: depot medroxyprogesterone acetate (MPA), etonogestrel implant, and levonorgestrel-releasing intrauterine device (IUD). Observational data showed that women with active dysmenorrhea symptoms who used a levonorgestrel-releasing IUD saw a reduction in their symptoms from 60% to 29% after 3 years of therapy.

Dysmenorrhea in Adolescents:

Dysmenorrhea is the most common gynecologic complaint amongst female adolescents, reported in 60% to 90%, and the most common reason for missed school or work. NSAIDs are the preferred initial treatment in adolescents, followed by hormonal treatment. Adolescents with symptoms unresponsive to NSAID therapy for three menstrual periods should be offered CHC, which can also provide effective contraception if desired. If symptoms do not improve within 3 to 6 months of NSAIDs and CHC, it is important to assess for medication adherence. If adherence is confirmed and patient still not experiencing symptom relief, further evaluation through laparoscopy is indicated. Since adolescence is a critical period for bone mineral density (BMD) accrual, and prolonged use of depot MPA may lead to significant loss of BMD that may not be completely reversible, other agents are considered first line.

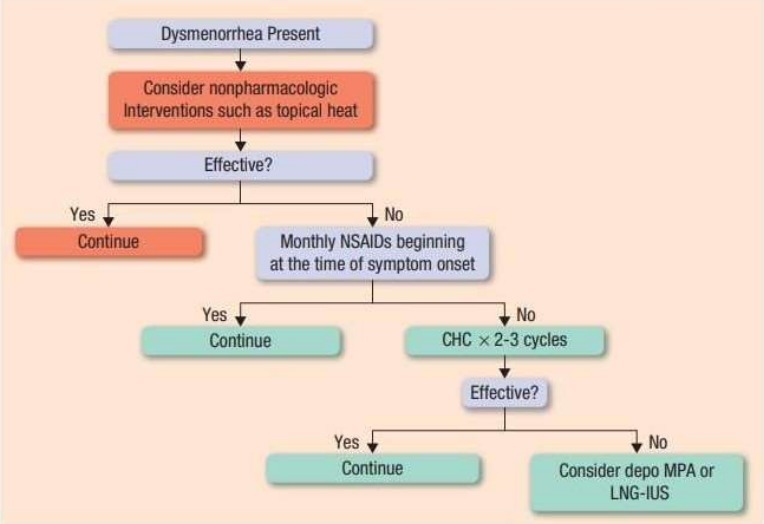


FIGURE 50–1. Treatment algorithm for dysmenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; MPA, medroxyprogesterone acetate; NSAID, nonsteroidal anti-inflammatory drug.) Reproduced with permission from DiPiro JT, Yee GC, Posey

Amenorrhea

Amenorrhea is the absence of menses over a 90-day period and can be primary or secondary. Primary amenorrhea is the failure to reach menarche by age 15, in women who have never menstruated. Secondary amenorrhea is the cessation of menses for 3 months in a previously regular menstruating woman or 6 months in a previously irregular menstruating woman.

Epidemiology and Etiology:

Unrecognized pregnancy can be a common cause of amenorrhea; therefore, a urine pregnancy test should be one of the first steps in evaluating amenorrhea. There are three main causes of amenorrhea: anatomical causes including pregnancy and uterine structural abnormalities, endocrine or hormone imbalances leading to chronic amenorrhea, and ovarian insufficiency or failure. Primary amenorrhea is often caused by chromosomal irregularities resulting in primary ovarian insufficiency or anatomic abnormalities. Causes of secondary amenorrhea include polycystic ovary syndrome (PCOS), hypothalamic suppression, thyroid disorders, hyperprolactinemia, or primary ovarian insufficiency. Additional causes include undernutrition, anorexia, and excessive exercise.

Pathophysiology

Normal menstrual cycle physiology depends on hormonal interactions involving the hypothalamus, anterior pituitary gland, ovary, and endometrium. Amenorrhea is a potential side effect from using low-dose or extended oral CHCs, MPA, or levonorgestrel-releasing IUD. Many women experience delayed return of menses after discontinuing hormonal contraception. If resolution of amenorrhea does not occur within 3 to 6 months after discontinuing contraception, evaluation for other conditions should be considered (eg, PCOS).

Treatment

▶ Desired Outcomes:

Treatment goals include ensuring normal puberty is occurring, restoring the normal menstrual cycle, preserving bone density, preventing bone loss, improving QOL, reduction of associated symptoms, and restoring ovulation, thus improving fertility.

▶ Nonpharmacologic Therapy

Nonpharmacologic therapy depends on the underlying cause. Amenorrhea secondary to undernutrition or anorexia may respond to weight gain and psychotherapy.11 If excessive exercise is the cause, exercise reduction is recommended.11 Women with functional hypothalamic amenorrhea should undergo a reasonable trial of psychological (such as cognitive behavior therapy), nutritional, and/or exercise intervention prior to starting pharmacologic therapy

▶ Pharmacologic Therapy

1. **Estrogen/Progestin Replacement Therapy:** For most conditions associated with primary or secondary amenorrhea, estrogen supplementation with either an oral contraceptive, conjugated equine estrogen (CEE), or estradiol patch has historically been recommended. However, CHCand synthetic estrogen are no longer recommended as first-line agents for patients with functional hypothalamic amenorrhea. The 2017 Endocrine Society Clinical Practice Guidelinefor functional hypothalamic amenorrhea recommends patients trial nonpharmacological therapy first (with psychological and nutritional interventions), and then start a short-term transdermal estrogen with cyclic oral progestins.
2. **Dopamine Agonists:** When hyperprolactinemia is the cause of amenorrhea, dopamine agonists are preferred. Dopamine agonists restore normal prolactin levels, resolve amenorrhea,and restore ovulation in 80% to 90% of women. Bromocriptine and cabergoline are the most commonly studied agents, with cabergoline being more effective in resolving amenorrhea.
3. **Progestins:** Progestins induce withdrawal bleeding in women with secondary amenorrhea.

Withdrawal bleeding occurs with intramuscularly injected progesterone and oral MPA in 70%and 95% of patients, respectively. The usual dose of oral MPA is 10 mg orally once daily for 7 to 10 days.

4. **Insulin-Sensitizing Agents**: PCOS-induced amenorrhea may respond well to insulin sensitizing agents. Using metformin for this purpose is discussed in the anovulatory bleeding section. All patients experiencing amenorrhea should follow a diet rich in calcium and vitaminD to support bone health. Supplemental calcium and vitamin D (1200 mg/800 IU/day) should be recommended for patients with inadequate dietary consumption.11 Figure 50–3 illustrates treatment recommendations for amenorrhea.

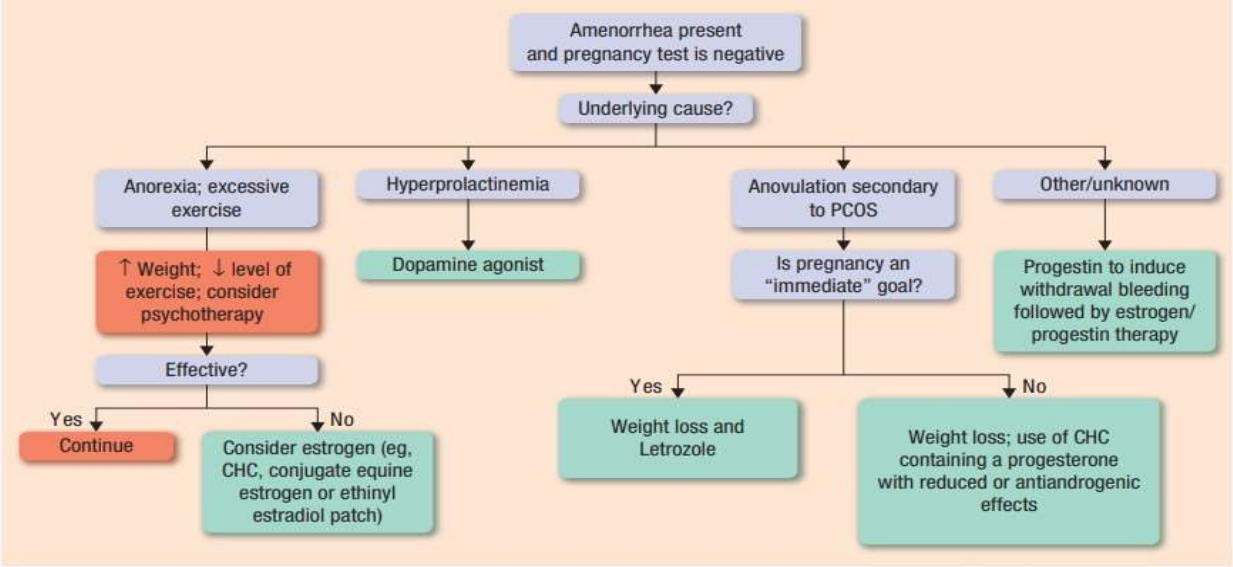


FIGURE 50–3. Treatment algorithm for amenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; PCOS, polycystic ovary syndrome.) Reproduced with permission from DiPiro JT, Yee GC, Posey IM, et al., eds. Pharmacotherapy: A Pathophysiologic Approach. 11th ed. New York City: McGraw-Hill; 2020.

Amenorrhea in Adolescents

Optimal treatment of adolescents diagnosed with amenorrhea, especially primary ovarian insufficiency, includes careful consideration to both the physical and emotional needs of a young patient receiving this diagnosis. It may be difficult to process the emotions to understand the immediate and long-term impacts of amenorrhea diagnosis on long-term fertility. Patients may need higher doses of estrogen than menopausal women in order to ensure adequate replacement and optimal bone health. For patients with absent or incomplete breast development, estrogen therapy should be started and increased slowly before adding progesterone in order to allow for breast development and prevent tubular breast development. Once puberty is complete, the goal becomes maintaining normal ovarian functioning levels of estradiol. Estradiol 100 mcg daily is recommended, either by transdermal, oral, or occasionally transvaginal administration may be considered. Cyclic progesterone should be added for 10 to 12 days each month to help protect against endometrial hyperplasia and endometrial cancer. Oral contraceptives often contain higher doses of estrogen than what is needed and are no longer recommended as first-line therapy.

Anovulatory bleeding

Anovulatory uterine bleeding is irregular menstrual bleeding from the endometrium ranging from light spotting to heavy blood flow.18 It includes menstrual bleeding that occurs outside of the normal cyclic bleeding. This bleeding occurs due to the effects of unopposed estrogen. Of

note, it does not include bleeding due to uterine anatomic lesions.18 Many women pursue medical care to regulate menstrual cycles or improve fertility.

Epidemiology and Etiology

Anovulatory uterine bleeding is the most common form of noncyclic uterine bleeding. PCOS is the most common cause, occurring in 8% to 13% of women. Anovulation results from dysfunction at any level of the hypothalamic–pituitary–ovarian axis which can be due to physiologic life stages such as adolescence, perimenopause, pregnancy, and lactation or pathologic causes. Anovulation may also occur at any time during the reproductive years due to a pathologic cause. The most common causes of nonphysiologic ovulatory dysfunction are PCOS, hypothalamic amenorrhea, hyperprolactinemia, and premature ovarian failure

Pathophysiology

In anovulation, a corpus luteum does not develop, and the ovary fails to secrete progesterone. This causes the endometrium to continue proliferation under the influence of unopposed estrogen, and eventually it becomes thick, vascular, and fragile. The clinical result is unpredictable, heavy, noncyclic bleeding, as sporadic sloughing of the endometrium begins to occur.

Treatment

▶ Desired Outcomes

The desired outcomes are to stop acute bleeding, restore natural cycle of endometrial growth and shedding, decrease long-term complications of anovulation (eg, osteopenia and infertility), and improve QOL.

▶ Nonpharmacologic Therapy

Nonpharmacologic treatment options depend on the underlying cause. For women with PCOS, weight loss of 5% to 10% may help improve menstrual regularity, decrease hirsutism, improve insulin sensitivity, and increase response to fertility treatments. In women who have completed childbearing or who have failed medical management, endometrial ablation or resection, and hysterectomy are considered surgical options.

▶ Pharmacologic Therapy

1. **Estrogen**: Estrogen is the recommended treatment for managing acute bleeding episodes because it promotes endometrial growth and stabilization. CHCs are useful for cycle regulation, helping to provide a more predictable menstrual cycle. For women with PCOS, CHCs also suppress ovarian hormones and adrenal androgen production, and oral agents also indirectly increase sex hormone-binding globulin. This, in turn, binds and reduces circulating androgen. Women with high androgen levels or signs of hyperandrogenism (eg, hirsutism, acne) are recommended to start low-dose CHCs (35 mcg or less ethinyl estradiol) and a progesterone with minimal androgenic side effects (eg, norgestimate and desogestrel) or antiandrogenic effects (eg, drospirenone).
2. **Progestins:** Women who experience side effects or have contraindication(s) to estrogen, or who have abnormal uterine bleeding due to anovulatory bleeding, should consider progesterone-only products. For women with PCOS, depot and intermittent oral MPA suppress pituitary gonadotropins and circulating androgens, leading to endometrial shedding. If contraception is desired, placement of a levonorgestrel-releasing IUD is an option.
3. **Estrogen Modulators:** Women with anovulatory bleeding from PCOS who are pursuing pregnancy should be seen by a fertility specialist. Women may be treated with letrozole or clomiphene citrate for ovulation induction under specialist care.

4. **Insulin-Sensitizing Agents:** Metformin improves insulin sensitivity, reduces circulating androgen concentrations, and improves ovulation rates and should be considered for women with PCOS for management of metabolic features. Notably, metformin may increase spontaneous ovulation, and contraception should be used in women with PCOS who do not desire pregnancy.

Anovulatory Bleeding in Adolescents

Anovulation is the most common cause of non-cyclic uterine bleeding in adolescents. Anovulatory bleeding in teenagers can become excessive, persistent, and require medications to treat. The differential diagnosis is similar to adults and should include evaluation for blood dyscrasias. Patients should also be evaluated for PCOS by assessing for signs of hyperandrogenism, including acne and hirsutism.

Cancer chemotherapy & treatment

Cancer (neoplasm, tumor, or malignancy) is a group of diseases (more than 100 disease characterized by uncontrolled cellular growth, tissue infiltration, and spread of abnormal cells (can't carry out normal physiological functions).

Cancer Prevention

- Most cancers are not curable in advanced stages.
- Both lifestyle modifications and chemoprevention agents may significantly reduce the risk of developing cancer.
- The Food and Drug Administration (FDA) has approved vaccines that can help prevent cancer. Available vaccines include those that prevent infection with human papillomavirus (HPV), responsible for cancers of the cervix, vulva, vagina, and anus and a vaccine that prevents hepatitis B viral infections,which can cause liver cancer.
- Additionally, medications, such as the selective estrogen receptor modulator (SERM) tamoxifen reduces the risk of breast cancer in premenopausal women,while raloxifene and the aromatase inhibitor (AI) exemestane reduce breast cancer in high-risk postmenopausal women. Because of possible long-term complications (eg, an increased risk of endometrial cancer with the use of tamoxifen) benefits versus risks needs to be weighed when making a recommendation.
- Smoking cessation is associated with a gradual decrease in the risk of cancer (e.g., lung, pharynx, mouth and esophageous), but more than 5 years is needed before a major decline in risk is detected.
- Proper sun protection, including minimizing sun exposure, using sunscreens with a sun protection factor (SPF≥15) on exposed areas, wearing protective clothing and sunglasses, avoiding tanning beds and sun lamps, can help in preventing the risk of skin cancer.

CARCINOGENESIS

- Carcinogenesis is the process by which normal cells are transformed into cancer cells.
- The exact cause of cancer remains unknown and is probably very diverse. It is thought that cancer develops from a single cell in which the normal mechanisms for control of growth and proliferation are altered.
- Evidence indicates that there are 4 stages in the cancer development process.

1. The first step, initiation, occurs when a carcinogenic substance encounters a normal cell to produce genetic damage and results in a mutated cell.
2. The environment is altered by carcinogens or other factors to favor the growth of the mutated cell over the normal cell during promotion. (reversible process)
3. Third, transformation (or conversion) occurs when the mutated cell becomes malignant
4. Finally, progression occurs when cell proliferation takes over and the tumor spreads or develops metastases

- There are two major classes of genes involved in carcinogenesis, oncogenes and mutation of tumor suppressor genes (eg. *p53* gene).

A. Protooncogens are normal genes present in cells that converted by carcinogenic substances (eg. Smoking or radiation) into oncogene.
B. Tumor suppressor genes are normal genes which have protective effects against oncogenes. They inhibit inappropriate cellular growth and proliferation.

Carcinogenic substances

1. Chemicals, such as aniline and benzene, are associated with the development of bladder cancer and leukemia, respectively.
2. Environmental factors, such as excessive sun exposure, can result in skin cancer, and smoking is widely known as a cause of lung cancer.
3. Viruses, including HPV, Epstein-Barr virus, and hepatitis B virus, have been linked to cervical cancers, lymphomas, and liver cancers, respectively.
4. Anticancer agents such as the alkylating agents (eg, melphalan), anthracyclines (eg, doxorubicin), and epipodophyllotoxins (eg, etoposide) can cause secondary malignancies (eg, leukemias) years after therapy has been completed.
   Note: The patient's age, gender, family history, diet, and chronic irritation or inflammation may be considered to be promoters of carcinogenesis.

Metastases

- A metastasis is a growth of the same cancer cell found at some distance from the primary tumor site. The presence of metastasis at diagnosis usually is associated with a poorer prognosis than the patient with no known metastatic disease. Usually, once distant metastases have occurred, the cancer is considered incurable.
- Cancers spread usually by two pathways: hematogenous (through the bloodstream) or through the lymphatics (drainage through adjacent lymph nodes).
- The usual metastatic sites for solid tumors are the brain, bone, lung, and liver.

PATHOPHYSIOLOGY

Tumor Origin

- Tumors may arise from the 4 basic tissue types: epithelial (carcinoma), connective (ie, muscle, bone, & cartilage) (called sarcoma), lymphoid, ornerve tissue.
- Adenocarcinomas arise from glandular tissue (eg. Lung, breast, colon, …) .
- Malignancies of the bone marrow or lymphoid tissue, such as leukemias orlymphomas, are named differently.
- The suffix -*oma* is added to the name of the cell type if the tumor cells arebenign (eg. Lipoma).
- Precancerous cells have cellular changes that are abnormal but not yetmalignant and may be described as *hyperplastic* or *dysplastic*.

Tumor Characteristics

- Tumors are either benign or malignant.
- Benign tumors often are encapsulated, localized, and indolent; they seldom metastasize; and they rarely recur once removed.
- Malignant tumors are invasive and spread to other locations even if the primary tumor is removed. The cells no longer perform their usual functions, and their cellular architecture changes (anaplasia).

TREATMENT

Desired Outcome

- Chemotherapy may be given to cure cancers, or it may be given to help control the symptoms of an incurable cancer (also known as palliation).
- Palliative care consists of pharmacologic and nonpharmacologic treatments and is most effective when initiated at the time of other treatments, improving quality of life.

Treatment of cancer

- The three primary treatment modalities of cancer are surgery, radiation, and pharmacologic therapy.

Non pharmacological therapy of cancer

- Surgery is useful to gain tissue for diagnosis of cancer and for treatment, especially those cancers with limited disease. However, when cancer is widespread, surgery may play little or no role, but radiation therapy localized to specific areas may palliate symptoms.
- Radiation plays a key role not only in the treatment and possible cure of cancer but also in palliative therapy.
- Together, surgery and radiation therapy may provide local control of symptoms of the disease.

Pharmacological therapy of cancer

- **Adjuvant therapy:** Systemic therapies that administered after surgery (surgery can remove all macroscopic but not all microscopic disease) to destroy microscopic malignant cells. The goals of adjuvant chemotherapy are to decrease the recurrence by eliminating microscopic malignant cells of the cancer and to prolong survival.
- **Neoadjuvant chemotherapy:** Chemotherapy that is given before surgical resection of the tumor to decrease the tumor burden to be removed and make the surgery easier to perform because the tumor has shrunk away from vital organs or vessels.

Dosing of Chemotherapy

- Chemotherapeutic agents typically have a very narrow therapeutic index.
- The doses of chemotherapy must be given at a frequency that allows the patient to recover from the toxicity of the chemotherapy; each period of chemotherapy dosing is referred to as a cycle.
- Each cycle of chemotherapy may have the same dosages; the dosages may be modified based on toxicity; or a chemotherapy regimen may alternate from one set of drugs given during the first, third, and fifth cycles to another set of different drugs given during the second, fourth, and sixth cycles.
- The dose density of chemotherapy refers to shortening of the period between cycles of chemotherapy. Administration of dose-dense chemotherapy regimens often used when goal of therapy is cure and it requires the use of colony-stimulating factors (eg, filgrastim or granulocyte–colony stimulating factor [G-CSF]) to be administered to shorten neutropenia duration & severity.
- When a chemotherapy regimen is used as *palliation* (to control symptoms), the dosages of chemotherapy may be decreased based on toxicity or the interval between cycles may be lengthened to maintain quality of life.
- Factors that affect chemotherapy selection and dosing are age, concurrent disease states (e.g., Renal failure, heart disease), and performance status (assessed through specific scales).

Combination Chemotherapy

- The principles of using combination therapy are to use:

1. Agents with different pharmacologic actions
2. Agents with different organ toxicities (e.g., Anthracyclines (eg, doxorubicin) have the potential to cause cardiac toxicity; Microtubule- targeting agents (eg, vincristine) are associated with various forms of neurotoxicity; Alkylating agents (eg, melphalan) are associated with secondary malignancies.
3. Agents that are active against the tumor and ideally synergistic when used together
4. Agents that do not result in significant drug interactions.

- When two or more agents are used together, the risk of development of resistance may be lessened, but toxicity may be increased.

The most commonly used anticancer agents

Class	Drugs	General comment
Antimetabolites	Pyrimidine analogues like fluorouracil Purine Analogues like mercaptopurine Folate Antagonists like Methotrexate	All can cause Myelosuppression
Vinca Alkaloids	Vincristine, vinblastine, and vinorelbine	Used mainly in hematological malignancies The dose-limiting toxicity of vincristine is neurotoxicity while for vinorelbine and vinblastine is myelosuppression.
Taxanes	Paclitaxel, Docetaxel, and Cabazitaxel.	They have activity in several solid tumors. Mainly cause myelosupression
Anthracyclines	Daunorubicin, doxorubicin, idarubicin, and epirubicin	They can cause cardiac toxicity.
Alkylating agents	Nitrogen mustard like Cyclophosphamide & ifosfamide	Cause hemorrhagic cystitis
	Nitrosoureas like carmustine and lumstine	Can cause myelosupression and used in brain tumors
	Platinum compounds like Cisplatin, carboplatin, and oxaliplatin	isplatin is highly emetogenic (higher than carboplatin and oxaliplatin). There is risk of nephrotoxicity, Ototoxicity and electrolyte abnormalities.
Antibiotics	Bleomycin	Pulmonary toxicity
Monoclonal antibodies	Like almetuzumab, obintuzumab, rituximab, etc	Hypersensitivity reactions
Checkpoint inhibitors	CTLA-4 inhibitors like ipilimumab PD-1 and PD-L1 inhibitors like pembrolizumab, durvalumab, atezolizumab,etc	They act by promoting activation and proliferation of T cells to induce tumor infiltration and regression. Used in many solid and hematological cancers
Tyrosine kinase inhibitors	BCR-ABL inhibitors like imatinib, dasatinib, ponatinib, etc	Used mainly for CML
	BRAF inhibitors like Dabrafenib, Vemurafenib, etc	They most often are used to treat melanoma and also some colon cancers with BRAF mutations
	Anaplastic Lymphoma Kinase (ALK) Inhibitors (Alectinib, Brigatinib, Ceritinib, Crizotinib, and Lorlatinib)	Mainly used in small cell lung cancer
	B-cell Lymphoma 2 (Bcl-2) Inhibitor (Venetoclax) and Bruton's Tyrosine Kinase (BTK) Inhibitors (Ibrutinib, Acalabrutinib, & Zanubrutinib)	Used in mainly CLL (Venetoclax may be effective in AML)

Leukemia Acute leukemia

- The acute leukemias are hematologic malignancies of bone marrow precursors characterized by excessive production of immature hematopoietic cells.
- This proliferation of "blast" cells eventually replaces normal bone marrow and leads to the failure of normal hematopoiesis (Resulting in anemia, neutropenia, and thrombocytopenia) and the appearance in peripheral blood as well as infiltration of other organs including the liver, spleen, bone, skin, lymph nodes, testis, and central nervous system (CNS).

Types of acute leukemia

Acute leukemias are classified according to their cell of origin.

1. Acute lymphocytic leukemia (ALL) arises from the lymphoid precursors.
2. Acute nonlymphocytic leukemia (ANLL) or acute myelogenous leukemia (AML) arises from the myeloid or megakaryocytic precursors.

Epidemiology

- Leukemia is a relatively uncommon disease. In the pediatric population, leukemia is a common cancer.
- ALL accounts for 75% to 80% of all cases of childhood leukemia.
- The average age of diagnosis for AML is about 65 years and is a result of an increasing incidence of AML with age.

Etiology

- The cause of acute leukemias is unknown; multiple influences related to genetics, socioeconomics, infection, environment (e.g. chemicals, pesticides, and radiation), hematopoietic development, and chance may play a role.
- Alkylating agents, such as ifosfamide and cyclophosphamide, and topoisomerase inhibitors, such as etoposide, are linked to an increased risk of AML and myelodysplastic syndrome (MDS).

Diagnosis of acute leukemia

- Immunophenotyping by flow cytometry has taken on an increasingly important role in the diagnosis of leukemia.
- Immunophenotyping is a test used to identify cells on the basis of the types of markers or antigens present on the cell's surface, nucleus, or cytoplasm.
- Flow cytometry is the preferred method for leukemic lineage as well as prognostic assignment.

Prognostic Factors

- Patients with leukemia are categorized based on clinical and biological features that mirror their risk of relapse.
- Risk assessment is an important factor in the selection of treatment (minimized overtreatment or undertreatment).
- Age, WBC, leukemic cell-surface markers, DNA content, and specific cytogenetic abnormalities predict response to therapy and are used to assign risk and associated treatment.
- On the basis of these prognostic variables, patients are assigned to standard-, high-, or very-high- risk groups that determine the aggressiveness of treatment.
- For ALL patients: Minimal residual disease (MRD) is a quantitative assessment (By PCR) of subclinical remnant of leukemic burden remaining at the end of the initial phase of treatment (induction) when a patient may appear to be in a complete morphologic remission. This measure has become one of the strongest predictors of outcome for patients with acute leukemia. The elimination of MRD is a principal objective of postinduction leukemia therapy. MRD is an important indicator of disease recurrence

Clinical Presentation of acute leukemia

- Typically, patients with acute leukemia have non-specific symptoms (fatigue, pallor and fever) with no obvious distress for 1 to 3 months before presentation.
- Patients with acute leukemia may present with malaise and weakness (due to anemia); bleeding due to thrombocytopenia; fever and high susceptibility to infection (due to neutropenia), bone pain (due to leukemic infiltration) and weight loss.
- Lymphoadenopathy is common seen in ALL patients.
- Chloromas (localized leukemic deposits named after their color) may be seen, especially in the periorbital regions and as skin infiltrates in AML patients. Gum hypertrophy is indicative of AML M4 and M5 subtypes.
- Potassium and phosphorus often are elevated. Uric acid is increased in approximately 50% of patients secondary to rapid cellular turnover.

Treatment Desired outcomes

- The primary objective in treating patients with acute leukemia is to achieve a continuous complete remission (CCR).
- Remission is defined as the absence of all clinical evidence of leukemia with the restoration of normal hematopoiesis.
- For both ALL and AML, remission induction is achieved with the use of myelosuppressive chemotherapy. Failure to achieve remission in the first 7 to 14 days of therapy is highly predictive of later disease recurrence. This again represents the growing importance of MRD in prognosis and treatment.

Non pharmacological treatment of acute leukemia

- Cancer survivors are at greater risk for developing second malignancies, cardiovascular disease, diabetes, and osteoporosis than those in the general population. Thus, it is important to provide supportive care and counseling related to nutrition, smoking cessation, and exercise as a part of their active treatment.

Pharmacologic Therapy: ALL

The treatment for ALL consists of five main elements:

1. Initial therapy is called induction (sometimes called remission induction) which aim to induce a remission, a state in which there is no identifiable leukemic cells in the bone marrow or peripheral blood with light microscopy. Current induction therapy for ALL typically consists of vincristine, L-asparaginase, and a steroid (prednisone or dexamethasone). An anthracycline is added for higher risk patients (e.g. adults). Dexamethasone often replaces prednisone because of its longer half-life and better CNS penetration.
2. CNS-directed treatment,
3. Post remission therapies include:

A. Intensive postremission consolidation regimens (for 1 month) to reduce the burden of residual leukemic cells

B. Reinduction (Interim maintenance for 2 months and delayed intensification by repetition of initial induction therapy given 3 months after remission): followed by

C. A prolonged maintenance phase to further eliminate leukemic cells and produce an enduring continuous complete remission (CCR). Maintenance chemotherapy is a combination of oral

methotrexate and 6- mercaptopurine.
The total duration of treatment is 2 to 3 years
Note: Improved outcome is associated with increasing 6-mercaptopurine doses to the limits of individual tolerance based on absolute neutrophil count (ANC).

CNS Prophylaxis

- Leukemic invasion of the CNS is an almost universal event in patients. Thus, all patients with ALL and AML leukemia receive intrathecal (IT) chemotherapy.
- CNS prophylaxis relies on IT chemotherapy (eg, methotrexate, cytarabine, andcorticosteroids), systemic chemotherapy with dexamethasone and high-dose methotrexate, and craniospinal irradiation (XRT) in selected high-risk patients (T-cell ALL).

Relapsed ALL

- Relapse is the recurrence of leukemic cells at any site after remission has been achieved.
- Bone marrow relapse is the major form of treatment failure in 15% to 20% of patients with ALL. Most relapses have the same immunophenotype and cytogenetic changes seen of the original disease. Extramedullary sites of relapse include the CNS and the testicles
- Site of relapse and the length of the first remission are important predictors of second remission and overall survival (OS).
- Treatment strategies for relapsed ALL include chemotherapy or allogeneic hematopoietic stem cell transplant (allo-HSCT).
- Clofarabine has shown considerable activity in refractory acute leukemias.
- Blinatumomab, a monoclonal antibody that targets CD19, was approved for Ph negative relapsed or refractory ALL.
- **Inotuzumab ozogamicin** (anti CD-22) is also used in relapsed and refractory B-ALL.
- Tisagenlecleucel is an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that has been shown to induce durable remissions in patients with relapsed and refractory B-cell ALL.
- Nelarabine is used in patients with relapsed or refractory T-lineage ALL.

Outcome evaluation

- Failure to obtain morphologic bone marrow remission by day 28 is a very adverse prognostic sign and dictates further induction treatment.
- For those who have a morphologic remission, quantification of MRD has become an increasingly important prognostic factor. Levels of residual less than 0.01% appear to be associated with better outcome.

Treatment of AML

Treatment of AML is divided into two phases:

1. Induction (to achieve remission): consists of a combination of cytarabine, and daunorubicin. Adding gemtuzumab ozogamicin to induction therapy for older patients improved relapsed rates and OS.
2. Consolidation (postremission) to further enhance remission with more cytoreduction and prevent relapse. Mainly through the use of 2-4 cycles of high-dose cytarabine
   Note: Midostaurin, an oral multi- target kinase inhibitor, was recently approved by theFDA for treatment of Fms-like tyrosine kinase 3(FLT3) positive AML

Allogeneic Hematopoietic Stem Cell Transplantation

- Hematopoietic stem cell transplantation (HSCT) is the most effective treatment for AML. Its promising benefit must be weighed against the potential risk of transplantation related sequelae. Patients who do not have an HLA-matched sibling proceed to postremission therapy with chemotherapy alone.
- The role of HSCT, particularly whether it should be performed during the first CR or reserved for second remission, remains the most controversial issue in pediatric AML. In certain institutions, HSCT is often reserved for patients thatare considered high risk.

CNS therapy

- Patients with CNS disease at diagnosis can be cured with IT therapy. In most cases, IT cytarabine with or without methotrexate and systemic high-dose cytarabine provide effective treatment.

Relapsed AML

- Even though there is no standard therapy for relapse, most studies have shown that high-dose cytarabine-containing regimens have considerable activity in obtaining a second remission.
- Cytarabine has been used in combination with mitoxantrone, etoposide, fludarabine, 2-chlorodeoxyadenosine, and clofarabine.
- For patients unable to tolerate intensive chemotherapy, low dose cytarabine and the hypomethylating agent, azacitidine, are also options for relapsed disease.
- Venetoclax in combination with either decitabine or azacitidine is also an alternative in the relapsed setting.
- Gilteritinib is an FLT3 inhibitor approved for AML patients with an *FLT3- ITD* mutation in relapsed setting.
- Enasidenib is an oral inhibitor of mutant *IDH2* proteins and is approved for use in patients with relapsed AML who harbor *IDH2* mutations. Similarly, ivosidenib is an *IDH1* inhibitor that is approved for use in relapsed AML patients with an *IDH1* mutation.
- After a patient has achieved a second remission with conventional chemotherapy, allo-HSCT is the therapy of choice.

Complications of Treatment

1. Tumor Lysis Syndrome

- Tumor lysis syndrome (TLS) is an oncologic emergency that is characterized by metabolic abnormalities resulting from the death of blast cells and the release of large amounts of purines, pyrimidines, and intracellular potassium and phosphorus.
- Measures to prevent TLS include aggressive hydration to increaseurine output, and allopurinol to reduce uric acid production. Rasipuricase is indicated in some cases.

Infection

- Anfection is a primary cause of death in acute leukemia patients. Both the disease and aggressive chemotherapy cause severe myelosuppression, placing the patient at risk for sepsis.
- Because the progression of infection in neutropenic patients can be rapid, empirical antibiotic therapy (usually 4th generation cephalosporins) is started whenever a fever is documented.

2. Secondary malignancy: discussed later

Supportive care

- Platelet transfusions are a common tool to prevent hemorrhage. Patients with uncomplicated thrombocytopenia can be transfused when the platelet count falls below 10 × 103/mm3. Patients who are either highly febrile or actively bleeding may require transfusions at higher levels.
- Red blood cell transfusions generally are not necessary for a hemoglobin concentration greater than 8 g/dL.
- The use of CSFs (G-CSF most commonly) generally is limited to those chemotherapy regimens that place the patient at highest risk for prolonged neutropenia.

Chronic leukemias

- The two most common forms are chronic myelogenous leukemia (CML) andchronic lymphocytic leukemia (CLL).
- The slower progression of the disease contrasts it from acute leukemia, withthe survival of chronic leukemia often lasting several years without treatment.

Clinical course of CML

- It is a triphasic disease based on % of myeloblasts in peripheral blood or bonemarrow:

1. Initial chronic phase
2. Accelerated phase (disease is progressing with worsening symptoms),
3. Blast crisis which resembles acute leukemia, immediate aggressive treatmentis required

Epidemiology and etiology of CML

- The incidence of CML increases with age, with the median age of diagnosisbeing 65 years.
- The etiology cannot be determined, but high doses of ionizing radiation andexposure to solvents such as benzene are recognized risk factors.

Ph Chromosome

- The Philadelphia chromosome (Ph) results from a translocation between chromosomes 9 and 22, leaving a shortened chromosome 22.
- The Ph results in the formation of an abnormal fusion gene (translocation of genetic material) between the chromosome 22 (breakpoint cluster region-BCR gene) and chromosome 9 (the Abelson proto-oncogene-ABL gene), which encodes an overly active tyrosine kinase. The loss of control of tyrosine kinase activity causes abnormal cellular proliferation and inhibition of apoptosis.
- Molecular tools such as quantitative reverse transcriptase-polymerase chain reaction (Q-PCR) and fluorescence in situ hybridization (FISH) are used in thedetection and monitoring of *BCR-ABL* transcripts found in CML

Clinical Presentation of CML

- ~50% are asymptomatic at diagnosis.
- Symptoms may include fatigue, fever, bleeding, and weight loss.
- Organomegaly consisting of splenomegaly and hepatomegaly occur in chronicleukemia.
- **Lab data:** Anemia and Leukocytosis (WBC count > 100 × 103/mm3).

Treatment of CML Desired Outcome

- The primary goal in the treatment of CML is to achieve long-term disease control with TKI therapy and possibly treatment-free remission (TFR).
- A deep, long-lasting molecular response (BCR-ABL <0.1%) is associated with long-term disease control and achievable for many patients with CP-CML through TKI therapy.
- Most recently, TFR (i.e. TKI discontinuation) has emerged as a goal for select patients who sustain a deep molecular response while on a TKI.
- A complete molecular response is defined as undetectable *BCR-ABL1* transcripts by the International Scale (IS).
- A cure from CML can only come from complete eradication of the Ph clone.

General approach to treatment of CML

- Nearly all patients with CML are initially treated with a TKI. These oral agents do not cure CML but produce long-term response in the vast majority of patients. They reduce peripheral WBC counts over several weeks.
- Hydroxyurea may be used after diagnosis to rapidly reduce high WBC counts and prevent potentially serious complications (respiratory and neurologic) associated with large numbers of circulating neutrophils. Hydroxyurea, though, does not alter the disease process.
- Allogeneic hematopoietic stem cell transplant (HSCT) is the only curative therapy for CML and is reserved for patients with TKI resistance. HSCT can be considered for patients who present in blast crisis phase of CML.

TKIs

- Four TKIs (imatinib, dasatinib, nilotinib, and bosutinib) may be used as first- line therapy for newly diagnosed CP-CML.
- Which agent to use depends on several factors, including disease risk score, age, comorbid conditions, medication safety profile, and financial accessibility.
- Dasatinib, nilotinib, bosutinib, and ponatinib are advanced generation TKIs that may overcome imatinib resistance or intolerance. Of the four, only ponatinib can overcome the *T315I* mutation.
- Studies suggest bosutinib, dasatinib, and nilotinib are superior to imatinib in achieving faster and deeper cytogenetic and molecular responses. However, there are no differences in overall survival reported between the agents.
- Common side effects include myelosuppression, gastrointestinal disturbances, and myalgias.
- A significant and potentially severe side effect of pleural effusions has been reported with the use of imatinib and dasatinib but not with the use of nilotinib. Additional side effects of nilotinib include QT prolongation and increases in indirect bilirubin. An increase in serious arterial thrombotic eventscan be seen with ponatinib.

Patient education on TKIs

- Imatinib and Bosutinib take with food; Nilotinib take on empty stomach.
- It is recommended that patients on imatinib to avoid use of acetaminophen.
- All TKI given orally with many drug interactions because they are CYP450substrate

Omacetaxine

- Omacetaxine is a subcutaneous injection indicated for patients in CP- or AP-CML who are resistant or intolerant to two or more TKIs.
- It may also be used in patients with the *T315I* mutation. Clinicians should noteomacetaxine may cause hyperglycemia.

Outcome evaluation

- Molecular response at 3, 6, and 12 months is assessed, as it has been associated with improved progression free and overall survival.
- Patients failing to achieve these milestones should undergo *BCR-ABL1* domain mutation testing to determine TKI resistance and be evaluated for medication adherence and possible drug interactions.
- Second-line CP-CML therapy should be selected based on mutational analysis with second-generation TKIs utilized.

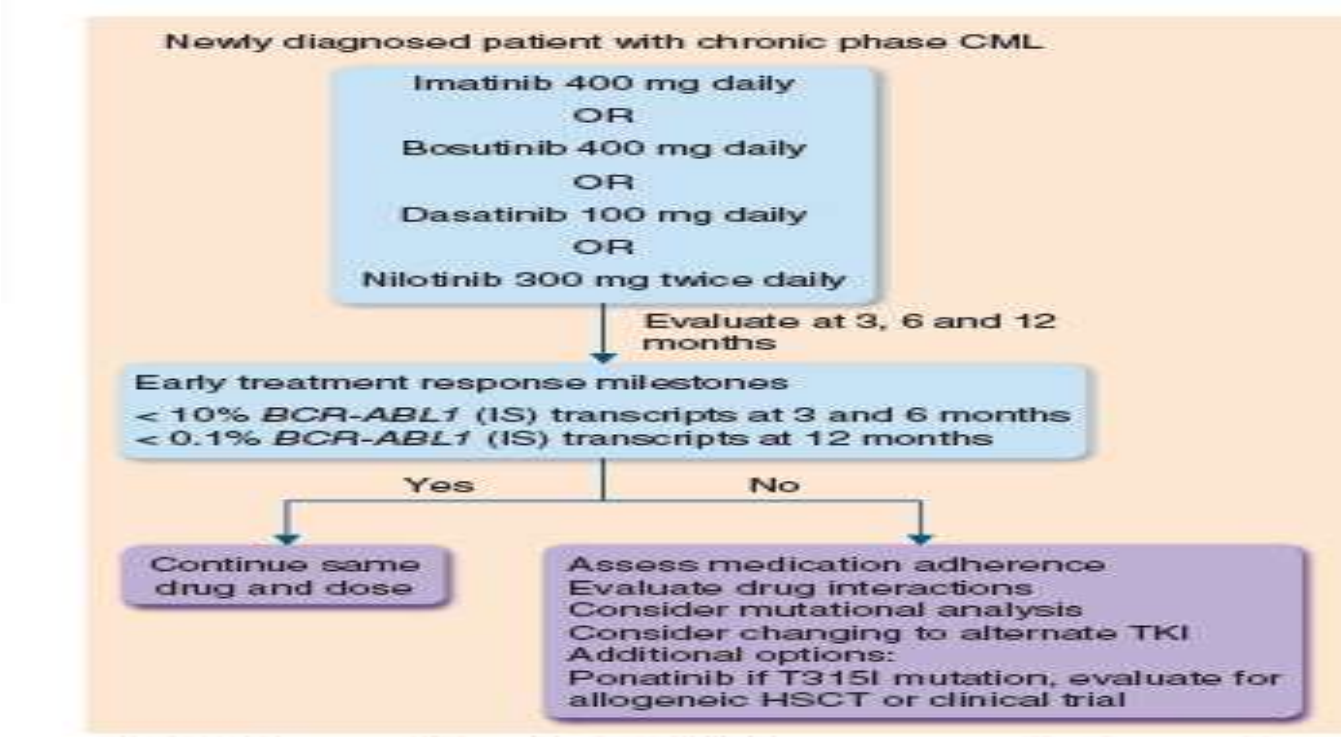


FIGURE 97–1. Algorithm for TKI therapy in newly diagnosed patient with CP-CML. (Data from NCCN.)

Chronic lymphocytic leukemia Epidemiology and etiology

- CLL is the most common type of leukemia diagnosed in adults. The median age at diagnosis is 70 years with the incidence increasing with age.
- The etiology of CLL is unknown, but hereditary factors may have a role.

Clinical course of CLL

- CLL can have a variable clinical course with survival ranging from months to decades.

1. Low-risk disease is asymptomatic.
2. Intermediate risk is associated with lymphadenopathy.
3. High-risk patients with anemia (median survival of only 2 years).

Clinical Presentation of CLL

- Same as CML 50% are asymptomatic at diagnosis. Organomegaly consisting of splenomegaly and hepatomegaly may occur.
- Symptoms may include fatigue, fever, night sweating, and weight loss. Besides chronic infections caused by immature lymphocytes.
- **Lab data:** Anemia and Leukocytosis (WBC count > 100 × 103/mm3), especially lymphocytosis (absolute lymph count > 5 × 103/mm3). Hypogammaglobulinemia, and thrombocytopenia.

Prognostic factors of CLL

- Increasingly, biological markers of the disease such as deletions of chromosome 17p (del(17p)) and 11q (del(11q)) and mutational status of immunoglobulin heavy chain variable region gene (IgVH) are being used to predict the likely clinical course. Patients with del(17p) or *TP53* mutations tend to have a poor response to therapy.

TREATMENT

Desired Outcomes

- Because the current treatments for CLL are not curative, reduction in tumor burden and improvement in disease symptoms are reasonable end points, particularly in older patients.
- A complete response (CR) to therapy can be defined as a resolution of lymphadenopathy and organomegaly, normalization of peripheral blood counts, and elimination of lymphoblasts in the bone marrow.

Non pharmacological treatment

- Asymptomatic early stage CLL (especially elderly people) can be observed (watch and wait) without treatment until evidence of disease progression.
- Allogeneic HSCT remains an option for younger patients with aggressive disease who have failed prior therapies.

Pharmacological treatment

- The NCCN guidelines provide recommendations on first-line and subsequent CLL therapies based on mutational status, age, and whether comorbidities are present.
- Oral small molecule inhibitor therapy (eg, ibrutinib, venetoclax) has established a pivotal role in the front-line treatment of symptomatic CLL. This has minimized the use of traditional chemotherapy-based regimens (eg, purineanalogs and alkylating agents).
- Monoclonal antibodies targeting CD20 antigen may also be incorporated into front-line therapy.

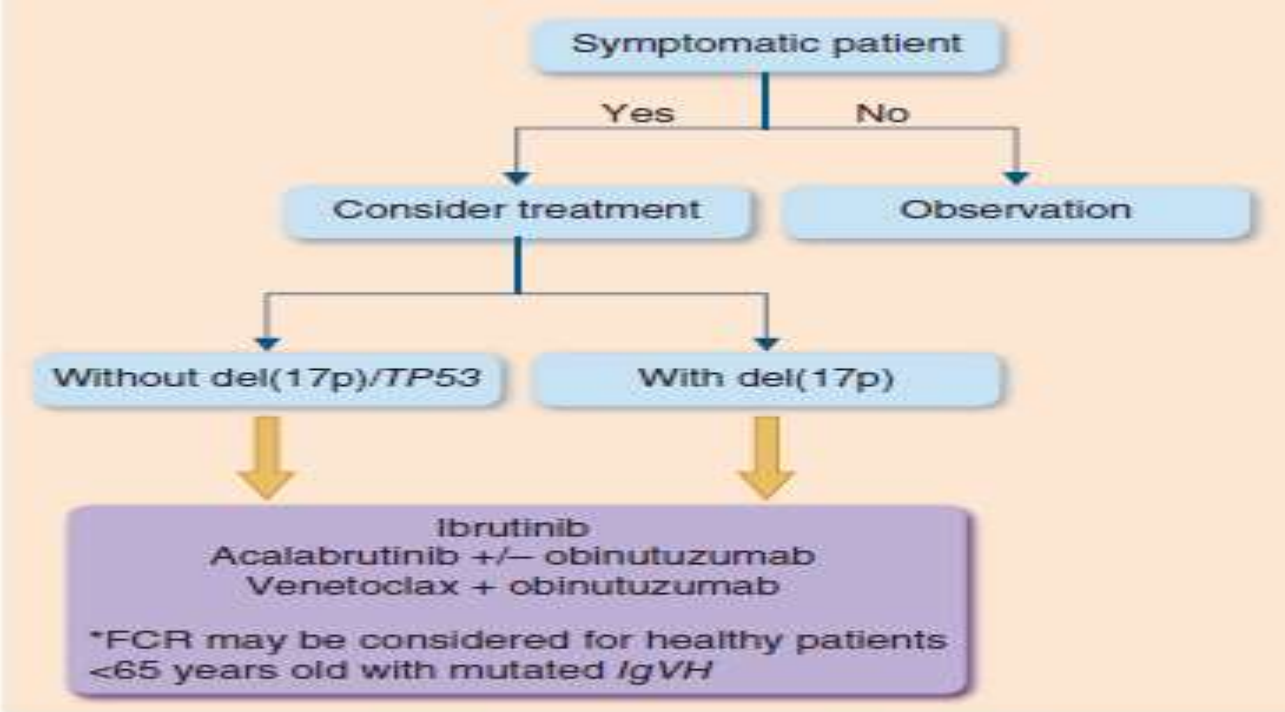


FIGURE 97–2. Possible treatment approach for first-line therapy in newly diagnosed CLL patients. (B, bendamustine; C, cyclophosphamide; F, fludarabine; R, rituximab.) (Data from NCCN.)

Treatment options of CLL

A. Cytotoxic chemotherapy
B. **Small-Molecule Inhibitors** (new novel oral therapies)
C. **Monoclonal antibodies**

Cytotoxic chemotherapy

- NCCN still recommends fludarabine, cyclophosphamide, and rituximab (FCR)as the preferred regimen for younger (< 65 years old) patients with *IgVH*- mutated CLL. The aggressive use of FCR may offer a potential cure for theseselect patients.
- Fludarabine is associated with myelosuppression and prolonged immunosuppression
- Clinicians should consider antibacterial and antiviral prophylaxis for *Pneumocystis* and varicella zoster when using fludarabine- based therapy.

Monoclonal antibodies

- Anti-CD20 monoclonal antibodies are widely used in the treatment of CLL. They include Rituximab, which has been largely replaced by the next- generation monoclonal antibodies, obinutuzumab, and ofatumumab.
- Obinutuzumab is different than the other anti-CD20 monoclonal antibodies, having a higher binding affinity to the CD20 epitope and causing direct cell death.
- The anti-CD20 monoclonal antibodies are often used in combination with targeted therapy or chemotherapy. They are less frequently used as a monotherapy. The selection and combination of the monoclonal antibody depends on clinical studies.
- The most common side effects for monoclonal antibodies include infusion reactions consisting of fever, chills, hypotension, nausea, vomiting, and headache. Premedication with diphenhydramine and acetaminophen is recommended to minimize infusion reactions.
- Reactivation of hepatitis B virus (HBV) is also a concern for patients on anti- CD20 therapy. Prophylactic hepatitis B antiviral therapy or treatment with entecavir may be warranted.

Small-Molecule Inhibitors

- An understanding of the B-cell receptor signaling pathways of CLL has led to the approval of oral targeted therapies. Many of these therapies have improvedthe median overall survival of CLL.

1. BTK inhibitors: BTK is an essential enzyme in the B-cell receptor pathway, they include:

A. Ibrutinib: may be used as first-line therapy for all patients (used as monotherapy), including patients with del(17p), regardless of age. Anincreased risk of atrial fibrillation has been also associated with ibrutinib.

B. Acalabrutinib is a second-generation BTK inhibitor. It has a higher BTK selectivity than ibrutinib which has led to promising results. The indications are similar to ibrutinib with acalabrutinib being used with or without obinutuzumab for first-line therapy of CLL and in relapsed and refractory CLL.

2. Oral Phosphatidylinositol-3-kinase (PI3-K) inhibitors include Idelalisib and duvelisib.

A. Idelalisib targets phosphatidylinositol-3-kinase (PI3-K). Idelalisib has been studied as monotherapy as well as combination therapy with rituximab.

B. Both idelalisib and duvelisib may be used for patients with relapsed/refractory CLL. Boxs warnings for idelalisib and duvelisib include hepatotoxicity, for idelalisib and colitis, infestion, cutaneous reactions and pneumonitis for duvelisib. Patients should receive *Pneumocystis* pneumonia prophylaxis and CMV antiviral prophylaxis should also be considered to prevent CML infection and reactivation.

3. Venetoclax (Venclexta) is a small molecular inhibitor that targets B-cell lymphoma 2 (BCL-2) protein and may be used as first line therapy or for patients with relapsed/refractory CLL. Adverse effects for venetoclax include tumor lysis syndrome and prolonged neutropenia (may require growth factor support). Venetoclax is used in combination with anti-CD20 monoclonal antibodies.

Breast Cancer

INTRODUCTION

Breast cancer is a malignancy originating from breast tissue. Disease confined to a localized breast lesion is referred to as early, primary, localized, or curable. Disease detected clinically or radiologically in sites distant from the breast is referred to as advanced or metastatic breast cancer (MBC), which is incurable.

EPIDEMIOLOGY

- Two variables most strongly associated with the occurrence of breast cancer arebiological sex and age. Additional risk factors include endocrine factors (eg, menarche before age 11, age 55, or later for natural menopause, nulliparity, late age at first birth, and hormone replacement therapy), genetic factors (eg, personal and family history, mutations of tumor suppressor genes [BRCA1 and BRCA2]), and environmental and lifestyle factors (eg, radiation exposure, tobacco use, and alcohol consumption).
- Breast cancer cells often spread undetected by contiguity, lymph channels, and through the blood early in the course of the disease, resulting in metastaticdisease after local therapy. The most common metastatic sites are lymph nodes, skin, bone, liver, lungs, and brain.

PREVENTION OF BREAST CANCER

- Risk reduction strategies include prophylactic mastectomy, oophorectomy, and pharmacologic agents.
- Agents available for pharmacologic risk reduction include selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs). The SERMs, tamoxifen and raloxifene taken for 5 years, reduce the risk of invasive andnoninvasive breast cancer by about 50% in women at high risk for developing thedisease. Tamoxifen increased the incidence of endometrial cancer and bothagents increased thromboembolic events.
- A similar reduction in the risk of contralateral primary breast cancers in high risk, postmenopausal individuals was demonstrated with the AIs, exemestane and anastrozole.
- Clinical guidelines recommend the use of SERMs or AIs for risk reduction in postmenopausal women at high risk.

CLINICAL PRESENTATION

- A painless, palpable lump is the initial sign of breast cancer in most women. The typical malignant mass is solitary, unilateral, solid, hard, irregular, and nonmobile.Nipple changes are less commonly seen. More advanced cases present with prominent skin edema, redness, warmth, and induration.
- Symptoms of MBC depend on the site of metastases but may include bone pain, difficulty breathing, abdominal enlargement, jaundice, and mental status changes.
- Many women first detect some breast abnormalities themselves, but it is increasingly common for breast cancer to be detected during routine screening mammography in asymptomatic women.

DIAGNOSIS

- Initial workup should include a careful history, physical examination of the breast, three-dimensional mammography, and, possibly, other breast imaging techniques, such as ultrasound, magnetic resonance imaging (MRI), digital mammography, and tomosynthesis.
- Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination.

Pathologic Evaluation

- Development of malignancy is a multistep process involving preinvasive (ornoninvasive) and invasive phases. The goal of treatment for noninvasive carcinomas is to prevent the development of invasive disease.
- Pathologic evaluation of breast lesions establishes the histologic diagnosis andconfirms the presence or absence of prognostic factors.
- Most breast carcinomas are adenocarcinomas and are classified as ductallobular.

Prognostic Factors

- The ability to predict prognosis is used to design personalized treatment by medications.
- Age at diagnosis and ethnicity can affect prognosis.
- Alcohol use, dietary factors, weight, and exercise are potentially modifiableprognostic factors.
- Tumor size and presence and the number of involved axillary lymph nodes areindependent factors that influence the risk for breast cancer recurrence and subsequent metastatic disease.
- Hormone receptors (estrogen [ER] and progesterone [PR]) are not strong prognostic markers but are used clinically to predict response to endocrine therapy.
- HER2 overexpression occurs in about 15%–20% of breast cancers and is associated with increased tumor aggressiveness, increased rates of recurrence, and increased rates of mortality.
- Genetic profiling tools provide additional prognostic information to aid in treatment decisions for subgroups of patients with otherwise favorable prognosticfeatures.

Staging

- Stage (anatomical extent of disease) is based on primary tumor extent and size (T1–4), presence and extent of lymph node involvement (N1–3), and presence or absence of distant metastases (M0–1). The staging system determines prognosis and assists with treatment decisions. Staging for breast cancer is separated into clinical and pathologic staging. Clinical stage is assigned before surgery and is based on physical examination, imaging (eg, mammography, ultrasonography), and pathologic examination of tissues (eg, biopsy results). Pathologic staging occurs after surgery and adds data from surgicalexploration and resection.

These stages may be represented as follows:

✓ *Early breast cancer*

Stage 0: Carcinoma in situ or disease that has not invaded the basement membrane.

Stage I: Small primary invasive tumor without lymph node involvement or with micrometastatic nodal involvement.

Stage II: Involvement of regional lymph nodes.

✓ *Locally advanced breast cancer*

Stage III: Usually, a large tumor with extensive nodal involvement in which the node ortumor is fixed to the chest wall.

✓ *Advanced or metastatic breast cancer*

Stage IV: Metastases in organs distant from the primary tumor.

TREATMENT

- **Goals of Treatment:** The intent of adjuvant systemic therapy for Stage I–III is to eradicate micro metastatic disease with cure as the desired outcome. Neoadjuvant systemic therapy may be administered for Stage III to decrease tumor size prior to surgery and/or to allow for breast conserving surgery if desiredby the patient. Palliation is the desired therapeutic outcome in the treatment of MBC.
- Treatment can cause substantial toxicity, which differs depending on the individual agent, administration method, and combination regimen. A comprehensive review of toxicities is beyond the scope of this chapter; consult appropriate references.

Curative Breast Cancer (Stages IIII)

Local- Regional Therapy

- Surgery alone can cure most patients with in situ cancers, 70%–80% of Stage I cancers, and approximately one half of those with Stage II cancers.
- Breast conserving therapy (BCT) maintains acceptable cosmetic results and rates of local and distant recurrence and mortality seen with mastectomy. BCT includes removal of part of the breast, surgical evaluation of axillary lymph nodes, and radiation therapy (RT) to prevent local recurrence.
- RT is administered to the entire breast to eradicate residual disease after BCT.
- Reddening and erythema of the breast tissue with subsequent shrinkage of total breast mass are less common complications associated with short-term RT.
- Multiple sites of cancer within the breast and the inability to attain negative pathologic margins are indications for mastectomy.
- Axillary lymph nodes should be sampled for staging and prognostic information.

Systemic Therapy

- **Chemotherapy, endocrine therapy, targeted therapy**, or some **combination** of these agents improves disease free and/or overall survival (OS) for high-risk patients in specific prognostic subgroups (eg, nodal involvement, menopausal status, hormone receptor status, or HER2 status).
- The National Comprehensive Cancer Network (NCCN) practice guidelines are updated at least every 2 years; treatment recommendations are complex and the reader is referred to the guidelines.

Cytotoxic Chemotherapy

- Systemic adjuvant therapy is the administration of systemic therapy following definitive local therapy (surgery, radiation, or both) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. The goal of such therapy is cure. It is recommended in most women with lymph node metastases or with primary breast cancers larger than 1 cm in diameter (both node negative and node positive).
- Neoadjuvant (preoperative) systemic therapy is the standard of care for patients with locally advanced breast cancer; it consists of chemotherapy, either alone or combined with biologic or targeted therapy, but in special circumstances may also include endocrine therapy.
- The most common cytotoxic drugs that have been used alone and in combination as adjuvant therapy for breast cancer include doxorubicin, epirubicin, cyclophosphamide, methotrexate, fluorouracil, carboplatin, paclitaxel, and docetaxel.
- Combination regimens are more effective than single agent chemotherapy.
- Anthracyclines (doxorubicin or epirubicin) and taxanes (paclitaxel or docetaxel) are the cornerstones of modern chemotherapy for adjuvant treatment of breast cancer.
- Initiate chemotherapy within 12 weeks of surgical removal of the primary tumor. Optimal duration of adjuvant treatment is unknown but appears to be 12— 24 weeks, depending on the regimen used.
- Dose intensity refers to the amount of drug administered per unit of time, which can be achieved by increasing dose, decreasing time between doses, or both.
  - Dose density is one way of achieving dose intensity by decreasing time between treatment cycles. Avoid dose reductions in standard regimens unless necessitated by severe toxicity.

Biologic or Targeted Therapy

- Targeted therapies are directed at molecular targets through novel mechanisms; many are also biologic therapies because they are monoclonal antibodies (mAbs).
- Trastuzumab is an mAb targeted against the HER2 receptor protein used in combination with or sequentially after adjuvant chemotherapy in patients with early stage, HER2 positive breast cancer. The risk of recurrence was reduced up to 50% in clinical trials.
- The risk of symptomatic heart failure with adjuvant trastuzumab regimens that contain an anthracycline ranges from 0.5% to 4%. Sequential administration of trastuzumab after chemotherapy and the use of non-anthracycline based regimens are strategies to lower the incidence of cardiac toxicity.
- Neratinib an oral tyrosine kinase inhibitor of EGFR, HER2, and HER4, is indicated for extended adjuvant therapy after completion of trastuzumab.

- Ado-trastuzumab emtansine (also known as TDM1) is used in the adjuvantsetting following neoadjuvant therapy when residual disease is found at the time of surgery.

Endocrine Therapy

- **Tamoxifen, toremifene**, oophorectomy, ovarian irradiation, luteinizing hormone– releasing hormone (LHRH) agonists, and AIs are endocrine therapies used in the treatment of primary or early-stage breast cancer. Menopausal status determinesthe agent of choice. Tamoxifen is generally considered the adjuvant endocrine therapy of choice for premenopausal women.
- Tamoxifen beginning soon after completing chemotherapy and continuing for 5– 10 years, reduces the risk of recurrence and mortality. It is usually well tolerated; hot flashes and vaginal discharge may occur. Tamoxifen reduces the risk of hip radius and spine fractures. It increases the risks of stroke, pulmonary embolism, deep vein thrombosis, and endometrial cancer, particularly in women aged 50 years or older.
- The combination of ovarian suppression with LHRH agonists (eg, goserelin, triptorelin, and leuprolide) and an AI is recommended in premenopausal women. Tamoxifen is an option with low risk of recurrence and/or intolerance to ovarian suppression plus AI.
- Guidelines recommend incorporation of AIs (anastrozole, letrozole, and exemestane) into adjuvant endocrine therapy for postmenopausal, hormone sensitive breast cancer.

Metastatic Breast Cancer (Stage IV)

- Treatment of MBC with cytotoxic, endocrine, or targeted therapy often results in regression of disease, improvements in quality of life, and improved OS with the addition of some biologic or targeted therapies.
- The choice of therapy for MBC is based on the extent of disease involvementand the presence or absence of certain tumor or patient characteristics.
- Consider adding bone modifying agents (eg, pamidronate, zoledronic acid, or denosumab) to treat breast cancer patients with metastases to the bone to decrease rates of skeletal related events, such as fractures, spinal cord compression, and pain, and the need for radiation to the bones or surgery.

Biologic or Targeted Therapy

- Cyclin-dependent kinases (CDK) form complexes that control cell cycling; DK inhibitors, abemaciclib, palbociclib, and ribociclib, that selectively inhibit CDK4 and 6, are approved for MBC.
- The mammalian target of rapamycin (mTOR) inhibitor everolimus improved PFS when used in combination with either exemestane, fulvestrant,or tamoxifen.
- The phosphatidylinositol 3kinase (PI3k) inhibitor apelisib is approved in combination with fulvestrant for postmenopausal women and men, with hormone receptor–positive, HER2negative, PIK3CAmutated, advanced, or metastaticbreast cancer as detected by an FDA approved test following progression on or after an endocrine based regimen.
- The poly (ADPRIBOSE) polymerase (PARP) inhibitors olaparib and talazoparib improve PFS in appropriate patients.
- HER2targeted agents available in the United States are trastuzumab, pertuzumab, adotrastuzumab emtansine, famtrastuzumab, deruxtecan, margetuximab, lapatinib, neratinib, and tucatinib.

- Firstline therapy with a **pertuzumab-trastuzumab-taxane combination** is the preferred option for HER2 over expressing MBC in patients who have not received pertuzumab in the neoadjuvant or adjuvant setting. Adotrastuzumab emtansine is the recommended second line HER2targeted therapy after a patientprogresses on or can no longer tolerate first line therapy.

Endocrine Therapy

- Consider endocrine therapy in combination with a targeted agent as first line therapy for patients with hormone positive MBC, when feasible. The choice of endocrine therapy is based on the menopausal status of the patient, prior therapies and previous response, duration of response, or disease-free interval.
- No one endocrine therapy has clearly superior survival benefit. The choice of agent is based primarily on mechanism of action, toxicity, and patient preference. Based on these criteria, AIs, tamoxifen or toremifene, and fulvestrant, are the preferred initial agents in MBC except when the patient's cancer recurs during or within one year of adjuvant therapy.
- Fulvestrant, an intramuscular agent, is approved for second line therapy of postmenopausal patients with hormone receptor–positive tumors either alone orin combination with targeted therapy.
- Medical ovarian suppression with an LHRH analog (goserelin, leuprolide, ortriptorelin) is a reversible alternative to oophorectomy in premenopausal women.

Chemotherapy

- Chemotherapy is used as initial therapy for women with hormone receptor negative tumors, with triple negative tumors, and after failure of endocrine/targeted therapy regimens.
- In the absence of predictive biomarkers, chemotherapy is chosen based onoverall efficacy, the risk of toxicity, performance status and presence of comorbidities in the patient, aggressiveness of disease (eg, indolent vs visceral crisis), and patient preferences related to chemotherapy schedules, dosing route (eg, oral vs intravenous), and frequency (eg, weekly vs every 3 weeks).
- Response rates are high with combination chemotherapy, but sequential use of single agents is an effective strategy and may be preferred due to decreasedrates of adverse events.
- Treatment with sequential single agents is recommended over combination regimens unless the patient has rapidly progressive disease, life-threatening visceral disease, or the need for rapid symptom control.
- Anthracyclines and taxanes produce response rates as high as 50% when used as first line therapy for MBC. Single agent capecitabine, vinorelbine, and gemcitabine have response rates of 20%–25% when used after an anthracycline and a taxane.

Immunotherapy

Pembrolizumab (mAb against programmed cell death protein 1 [PD1]) is approved in combination with album inbound paclitaxel, paclitaxel, or the combination of carboplatin + gemcitabine. Atezolizumab (mAb against programmed death ligand [PDL1]) is approved in combination with albumin bound paclitaxel.

Radiation Therapy

Commonly used to treat painful bone metastases or other localized sites of refractory disease, including brain, spinal cord, eye, or orbit lesions. Pain relief is seen in approximately 90% of patients who receive RT for painful bone metastases.

EVALUATION OF THERAPEUTIC OUTCOMES

- The goal of surgery, radiation, neoadjuvant/adjuvant therapy for early stage breast cancer—chemotherapy, biologic or targeted therapy, and endocrine therapy—is cure which cannot be fully evaluated for years after initial diagnosis and treatment.
- Patients are recommended to have a history and physical every 3–6 months for the first 3 years after completion of primary therapy, every 6 months for the following 2 years, and then yearly thereafter.

Metastatic Breast Cancer

- Palliation is the therapeutic endpoint in the treatment of MBC. Optimizing benefits and minimizing toxicity are general therapeutic goals; careful consideration of quality of life is important in this setting and is an important therapeutic
- Tumor response is measured by changes in laboratory tests, diagnostic imaging, or physical signs or symptoms

Endpoint

Prostate Cancer

INTRODUCTION

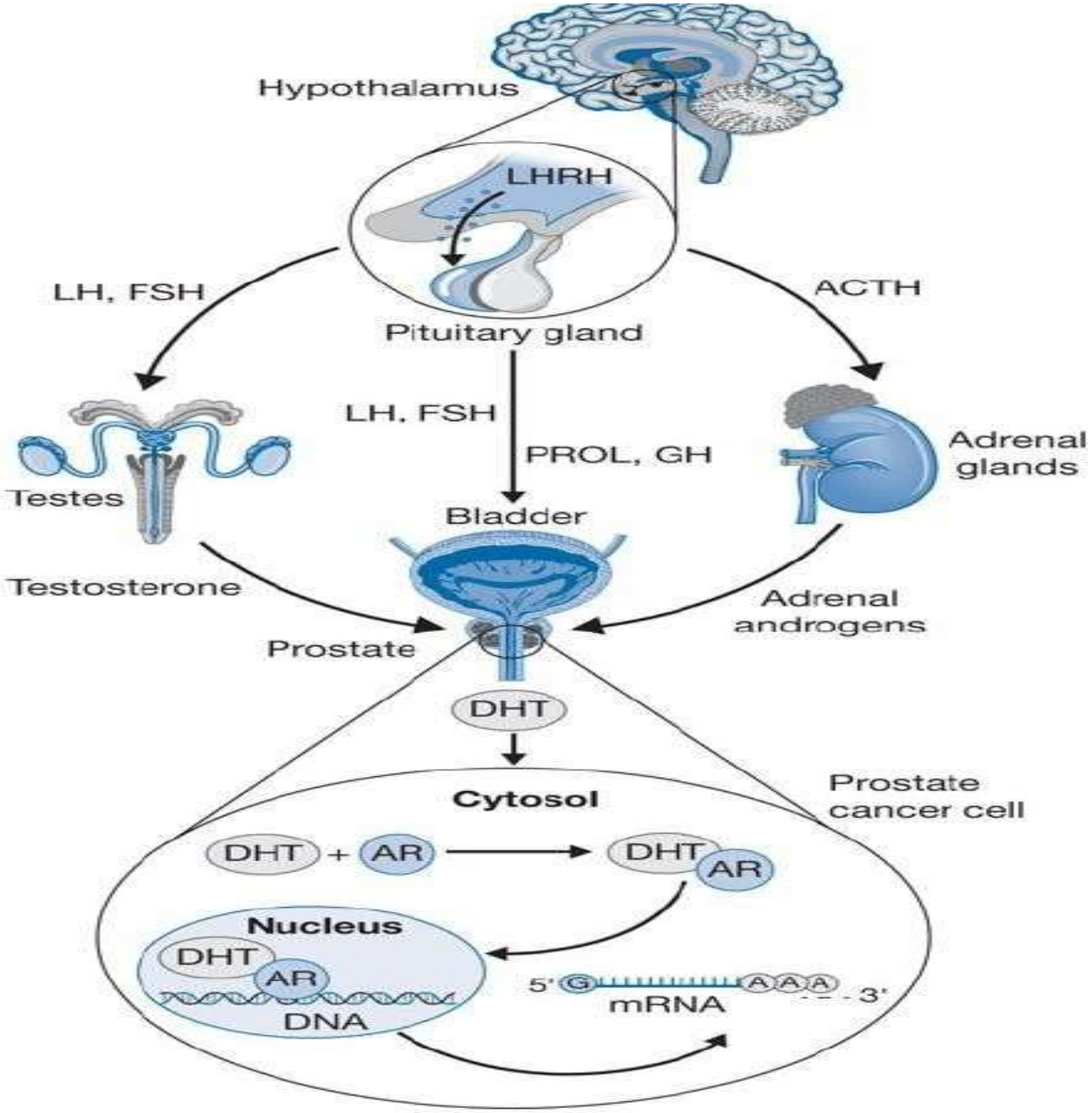
Prostate cancer is a malignant neoplasm that arises from the prosta surgery orradiation therapy, but advanced prostate cancer is not yet curable.

PATHOPHYSIOLOGY

- The normal prostate is composed of acinar secretory cells that are altered whe invaded by cancer. The major pathologic cell type is adenocarcinoma (>95% of cases).
- Prostate cancer can be graded. Well differentiated tumors grow slowly, whereas poorly differentiated tumors grow rapidly and have a poor prognosis.
- Metastatic spread can occur by local extension, lymphatic drainage, or hematogenous dissemination. Skeletal metastases from hematogenous spread are the most common sites of distant spread. The lung, liver, brain, and adrenal glands are the most common sites of visceral involvement, but these organs are not usually involved initially.
- Hormonal regulation of androgen synthesis is mediated through a series of biochemical interactions between the hypothalamus, pituitary, adrenal glands,and testes (Fig. 1). The testes and the adrenal glands are the major sources of androgens, specifically dihydrotestosterone (DHT). Luteinizing hormone– releasing hormone (LHRH) from the hypothalamus stimulates the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. LH complexes with receptors on the Leydig cell testicular membrane, stimulating the production of testosterone and small amounts of estrogen. FSH acts on testicular Sertoli cells to promote maturation of LH receptors and produce an androgen binding protein.
- Circulating testosterone and estradiol influence the synthesis of LHRH, LH, and FSH by a negative feedback loop at the hypothalamic and pituitary level.

Hormonal regulation of the prostate gland.

ACTH, adrenocorticotropic hormone; DHT, dihydrotestosterone; DNA, deoxyribonucleic acid; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; LHRH, luteinizing hormone–releasing hormone; mRNA, messenger RNA; PROL, prolactin.



CHEMOPREVENTION

The use of 5αreductase inhibitors, finasteride and dutasteride, to prevent prostate cancer has been debated for more than a decade. Based on the concern for the development of more aggressive tumors, lack of survival benefit, and increased risk of adverse drug reactions, these agents are not approved or recommended for preventingprostate cancer.

SCREENING

- Screening recommendations for prostate cancer have changed, and digital rectal examination (DRE) and prostate specific antigen (PSA) are no longer recommended for patients without a discussion with their clinician about risks versus benefits. The American Urologic Association does not recommend routinescreening in biologic males between the ages of 40 and 54 years of average risk but recommends that the risks and benefits of prostate cancer screening are discussed with individuals aged 55–69 years. Biologic males who elect to have screening should do so no more than every 2 years and screening every 5 years may be adequate.
- PSA is a glycoprotein produced and secreted by prostate epithelial cells. Acute urinary retention, acute prostatitis, prostatic ischemia or infarction, and benign prostatic hypertrophy (BPH) increase PSA, thereby limiting the usefulness ofPSA alone for early detection, but it is a useful marker for monitoring response to therapy.

CLINICAL PRESENTATION

- Localized prostate cancer is usually asymptomatic.
- Locally invasive prostate cancer is associated with ureteral dysfunction or impingement, such as alterations in micturition (eg, urinary frequency, hesitancy, and dribbling), and impotence.
- Advanced disease commonly presents with back pain and stiffness due to osseous metastases. Untreated spinal cord lesions can lead to cord compression. Lower extremity edema can occur as a result of lymphatic obstruction. Anemia and weight loss are nonspecific signs of advanced disease.

TREATMENT

Goals of Treatment: In early-stage prostate cancer, the goal is to minimize morbidityand mortality. Early-stage disease may be treated with surgery, radiation, or expectant management; surgery and radiation are curative but also associated withsignificant morbidity and mortality. In advanced prostate cancer, treatment focuses on providing symptom relief and maintaining quality of life.

General Approach

- Initial treatment depends on disease stage, Gleason score, presence of symptoms, and patient's life expectancy.
- Initial treatment modality for advanced prostate cancer is androgen ablation (eg, orchiectomy or LHRH agonists with or without antiandrogens). Patients with metastatic castration resistant prostate cancer (CRPC) should receive best supportive care in addition to other treatments; genetic testing is recommended to help direct therapy.

Nonpharmacologic Therapy

Observation

- Observation involves monitoring the course of disease with laboratory testing and imaging, and starting palliative treatment if the cancer progresses.
- Advantages include avoiding adverse effects of definitive therapies and minimizing risk of unnecessary therapies. The major disadvantage is the risk of cancer progression requiring more intense therapy.

Surgery and Radiation Therapy

- Bilateral orchiectomy rapidly reduces circulating androgens to castrate levels. Many patients are not surgical candidates due to advanced age, and other patients find this procedure psychologically unacceptable. Orchiectomy is the preferred initial treatment for patients with impending spinal cord compression or ureteral obstruction.
- Radical prostatectomy and radiation therapy are potentially curative therapies but are associated with complications that must be weighed against expected benefit.
- Complications of radical prostatectomy include blood loss, stricture formation, incontinence, lymphocele, fistula formation, anesthetic risk, and impotence. Nerve sparing techniques facilitate return of sexual potency after prostatectomy.
- Acute complications of radiation therapy include cystitis, proctitis, hematuria, urinary retention, penoscrotal edema, and impotence. Chronic complications of radiation therapy include proctitis, diarrhea, cystitis, enteritis, impotence, urethral stricture, and incontinence.

Pharmacologic Therapy

➢ ***Drug Treatments of First Choice***

1- Luteinizing Hormone–Releasing Hormone Agonists

- LHRH agonists are a reversible method of androgen ablation and are as effectiveas orchiectomy.
- There are no comparative trials of LHRH agonists, so the choice is usually based on cost and patient and physician preference for a dosing schedule. Leuprolide acetate in different forms and goserelin acetate implant are currently available. Dosing intervals range from once monthly to every 6 months. Testosterone castration levels are achieved in 28 days with leuprolide.
- The most common adverse effects of LHRH agonists include disease flareups during the first week of therapy (eg, increased bone pain or urinary symptoms), hot flashes, erectile impotence, decreased libido, and injection site reactions. Useof an antiandrogen (eg, flutamide, bicalutamide, or nilutamide) prior to initiation ofLHRH therapy and continuing for 2–4 weeks is a strategy to minimize initial tumor flare.
- Decreases in bone mineral density complicate androgen deprivation therapy (ADT), resulting in increased risk of osteoporosis, osteopenia, and skeletal fractures. Calcium and vitamin D supplements and a baseline bone mineral density are recommended. Initiate an antiresorptive agent (eg, alendronate, denosumab, or zoledronic acid) to reduce the risk of skeletal related events.

2- Leutinizing Hormone–Releasing Hormone/Gonadotropin Releasing– Hormone Antagonists (GnRH Antagonists)

- GnRH antagonists degarelix and relugolix bind reversibly to GnRH receptors in the pituitary gland, reducing the production of testosterone to castrate levels in 7 days or less. A major advantage of GnRH antagonists over LHRH agonists is the lack of tumor flare.
- Degarelix is administered as a subcutaneous injection every 28 days. Injection site reactions, Osteoporosis may develop, and calcium and vitamin D supplementation should be considered.
- Relugolix is an oral agent taken daily; adherence is critical for maintenance of testosterone suppression. Hot flashes, hyperglycemia, hypertriglyceridemia, musculoskeletal pain, and fatigue were common toxicities, and providers should use with caution the medications that increase QTC interval, or are inhibitors of cytochrome P450 (CYP) 3A4 or the p-glycoprotein (Pgp) efflux transporter.

3- Antiandrogens

- Monotherapy with first generation antiandrogens flutamide, bicalutamide, and nilutamide is no longer recommended due to decreased efficacy as compared with patients treated with LHRH agonist therapy. Antiandrogens are indicated for advanced prostate cancer only when combined with an LHRH agonist (flutamide and bicalutamide]) or orchiectomy (nilutamide).
- Adverse reactions with first generation antiandrogens include gynecomastia, hot flashes, GI disturbances, decreased libido, LFT abnormalities, and breast tenderness.
- Apalutamide, enzalutamide, and darolutamide are second generation antiandrogens. Enzalutamide may be used in the first line setting to delay the initiation of chemotherapy in nonmetastatic CRPC, as well as metastatic castration naïve and metastatic CRPC. Darolutamide is approved for nonmetastatic CRPC.
- Adverse effects of second-generation antiandrogens include, but are not limited to, fatigue, GI disturbances, musculoskeletal disorders, and seizures.

4- Combined Androgen Blockade

Up to 80% of patients with advanced prostate cancer will respond to initial hormonal manipulation with disease progression seen within 2–4 years. The rationale for combined androgen blockade (CAB) is to interfere with multiple hormonal pathways to completely eliminate androgen action.

5- Alternative Drug Treatments

- Selection of salvage therapy depends on what was used as initial therapy. Radiotherapy can be used after failed radical prostatectomy. ADT can be used after progression of disease following radiation therapy or radical

- Abiraterone an androgen synthesis inhibitor that targets CYP17A1, resulting in decreased circulating levels of testosterone. It is indicated in patients with metastatic castration naïve prostate cancer or metastatic CRPC. Prednisone is prescribed concurrently to mitigate potential adverse reactions due to abirateroneinduced hypoadrenalism (eg, hypertension, hypokalemia, and edema).

6- Chemotherapy

- Docetaxel, combined with prednisone, improves survival in CRPC. The most common adverse events include nausea, alopecia, and myelosuppression.
- Cabazitaxel with prednisone significantly improves progression free and overall survival in patients previously treated with docetaxel and prednisone.

7- Immunotherapy

- SipuleucelTis a novel autologous cellular immunotherapy approved forasymptomatic or minimally symptomatic metastatic CRPC.
- The immune checkpoint inhibitor pembrolizumab inhibits signals that lead to T-cell senescence which increases the immune response to cancer. Fatigue and immunemediated adverse reactions are most commonly seen.

8- Targeted Therapy

- Poly (ADP ribose) polymerase (PARP) inhibitors, including olaparib and rucaparib, can be considered in men with metastatic CRPC who have specific somatic or germline alterations in genes involved in homologous recombination, such as BRCA1 and BRCA2.

9- Nuclear Medicine

- Radium223, an alpha emitter, can be used in first, second-, or third-line therapyin patients with metastatic CRPC with symptomatic primary bone metastases. It has not been approved for use with concomitant abiraterone, second generation antiandrogens, chemotherapy, immunotherapy, or targeted therapy.
- Radium223 improved survival, pain related outcomes, quality of life, anddecreased opioid needs.

The most common adverse effects include nausea, diarrhea, vomiting, peripheral edema, and bone marrow suppression.

EVALUATION OF THERAPEUTIC OUTCOMES

- Monitor primary tumor size, involved lymph nodes, and tumor marker response such as PSA with definitive, curative therapy. PSA level is checked every 6–12 months for the first 5 years, then annually.
- Monitor medication adherence for orally administered treatments.

Adverse effects of chemotherapy

Introduction

- Patients with cancer are at risk for serious adverse events that result from their treatment, the cancer, or both. The management of these complications is generally referred to as supportive care (or symptom management).
- Examples of treatment-related complications include chemotherapy-induced nausea and vomiting (CINV), myelosuppression, febrile neutropenia (FN), hemorrhagic cystitis, mucositis, tumor lysis syndrome (TLS), and immunotherapy-related toxicities.

Nausea and vomiting

- Nausea and vomiting are among the most commonly feared toxicities by patients undergoing chemotherapy treatment.
- The optimal method of managing chemotherapy induced nausea and vomiting (CINV) is to provide adequate pharmacologic prophylaxis given a patient's risk level for emesis. Insufficient control during the first cycle of chemotherapy leads to more difficulty in controlling emesis for subsequent cycles.

Etiology

- The rate of emesis varies depending on individual patient risk factors and drug therapy regimen. Therefore, cancer treatments are stratified into varying risk levels: high, moderate, low, and minimal.
- Agents with a "high" emetic risk cause emesis in more than 90% of cases if not given anyprophylaxis (such as cisplatin). The rates of emesis for "moderate," "low," and "minimal" are 30% to 90%, 10% to 30%, and less than 10%, respectively.

Pathophysiology

- Specific to CINV, the key receptors include serotonin (5-HT3) receptors (located in the chemoreceptor trigger zone, emetic center of the medulla, and gastrointestinal [GI] tract) and neurokinin-1 (NK1) receptors (located in the emetic center of the medulla).
- Serotonin plays an important role in the genesis of acute vomiting because some cancer drug therapies can stimulate a release of serotonin from enterochromaffin cells in the GI tract. Serotonin then activates the emetic response by binding to 5HT3 receptors in the emetic center. This short-lived release of serotonin likely explains why serotonin antagonists are more beneficial for preventing acute versus delayed vomiting.
- Other sites that are targeted by antiemetics include dopamine, muscarinic (acetylcholine),histamine, and cannabinoid receptors.

Etiology and diagnosis of CINV

- Nauseous patients may present with general GI upset and reflux and may report a sensation or desire to vomit without being able to do so.
- In all cases, it is important that other etiologies of nausea and vomiting are ruled out before diagnosing chemotherapy as the cause. Other causes of nausea and vomiting may include bowel obstruction, opioid intolerance, electrolyte imbalances, brain metastases, and vestibular dysfunction.

Clinical presentation (Types of CINV)

- **Acute Nausea/Vomiting**: Occurs within the first 24 hours after chemotherapyadministration
- **Delayed Nausea/Vomiting**: Occurs between 24 hours and 5 days after chemotherapy administration
- **Anticipatory Nausea/Vomiting**: A learned, conditioned reflex response to a stimulus (sight, sound, smell) often associated with poor emetic control in a previous cycle of chemotherapy
- **Breakthrough Nausea/Vomiting**: Occurs despite prophylaxis with an appropriate antiemetic regimen

TREATMENT

Desired Outcomes

- The desired outcome is to completely prevent or minimize the severity of nausea, vomiting, and the use of breakthrough antiemetic medications.

Factors or risks related with patients development of CINV

- **Treatment-related factors** include those chemotherapy agents with high and moderate levels of emetogenicity, dose, and schedule.
- **Patient-related factors** such as female gender, age less than 50, history of motion sickness, pregnancy-induced nausea or vomiting, and poor emetic control in previous chemotherapy cycles increase the risk of emesis.

General approach to treatment of CINV

- For "breakthrough" CINV, it is best to choose a drug with a different mechanism of action compared with the drugs used for prophylaxis.

Nonpharmacologic Therapy

- Nonpharmacologic therapy for CINV can be useful adjuncts to drug therapy, particularly in the setting of anticipatory nausea and vomiting. Behavior therapies such as relaxation, guided imagery, and music therapy as well as acupuncture or acupressure may be useful in this setting.
- Other general measures that can be taken include ensuring adequate sleep before treatment, eating smaller meals, and avoiding spicy and greasy foods and foods with strong odors.

Pharmacologic Therapy

- Four drug classes are highly effective in preventing CINV: corticosteroids (dexamethasone), serotonin receptor antagonists (e.g., Ondansetron, granisetron, palonosetron, and dolasetron), NK1 receptor antagonists (aprepitant, rolapitant or fosaprepitant), and the thienobenzodiazepine, olanzapine.
- Drugs with differing mechanisms of action are combined, depending on the emetic risk level of the chemotherapy regimen.
- Intravenous (IV) antiemetics are usually administered 30 minutes before chemotherapy, and oral antiemetics are administered 60 minutes before chemotherapy.
- Dexamethasone is the preferred agent to prevent CINV in the delayed setting (days 2–4 after chemotherapy administration).
- In some cases, the serotonin antagonists may also be continued orally for 2 to 3 days after chemotherapy or be used in place of dexamethasone (because of dexamethasone side effects).
- **A prophylactic antiemetic regimen for high emetic risk levels of IV chemotherapy** should be with a four-drug combination using dexamethasone, olanzapine, NK1 receptor antagonist, and 5-HT3 antagonist to prevent both acute and delayed emesis. Dexamethasone and olanzapine should be continued until day 4, and aprepitant is also administered on days 2 and 3 if the oral formulation is used.
- **For moderately emetogenic regimens**, acute emesis is still of major concern, but the incidence of delayed emesis is less. Therefore, dexamethasone plus a 5-HT3 antagonist should be given on day

1. On days 2 to 3, choose to continue either the dexamethasone orthe 5-HT3 antagonist

Note: When palonosetron is given as the 5-HT3 antagonist on day 1. no re-dosing is necessary on subsequent days (because of its half-life is long).

- **For low emetic risk IV chemotherapy regimens**, single-agent antiemetic prophylaxis with either dexamethasone or 5HT3 antagonist is recommended 30 minutes before chemotherapy.
- **For breakthrough nausea or vomiting**, the dopamine antagonists prochlorperazine and metoclopramide are usually recommended because they antagonize a different receptor than the drugs already given for prophylaxis.

Outcome Evaluation

- Patients should also be encouraged to self-report symptoms of nausea and vomiting whileat home. Patients should be educated on appropriate usage of antiemetics at home, and side effects of the antiemetic regimen should be routinely assessed and reported.

Mucositis

- Mucositis is the inflammation of the mucosal lining in the oral cavity and GI tract caused by damage from radiation or cytotoxic chemotherapy, often leading to ulcers.
- Stomatitis is a related term that is specific to inflammation in the oral cavity and associated with mammalian target of rapamycin (mTOR) inhibitors, such as everolimus (targeted anticancer agents).

Epidemiology and Etiology

- The incidence of chemotherapy or radiation-induced mucositis depends mostly on the type of chemotherapy, the type and area of radiation, and the specific cancer. Studies have reported an incidence of about 85% in head and neck cancer patients receivingchemoradiation.
- Specific chemotherapy agents associated with moderate–severe mucositis include taxanes, anthracyclines, platinum analogues, methotrexate, and the fluoropyrimidines.

Pathophysiology

- The classical concept of mucositis pathophysiology asserts that direct cytotoxicity from chemotherapy or radiation to basal epithelial cells results in ulcerative lesions caused by alack of regeneration. These lesions are further complicated by trauma or microorganism growth.

Clinical presentation of mucositis

- Painful, erythematous ulcers develop on the lips, cheeks, soft palate, floor of mouth, and throughout the entire gastrointestinal (GI) tract. It may interfere with eating and swallowing
- Symptoms appear within 5 to 7 days after chemotherapy and resolve in 2 to 3 weeks.
- Pain may affect ability to swallow and eat.
- The patient may have concomitant localized or systemic infection.
- Diarrhea is a symptom of mucositis in the lower GI tract; can lead to electrolyteimbalances

TREATMENT

Nonpharmacologic Treatment

- The goal of nonpharmacologic measures to prevent mucositis is to reduce the bacterial load.
- The fundamental approach to lessen the severity of mucositis begins with basic, good oralhygiene (brushing with a soft-bristled toothbrush at least twice daily, flossing, bland rinses, and saliva substitutes) and maintaining optimal nutritional support.
- Cryotherapy with ice chips is also helpful for patients at risk for mucositis who are receiving 5-FU–based chemotherapy.
- Low-level laser therapy is also helpful to prevent mucositis in the hematopoietic cell transplant (HCT) setting.

The goal of therapy

- The goal of therapy is to prevent or decrease the severity and duration of mucositis.

Pharmacologic Treatment

- In the setting of radiation therapy, **Amifostine**, a free radical scavenger is given intrarectal before each dose of radiation therapy for rectal cancer may be considered to prevent GI mucositis.
- **Gelclair, Caphasol, and Biotene** are gels that provide a protective barrier between damaged oral mucosa and the environment, lessening pain and irritation and are also sometimes used as part of the overall treatment of patients with mucositis.
- **Benzydamine** mouthwash is recommended by practice guidelines, antimicrobial mouth washes and lozenges, **sucralfate and chlorhexidine rinses**, and "magic-mouthwash"compounded rinses are not generally recommended by clinical practice guidelines for mucositis prevention even though they are sometimes used in practice.
- **H2 antagonists or omeprazole** orally are recommended to prevent pain associated with mucositis and reflux following offending chemotherapy.
- Pain management may be achieved with oral or intravenous **opioids**, topical anesthetic products, and compounded rinses that incorporate lidocaine. In more severe cases in which infection of the oral mucosa is suspected, appropriate antimicrobial therapy is necessary to prevent systemic infection.
- **Palifermin** is FDA-approved for the **prevention and treatment of mucositis in patients receiving high-dose chemotherapy** as part of stem cell transplant or induction regimens for leukemia. Palifermin is administered as an IV bolus injection for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of six doses.

Outcome Evaluation

- Outcomes measured in clinical trials often assess the incidence, duration, and severity of mucositis with a given intervention intended to prevent or treat mucositis. Agents that areintended to palliate the symptoms of mucositis are usually assessed by measures in pain scales and the ability to eat or drink.

Febrile neutropenia (FN)

- FN is a common adverse effect after administration of cytotoxic chemotherapy. The mortality rate in neutropenic patients caused by infectious complications.
- Mortality can be as low as 2.8% but can exceed 50% mortality depending on resistant bacterial type, effective antimicrobial therapy, and patient Comorbidities. Therefore, FN is considered a true oncologic emergency.
- Patients frequently require hospitalization for prompt administration of broad-spectrum antibiotics that are critical to avoid morbidity and mortality.
- Neutropenia is defined as an absolute neutrophil count (ANC) less than 500/μL cells or an ANC less than 1000/μL cells with a predicted decrease to less than 500/μL cells over the next 48 hours. The ANC is calculated by multiplying the total WBC by the percentage of neutrophils (segmented neutrophils plus "bands").
- Fever is defined as a single oral temperature greater than or equal to 38.3°C (101°F) or a temperature greater than or equal to 38.0°C (100.4°F) for at least 1 hour. The combination of these two factors defines FN.
- The risk of infection during the period of neutropenia depends primarily on two factors:
- The duration of the neutropenia (time period of ANC < 500/μL cells)
- The severity of the neutropenia (lowest ANC level reached [nadir])

Etiology

- Recent data indicate that incidence of gram-positive to gram-negative organisms isolated in bloodstream infections (BSI) in cancer patients were 60% to 40%.
- The causes of this shift from Gram-negative to positive are attributed to the widespread use of central venous catheters and more aggressive chemotherapy regimens as well as the use of prophylactic antibiotics with relatively poor gram-positive coverage (quinolones).
- Fungal infections caused by Candida spp. (especially Candida albicans) have emerged as significant pathogens, especially in patients with hematologic malignancies and those undergoing bone marrow transplantation (BMT). In addition, Aspergillus spp. are important pathogens in patients with prolonged and severe neutropenia

Pathophysiology

- The neutrophils are the primary defense mechanism against bacterial and fungal infection.
- Most infections in neutropenic patients are a result of organisms contained in endogenousflora, both on the skin and within the GI tract. These organisms are provided access to thebloodstream through breakdowns in host defense barriers (mucositis, use of central venous catheters).
- Cancer drug therapy regimens are also categorized as being high risk (> 20% incidence ofFN reported in clinical trials) or intermediate risk (10%–20% risk of FN reported in clinical trials)

Signs and Symptoms

- Fever is typically the only sign of infection, although septic patients may have chills.
- Infected catheter sites may be erythematous and tender to the touch.

Laboratory Tests

- CBC with differential
- Two blood cultures from each access site (peripheral and central), urinalysis, urineculture, chest x-ray, sputum cultures

Risk factors for FN:

1- **Patient factors**
   A- Age ≥ 65years
   B- Bone marrow involvement
   C- Low Hb level or albumin level
   D- Renal or liver insufficiency
   E- Advanced cancer stage
   F- Recent surgery
   G- Persistent neutropenia
2- **Chemotherapy factors**
   A- History of previous chemotherapy
   B- Chemotherapy regimen (dose density)
   C- Treatment intent (curative or palliative)
   D- Incidence of FN in clinical trials

Note: Hospitalization of FN patient depending on MASCC risk-index score of ≥ 21 (patient at low risk for morbidity and complication, then treated as outpatient care) (score < 21 then patient at high risk of morbidity and complications need to be treated as inpatient care).

Prevention

Three primary modalities for preventing infection in patients who are expected to becomeneutropenic

1. Vigilant hand hygiene (the least expensive and simplest)
2. Prophylactic antibiotics (Routine antibacterial prophylaxis is controversial and has been attempted primarily with sulfamethoxazole–trimethoprim (SMZ-TMP) and quinolones. SMZ-TMP offers improved prophylaxis against gram-positive organisms compared with quinolones; quinolones are more effective prophylaxis against gram-negative infections. The use of prophylactic quinolones in patients who are at high risk for infection (ie, hematologic malignancies receiving high-dose chemotherapy for allogeneic stem cell transplant) is reasonable. If prophylactic quinolone use is adopted, changes in local patterns of resistance should be closely monitored.

   Note: SMZ-TMP is recommended for prophylaxis of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonitis (PCP) in all at-risk patients (ie, hematopoietic cell transplant recipients, AIDS, those on long term high dose steroids), regardless of the presence of neutropenia.
3. Colony-stimulating factors (CSFs) (Filgrastim, pegfilgrastim, and sargramostim): stimulate the maturation and differentiation of neutrophil precursors. The prophylactic use of these agents decreases days of hospitalization and use of empiric antibiotics by shortening the duration of severe neutropenia (defined as ANC < 500/µL). The primary limitation of the use of these agents is cost.

Note: Use of biosimilar filgrastim offers significant cost saving over standard filgrastim or pegfilgrastim and would be the most cost-efficient approach to prophylaxis

CSFs are recommended beginning with the first cycle (primary prophylaxis) of chemotherapy when the risk of FN is greater than or equal to 20%, regardless of whether the goal of therapy is curative or palliative. Secondary prophylaxis refers to the subsequent prophylactic use of a CSF after a patient has had an episode of FN. This strategy should be used especially when the chemotherapy is being given in patients with the intention of cure (ie, Hodgkin lymphoma, early breast cancer).

Treatment

Desired Outcomes

- The primary goal is to prevent morbidity and mortality during the neutropenic period. This is accomplished by effectively treating subclinical or established infections.

General Approach to Treatment

- A risk assessment should be performed at presentation of FN to identify low-risk patients for potential outpatient treatment. Patients who do not meet low-risk criteria should be hospitalized for parenteral administration of broad-spectrum antibacterials.
- The choice of initial antimicrobial agent(s) depends on the following factors:
  - Presence of a central venous catheter
  - Drug allergies
  - Concurrent renal dysfunction or use of nephrotoxic agents
  - Use of prophylactic antibiotics
  - Institutional and/or community susceptibility patterns
  - Cost
- The administration of empiric therapy should begin immediately after cultures are taken. Therapy should not be withheld until after culture results are obtained.
- In general, all empiric therapy is continued until recovery of the ANC to levels above 500cells/µL in patients with negative culture result. If a specific etiology is identified, appropriate therapy should generally be continued until 7 days after neutropenia resolves.

Non-pharmacologic Therapy

1. Hand washing is critical in the prevention of disease transmission.
2. It is also important to ensure that patients receive annual influenza vaccines and have hada pneumonia and meningococcal vaccine, and neutropenic patients should avoid individuals with active respiratory infections.
3. Indwelling catheters are often sources of infection; however, the IDSA acknowledges thatcatheters do not always need to be removed. Catheters should be removed in the following circumstances:
   A- established tunnel infection
   B- recurrent infection, or no response to antibiotics within 2 or 3 days.
   Note: Wound debridement should also be performed upon catheter removal.
4. In the setting of peripheral blood stem cell or bone marrow transplant, the Centers for Disease Control and Prevention recommends the use of high efficiency particulate air (HEPA) filtration systems in patient rooms.

Pharmacologic Therapy

- There are two primary choices for the initial management of high-risk FN: monotherapy and dual therapy. Both regimens have been shown to be equivalent; However, monotherapy avoids the nephrotoxicity of the aminoglycosides and is potentially less expensive but lacks significant gram-positive coverage and may increase selection of resistant organisms.
- Dual therapy provides synergistic activity, decreased resistance, and dual coverage of Pseudomonas aeruginosa but also lacks gram-positive coverage and requires therapeutic monitoring for aminoglycosides.
- The choice between monotherapy and dual therapy is usually provider and institution preference, although dual therapy may be preferred in an acutely symptomatic patient (eg, hypotensive) or cases of bacterial resistance.
- Vancomycin adds broad-spectrum gram-positive coverage; however, the increasing emergence of vancomycin-resistant organisms (ie, Enterococcus spp.) prompts conservative use of this medication. Vancomycin should only be included as part of the initial therapy if the following are present:

- Soft tissue infection
- Blood cultures positive for gram-positive bacteria before final identification andsusceptibility testing
- Clinically unstable (eg, hypotension or shock), pending the results of cultures
- Known colonization with penicillin/cephalosporin-resistant pneumococci or MRSA
- Clinically apparent, serious IV catheter-related infection

- Vancomycin may be added to the empiric regimen after 3 to 5 days in persistently febrile patients or if cultures reveal gram-positive organisms. Vancomycin should be changed if the gram-positive organism is susceptible to other anti-bacterials or discontinued inpatients with persistent fever after 3 days with negative culture results.
- Linezolid, quinupristin–dalfopristin, tigecycline, and daptomycin may be used in cases ofvancomycin-resistant organisms or if vancomycin is not an option because of drug allergy or intolerance.
- Empiric antifungal agents are typically added in persistently febrile patients after 5 to 7 days, especially if continued neutropenia is expected. Amphotericin B has historically been the drug of choice because of its broad-spectrum activity against both yeast (Candida spp.) and mold (Aspergillus spp.) infections. However, its usage is limited by its toxicity (nephrotoxicity).
- Liposomal amphotericin B (AmBisome) has been shown to be equivalent to conventionalamphotericin B as empiric therapy, less toxic but is significantly more expensive. Caspofungin is equivalent with less toxicity compared with liposomal amphotericin B. Posaconazole and isavuconazonium sulftate should be considered for invasive, refractory fungal infections or those with intolerance to

amphotericin B formulations.

- The CSFs should not routinely be used for treatment of FN in conjunction with antimicrobial therapy. However, the use of CSFs in certain high-risk patients with hypotension, documented fungal infection, pneumonia, or sepsis is reasonable. Since hospitalization and neutrophil recovery are shortened and infection-related mortality is marginally improved with CSF prophylaxis in high-risk patients.

Outcome Evaluation

- The success of the treatment of FN depends on the adequate recovery of the ANC and either optimal antimicrobial coverage of identified organisms or empiric coverage of unidentified organisms.
- Daily evaluation of response to empiric antimicrobial therapy, in terms of changes in sign and/or symptoms of infection and fever trends
- Monitor the complete blood count (CBC) with differential and Tmax (maximum temperature during previous 24 hours) daily.
- Assess renal and hepatic function at least twice weekly, especially in patients receiving nephrotoxic agents.
- Vital signs should be taken every 4 hours.
- Follow up on blood & urine culture results daily because many cultures do not become positive for several days.
- Assess the patient daily for pain that may indicate an infectious source.
- Conduct daily physical examination of common sites of infection.
- Repeat cultures and chest x-ray in persistently febrile patients and culture developing sources of infection (ie, stool cultures for diarrhea).

Hemorrhagic cystitis

- Hemorrhagic cystitis is defined as acute or insidious bleeding from the lining of the bladder. Although therapy with certain medications is the most common cause, it is also the most preventable. Once it occurs, hemorrhagic cystitis causes significant morbidity and mortality

Etiology

- Alkylating agents (cyclophosphamide and ifosfamide) are most frequently implicated in hemorrhagic cystitis.
- Hemorrhagic cystitis is the dose-limiting toxicity of ifosfamide and cyclophosphamide (specifically for bladder cancer). Chronic, low-dose oral cyclophosphamide as typically used in autoimmune disorders and chronic lymphocytic leukemia is infrequently associated with hemorrhagic cystitis.
- Around 20% patients receiving pelvic irradiation may experience hemorrhagic cystitis, especially with concurrent cyclophosphamide. Notably, this toxicity can present acutely or long after treatment with radiation has ended (up to 15 years). Viral infections commonly associated with this condition most frequently occur in bone marrow transplant recipients who may also receive cyclophosphamide.

Pathophysiology

- Cyclophosphamide- or ifosfamide-induced damage to the bladder wall is primarily caused by their shared metabolite known as acrolein. Acrolein causes sloughing and inflammation of the bladder lining, leading to bleeding and hemorrhage. This is most common when urine output is low because higher concentrations of acrolein come into contact with the bladder urothelium for longer periods of time.
- Radiation treatment directly damages the protective glycosaminoglycan layer of the bladder epithelium.

Prevention

- The use of effective prevention strategies can decrease the incidence of hemorrhagic cystitis to fewer than 5% in patients receiving cyclophosphamide or ifosfamide. Three methods are used to reduce the risk: administration of Mesna (2-mercaptoethane sulfonate), hyperhydration (with normal saline at 3 L/m2/day with IV furosemide to maintain urine output greater than 100 mL/hour), and bladder irrigation with catheterization.

Clinical Presentation and Diagnosis of Hemorrhagic Cystitis

General

- Presentation may be mild (microscopic hematuria) or severe (massive hemorrhage) and develops during or shortly after chemotherapy infusion.
- Presentation may be delayed when associated with pelvic radiation.

Signs and Symptoms

- Suprapubic pain and cramping, urinary urgency and frequency, dysuria and burning, hematuria
- Urinary retention leading to hydronephrosis and renal failure may occur if large blood clots obstruct the ureters or bladder outlet.

Laboratory Tests

- Urine dipsticks for blood
- Urinalysis reveals more than three RBCs per high-power field: microscopic hematuria
- CBC with differential, prothrombin time or international normalized ratio, activated partial thromboplastin time, blood urea nitrogen, creatinine

Treatment

Desired Outcomes

- To decrease exposure to the offending etiology, establish and maintain urine outflow, avoid obstruction and renal compromise, and maintain blood and plasma volume. Restoration of normal bladder function is the ultimate goal following acute treatment.

General Approach to Treatment

- The treatment of hemorrhagic cystitis first involves discontinuation of the offendingagent.
- Agents such as anticoagulants and inhibitors of platelet function should also bediscontinued.
- IV fluids should be aggressively administered to irrigate the bladder.
- Blood and platelet transfusions may be necessary to maintain normal hematologic values.
- Pain should be managed with opioid analgesics.
- Local intravesicular therapies may be necessary if hematuria does not resolve.

Nonpharmacologic Therapy

- A large-diameter, multihole urethral catheter should be inserted to facilitate saline lavage and evacuation of blood clots.
- Surgical removal of blood clots under anesthesia may be required if saline lavage isineffective.

- Active bleeding from isolated areas may be cauterized with an electrode or laser.
- In severe cases that are unresponsive to local or systemic pharmacologic intervention, urinary diversion with percutaneous nephrostomy or surgical removal of the bladder may be required.

Pharmacologic Therapy

- Local (direct instillation into the bladder), one-time administration of hemostatic agentssuch as **alum, prostaglandins, silver nitrate, and formalin** may be used;
- However, general anesthesia is required, especially with formalin, because of pain.
- Aluminum toxicity has been noted with alum irrigation, particularly in children.
- Systemic agents, including estrogens, vasopressin, aminocaproic acid, and hyperbaric oxygen (HBO), may be used in patients who are refractory to local therapy, although theyintroduce the risk of systemic side effects. HBO is particularly useful for radiation- and cyclophosphamide-induced cystitis.
- These agents should be continued until bleeding stops.
- Antispasmodic agents such as oxybutynin 5 mg by mouth two to three times daily may beused for bladder spasms.
- In patients with refractory pain, opioid analgesics should be titrated to adequate pain control. In very severe cases refractory to medical therapy, surgical procedures may be warranted.

Outcome evaluation

- The goal of treatment is resolution of bladder symptoms (pain and hemorrhage) andappropriate pain management.
- Monitor urinary output and serum chemistries (including sodium, potassium, chloride,blood urea nitrogen [BUN], and serum creatinine) daily for renal dysfunction.
- Check the CBC at least daily to monitor hemoglobin and platelet count.