- Primarily eliminated by biliary clearance (30–40%) with up to 30% of the dose excreted in urine.
- Half-life 3–5 h; increased with hepatic dysfunction.

Worry About

- Induces hepatic microsomal (P450, CYP2D6) activity and decreases half-life of hepatically metabolized drugs; this effect may last for several weeks after the drug is discontinued.
- Theoretically increases risk of halothane hepatitis.
- Hemolytic anemia, thrombocytopenia (rare).

Drug Class/Mechanism of Action/Dose

- Semisynthetic derivative of rifamycin B, produced by *Streptomyces mediterranei*.
- Inhibits DNA-dependent RNA polymerase in bacteria and mycobacteria; nuclear eukaryotic RNA polymerase not affected.
- Administered for chemoprophylaxis of meningococcal infections, with beta lactams for staphylococcal endocarditis, osteomyelitis, and methicillin-resistant *Staphylococcus aureus* infections; also used in conjunction with isoniazid and streptomycin for active TB.
- Typical adult and pediatric dose: Tuberculosis—10 mg/kg/d or 10 mg/kg PO twice weekly (max 600 mg); *Neisseria meningiditis*—600 mg q12h for 2 d; *Haemophilus influenzae* Type B prophylaxis—600 mg/d PO/IV for 4 d.
- Possible interaction of rifampin with 5HT3 and opioid system as well as mediators of itching proposed. Dose: 300 mg IV 3 times daily.
- Should be administered PO 1 h before or 2 h after meals.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
GENERAL		Fatigue, drowsiness, dizziness, ataxia, confusion, weakness		
HEENT	Secreted in saliva, tears		Orange sputum, tears, conjunctiva, sweat	
GI	Hepatic dysfunction (rare with normal pre-Rx hepatic function)	N/V	Jaundice	Elevated transaminases
HEME	Thrombocytopenia, hemolytic anemia	Bruising/ bleeding		Plt count, Hgb/Hct, microscopic exam
RENAL	Interstitial nephritis, ATN, renal failure (with high doses)		Orange urine	Cr clearance, light-chain proteinuria

Key References: Wallace R, Philley J, Griffith D: Antimycobacterial agents. In Bennett J, Dolin R, Blaser M, editors: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 8, Philadelphia, PA, 2015, Elsevier, pp 463–478; Stoelting R, Hillier S: Antimicrobials. In Stoelting R, Hillier S, editors: *Pharmacology & physiology in anesthetic practice*, ed 4, Philadelphia, PA, 2006, Lippincott Williams & Wilkins, pp 542–543.

Perioperative Implications/Possible Drug Interactions

Preoperative Concerns

- Decreased duration of action of benzodiazepines, narcotics, barbiturates due to hepatic (P450, CYP2D6) enzyme induction.
- Adequacy of preexisting drug regimens should be verified (see Special Considerations).

Induction/Maintenance

- Decreased narcotic and analgesic efficacy: barbiturates, methadone, diazepam, midazolam; beta-blockers have increased clearance, decreased duration of action.
- Halothane metabolism increases, with increased risk of hepatotoxicity.

Adjuvants/Reversal

- Mycobacteria quickly develop resistance when rifampin is used alone (within 40 h); administer with isoniazid and/or streptomycin.

Special Considerations

- Risk of hepatic dysfunction increased periop due to preexisting hepatic disease and alcohol use.
- Delays oral absorption of ASA.
- Decreases in half-life requiring larger doses to maintain adequate therapeutic levels: Digoxin, digitoxin, quinidine, propranolol, metoprolol, verapamil, coumadin, theophylline, phenytoin, prednisone, cortisol, cyclosporine, oral hypoglycemic agents, ketoconazole, fluconazole
- Can precipitate opioid withdrawal symptoms in an opioid-dependent pt by enhancing the hepatic enzymatic metabolism of opioids.
- May increase metabolism of oral contraceptives and anticoagulants, thus decreasing the effectiveness of these medications.

Anticipated Problems/Concerns

- 10% of pts may develop hepatitis; pts with preexisting liver disease are at higher risk.
- Rifampin induces microsomal enzyme activity in the liver, resulting in decreased efficacy and duration of action of hepatically metabolized drugs; this may last for weeks after the drug is discontinued.

Selective Estrogen Receptor Modulators

Lyndsay M. Hoy | Lee A. Fleisher

Uses

- Critical components in treatment algorithm for invasive and/or in situ breast cancer, breast cancer chemoprevention in high-risk pts, and postmenopausal osteoporosis (raloxifene only)

Perioperative Risks

- VTE, particularly if the pt has a history of recent chemotherapy, prior irradiation, or long-term SERM use
- Microvascular complications following free-flap breast reconstruction surgery

Worry About

- Periop SERM management
- Endometrial cancer (tamoxifen only)
- Unpleasant side effect profile affecting pt quality of life and medication adherence

Overview/Pharmacology

- SERMs inhibit breast tumor growth via competitive antagonism of estrogen; also decrease bone demineralization and improve lipid profile via estrogen agonist properties.
- Shape of ligand binding to ERs is highly influential in determining spectrum of estrogen agonist/antagonist expression in target tissues.
  - SERMs competitively bind to shape-sensitive ligand binding domain on ERs, triggering a complex cascade of molecular networks.
  - SERM-ER complex undergoes conformational dynamic changes to become estrogenic or antiestrogenic, thereby recruiting subsequent cofactors and promoting or degrading specific gene transcription via posttranslational modification of multiple kinase pathways.
  - Differential expression of two ER isoforms (alpha, beta) at target sites with varying levels of ligand affinity, cofactor binding, and estrogen activity may contribute to intrinsic SERM success vs. resistance.

Mechanism of Action/Usual Dose

- Tamoxifen
  - Routinely used for prevention of breast cancer in women at high risk and also as adjuvant endocrine therapy in pts who are ER-positive.
  - Metabolically activated to hydroxylated metabolites with high ER affinity.
  - Long half-life (2 wk).
  - Blocks effects of endogenous estrogen in normal and neoplastic breast tissue; conversely produces estrogen-like effects in uterus, bone, liver, and coagulation system.
  - Adjuvant tamoxifen therapy for 5–10 y may reduce 15-y risk of mortality and local breast cancer recurrence.
  - Administered as a 20-mg pill taken daily.
- Raloxifene
  - Alternative to tamoxifen for women at increased risk of uterine cancer; unlike tamoxifen, lacks estrogen activity in uterus.
  - Estrogen effects on bone/lipids; estrogen antagonist effects on breast/uterus.
  - Only agent currently approved for prevention and treatment of postmenopausal osteoporosis.
  - Short-acting.
  - Administered as 60-mg pill taken daily.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CNS	Vasomotor symptoms (T, R) Stroke (T, R) Cataracts (T)	Hot flashes, night sweats		
CV	Possible cardioprotective effect (T)			
RESP	Pulm embolus (T, R)	Respiratory distress	Tachypnea	CXR, ABG, V/Q scan, spiral CT
ENDO	Decreased cholesterol (T, R)			Lipid panel
HEPAT	Fatty liver (T)			LFTs, hepatic US/CT
GYN	Endometrial hyperplasia (T) Menstrual irregularities (T) Sexual dysfunction (T)	Irregular menstrual cycle Reduced libido, dyspareunia		Uterine US
HEME	Thromboembolic event (T, R)			Coag
ONC	Reduced risk of breast cancer (T, R) Increased risk of endometrial cancer (T)			ER/PR status

R, Raloxifene; *T*, tamoxifen.

Key References: Maximov PY, Lee TM, Jordan VC: The discovery and development of selective estrogen receptor modulators (SERMs) for clinical practice, *Curr Clin Pharmacol* 8(2):135–155, 2013; Mirzabeigi MN, Nelson JA, Fischer JP, et al.: Tamoxifen (selective estrogen-receptor modulators) and aromatase inhibitors as potential perioperative thrombotic risk factors in free flap breast reconstruction, *Plast Reconstr Surg* 135(4):670–679, 2015.

Perioperative Implications

Preoperative Concerns

- Consider discontinuation of SERMs 2–4 wk preop, particularly if surgery is associated with moderate/high risk of VTE.

Adjuvants/Regional Anesthesia/Reversal

- No contraindications/known reactions

Postoperative Period

- Ideal time to restart SERM therapy postop should be considered on individual pt basis in conjunction with surgical and oncologic teams.

Anticipated Problems/Concerns

- SERMs may increase risk of VTE during periop period.
- Correlation between length of periop SERM cessation and oncologic outcome (i.e., altered progression of disease if SERM held for >1 mo) unknown. However, full compliance with SERM therapy clearly associated with reduction in long-term mortality.

Serotonin: Agonists, Antagonists, and Reuptake Inhibitors

David F. Stowe

Uses

- Serotonin (5-hydroxytryptophan [5-HT]) not given as a drug; is a neurotransmitter that plays many roles within the body; serotonin levels can be affected by drugs called serotonin agonists and antagonists
- Partially selective receptor *agonists* used mostly for Rx of acute migraine headaches; they include:
  - Sumatriptan (Imitrex) 5–20 mg IN, 25–100 mg/d PO
  - Naratriptan (Amerge) 2.5 mg/d PO
  - Rizatriptan (Maxalt) 5 mg/d PO
  - Zolmitriptan (Zomig) 5 mg IN, 2.5 mg/d PO
- Partially selective receptor 5-HT_3 *antagonists* used to treat N/V
  - Metoclopramide (Reglan) 5–15 mg qid PO, 2–10 mg IV, 10–20 mg IM (used to treat GERD, gastroparesis, N/V)
  - Dolasetron (Anzemet) 12.5 mg IV or 100 mg PO 30–60 min before emergence to prevent postop N/V or before chemotherapy
  - Ondansetron (Zofran) 4–8 mg tid PO to prevent N/V due to emergence or emetogenic chemotherapy treatment
  - Granisetron (Kytril) 10 µg/kg IV, 1 mg bid PO, TD patch (Sancuso) for prevention of N/V due to chemotherapy and for postop N/V
  - Palonosetron (Aloxi) 0.25 mg IV 30 min before and days after chemotherapy
- SSRIs (all used PO to treat major depression and personality disorders (e.g., OCD, PTSD)
  - Citalopram (Celexa) 20–40 mg/d PO (fewest side effects)
  - Escitalopram (Lexapro) 10 mg/d PO
  - Fluoxetine (Prozac, Sarafem) 20–80 mg/d PO
  - Paroxetine (Paxil, Pexeva) 20–50 mg/d PO
  - Sertraline (Zoloft) 50–200 mg/d PO (least tolerated)

Perioperative Risks

- Sumatriptan, etc: Not for pts with IHD, angina, Prinzmetal angina, severe Htn
- Metoclopramide, etc: Not for pts with pheochromocytoma, long-QT syndrome, or those taking MAOIs or TCA; may worsen mental depression/Parkinson disease; antagonized by narcotics; may cause tardive dyskinesis.
- SSRIs can cause serotonin syndrome (hyperthermia, muscle rigidity, myoclonus, rapid mental change) if given in the presence of MAOIs; may increase coumadin, digitalis effects by reducing plasma protein binding; increased suicide risk in pts <24 y of age.

Worry About

- Sumatriptan and other 5-HT agonists: Pts may have exacerbation of anginal symptoms, experience drowsiness, dizziness, flushing.
- Ondansetron, granisetron, etc: Chemotherapy pts may exhibit increased N/V during anesthesia.
- SSRIs: Serotonin syndrome: Increased threshold for N/V; concomitant use of MAOIs; displacement of other drugs highly bound to plasma protein (digoxin, antianginals, beta-blockers, tricyclic antidepressants); increased bleeding with coumadin, so monitor prothrombin time.

Overview/Pharmacology

- 90% of serotonin is secreted by enterochromaffin cells of GI tract; released into plasma by unclear mechanisms including neuronal stimuli; some taken up, much is stored in plts; 5-HT receptors on vascular endothelium stimulate release of NO to promote vasodilation, but receptors on vascular smooth muscle promote vasoconstriction. Excess release involved in carcinoid syndrome due to enterochromaffin cell neoplasm. As an amine neurotransmitter, serotonin is also secreted, stored, and released by raphe nuclei in brain stem (serotonergic neurons).
- Serotonergic neurons diffusely innervate most regions of CNS; with other neurotransmitters, is involved in modulating mood, depression, sexual function, anxiety, migraine headache, sleep, appetite, temp regulation, perception of pain and itch, regulation of BP.
- Abn in secretion or receptor activation likely underlies mental depression, migraine headache, sensitivity to pain, sleep pattern, and central BP control. In CNS, 5-HT receptor activation increases K^+ conductance to promote membrane hyperpolarization, leading to a mostly inhibitory action. As a CNS neurotransmitter, 5-HT modulates effects of other monoamine transmitters (e.g., norepinephrine, dopamine, other transmitters such as Ach, glycine, and GABA). Inhibition of 5-HT reuptake elevates mood and normalizes behavior.
- Side effects of SSRIs: Sexual dysfunction, weight gain, sleep dysfunction, withdrawal symptoms.