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.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Htn, IHD (agonists)	MAO drug interaction	BP	Drug levels
	Longer P-R and QT_c intervals (antagonists)	Dysrhythmias, bleeding	ECG	INR
	Hypotension (SSRIs)		BP	
	Serotonin syndrome (SSRIs)		BP, CNS	
	Altered drug levels (SSRIs)		Bleeding	
ENDO	Carcinoid syndrome (increased 5-HT)	Diarrhea, abdominal pain, asthma, flushing, increased glucose, dizziness, drowsiness, PAT, SVT		5-HT, kallikreins
HEME	Leukopenia (antagonists)			CBC
CNS	Psychosis, depression, altered mood, seizure disorder	Mental disorder	CNS evaluation	Drug levels

Key References: Lacasse JR, Leo J: Serotonin and depression: a disconnect between the advertisements and the scientific literature, *PLoS Med* 2(12):e392, 2005; Meltzer HY, Massey BW, Horiguchi M: Serotonin receptors as targets for drugs useful to treat psychosis and cognitive impairment in schizophrenia, *Curr Pharm Biotechnol* 13(8):1572–1586, 2012.

Perioperative Implications

- Avoid narcotics in pts with carcinoid syndrome (surgery or 5-HT antagonists usually used to treat carcinoid tumor).
- Use caution in giving metoclopramide; pt must not be taking MAOIs—for example, isocarboxazid (Marplan), phenelzine (Nardil), or tranylcypromine (Parnate).
- Check pt's drug profile for Hx of migraine; increased risk of coronary vasoconstriction with sumatriptan.
- Check pt's drug profile for Hx of schizophrenia; may have low WBC count if taking clozapine.
- If pt is taking an SSRI, lowered threshold for N/V.
- Check pt's drug profile for Hx of major depression; if taking coumadin or digitalis, levels may be increased.

Sildenafil Citrate

John G. Augoustides | Lee A. Fleisher

Uses

- Treatment of erectile dysfunction (Viagra)
- Sildenafil (Revatio) is used to improve the ability to exercise in people with pulm arterial Htn
- Oral sildenafil is used as part of multimodal management of severe periop pulm Htn and right ventricular dysfunction in clinical settings such as:
  - Heart transplantation
  - Pulm Htn associated with CHD
  - Pulm Htn associated with mitral valve disease

Perioperative Risks

- None for elective surgery based on the half-life of sildenafil.
- Drug may still be present in emergent surgery.

Worry About

- Potentiation of vasodilating agents
- Hx of coronary ischemia or congestive heart failure
- Severe hepatic impairment

Overview/Pharmacology

- Sildenafil citrate was discovered by accident during testing as a treatment for heart disease.
- Terminal half-life 4–6 h.
- Total protein binding 96%, also distributed in tissues.
- Bioavailability 41%.
- Metabolized in liver via the cytochrome P450 isoenzymes, 3A4 (major route) and 2C9 (minor route).
- Active *N*-desmethyl metabolite.
- Peak plasma concentration reached in 60 min.
- Excreted via feces (80%), kidney (13%), and semen (<0.001% of a dose).
- Metabolism may be delayed after a high-fat meal and in pts with liver disease.
- Contraindicated in pts with hypersensitivity to sildenafil products and those taking nitroglycerin or other organic nitrates.
- Precautions: Anatomic deformities of the penis, conditions predisposing pts to priapism, bleeding disorders or active peptic ulceration, retinitis pigmentosa or other retinal abn, coronary ischemia or CHF, multidrug antihypertensive regimens.
- Excretion in breast milk is unknown.

Drug Class/Mechanism of Action

- Potent and selective inhibitor of PDE V.
- PDE V isoform is responsible for breaking down cGMP in the corpus cavernosum. cGMP relaxes smooth muscle to cause local vasodilatation and swelling of corpora as they fill with blood.
- With sexual arousal, NO is produced in cavernosal tissue to stimulate the secretion of cGMP.
- Sildenafil inhibits PDE V, causing a 35% increase in cGMP levels.
- Sildenafil inhibits PDE V in the lung, thus increasing cGMP levels in the lung to cause pulm vasodilatation and improvement in pulm Htn.

Usual Dose

- Supplied in 100-, 50-, and 25-mg tablets.
- May be taken 0.5–4 h prior to sexual activity.
- Dose ranges from 25–100 mg, with a maximum frequency of once a d orally.
- Dose adjustments required in pts with severe renal and hepatic impairment.
- For geriatric pts (above 65 y of age), starting dose should be 25 mg.

Assessment Points

System	Effect	Assessment by Hx	PE
HEENT	Activity on PDE VI (PDE VI is important for phototransduction in the retina)	Transient disturbance of blue-green color discrimination	
CV	Dilation of systemic blood vessels	Transient drop in BP, flushing, Hx of nitrate use	Low BP
GI	Relaxation of lower esophageal sphincter	Dyspepsia, diarrhea	
CNS		Headache, dizziness	
RESP	Mucosal vasodilation	Nasal congestion	

Key References: Schwartz BG, Kloner RA: Drug interactions with phosphodiesterase-5 inhibitors for the treatment of erectile dysfunction or pulmonary hypertension, *Circulation* 122(1):88–95, 2010; Vassalos A, Peng E, Young D, et al.: Pre-operative sildenafil and pulmonary endothelial-related complications following cardiopulmonary bypass: a randomised trial in children undergoing cardiac surgery, *Anaesthesia* 66(6):472–480, 2011.