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.

Perioperative Implications

- Risk primarily related to emergent cases based on half-life.
- Caution with the concomitant use of hypotensive agents.
- Precautions to prevent reflux and regurgitation.
- Pts on regular sildenafil for pulm vasodilation will have significant pulm Htn that is often assoc with significant underlying lung disease and right ventricular dysfunction.
- Pts on regular sildenafil for pulm vasodilation may require aggressive periop management of severe pulm Htn to maintain adequate cardiac output. Adequate pulm vasodilation may require periop therapy with IV inodilators such as milrinone and/or inhaled selective pulm vasodilators such as NO or prostacyclin.
- A randomized trial of preop sildenafil did not show reduction in pulm vascular resistance.

Drug Interactions

- Concurrent use of nitrates may cause hypotension.
- Drug interactions with cytochrome P450 inhibitors (e.g., ketoconazole, erythromycin, cimetidine) can be expected; during concomitant therapy a lower dose is suggested.

Statins

Frederic T. Billings IV

Uses

- Incidence in USA: Estimated 20 million
- Primary indications include:
  - Hyperlipidemia: HMG-CoA reductase inhibitors (statins) are powerful drugs for lowering LDL cholesterol concentrations, and certain statins—atorvastatin in high doses and rosuvastatin—increase concentrations of healthy HDL cholesterol.
  - Primary and secondary prevention of CV disease: CV benefits (reduction in myocardial infarction and stroke) in pts with hypercholesterolemia. Benefits also in normocholesterolemic pts with elevated markers of inflammation (e.g., CRP, Jupiter trial).
  - Unproven benefits: Conflicting data on effect of statins to reduce risk of sepsis, thrombotic disease, acute kidney injury following surgery or radiocontrast administration, ARDS, or mortality in ICU patient populations. Recent (2010–2015) multicenter clinical trials testing the impact of statins on these acute illnesses have largely been negative despite prior promising data.

Perioperative Risks

- Myopathy: Incidence among nonoperative chronic statin users is 2–11% for myalgias, 0.5% for myositis, <0.1% for rhabdomyolysis. Incidence increased in severe renal insufficiency (CrCl <30 mL/min). Reversible following statin discontinuation.
- Hepatic dysfunction: Incidence of persistent elevations in aminotransferases is 0.5–3%; it is 0.1% for a 10-fold increase in alanine aminotrasferase. Effect is reversible following statin discontinuation.
- The incidence of myopathy and transaminitis increases when cytochrome P-450 3A4 inhibitors—including cyclosporine, tacrolimus, azole antifungals, fenofibrates, protease inhibitors, and macrolide antibiotics—are used together with statins that are extensively metabolized by cytochrome P-450 3A4 (lovastatin, simvastatin, and to a lesser extent atorvastatin).
- Lipophilic statins may be associated with more adverse events than hydrophilic statins.
- Data do not suggest, however, that periop statin use increases risk of periop myopathy or hepatic dysfunction.

Overview/Pharmacology

- Statins inhibit the reduction of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis. Statins primarily inhibit hepatocyte cholesterol synthesis and increase LDL receptor transcription and hepatic LDL cholesterol uptake. Consequently statins reduce systemic concentrations of LDL cholesterol by 25–55%. Plasma HDL cholesterol levels may rise by 8–10% with atorvastatin and rosuvastatin.
- The reduction in intracellular isoprenoid synthesis, which reduces prenylation of small GTPases (e.g., Rac, Rho), may mediate the beneficial pleiotropic (non-lipid-lowering) effects of statins observed in preclinical studies and small human studies. These effects include stabilization of atherosclerotic plaque, reduction of inflammation, reversal of endothelial dysfunction (through upregulation of eNOS), decreased thrombogenicity, and reduced generation of reactive oxygen species (through inhibition of NADPH-oxidase assembly). These effects are observed within 6–18 h in rodents and cells.
- Statins are orally administered once daily, and peak plasma concentrations are achieved in 1–3 h.
- The hepatic cytochrome P-450 system metabolizes most statins to active and inactive metabolites, and statins are primarily excreted in bile.

Pharmacokinetics

Statin	Dose (mg)	Elimination Half-Life, hr	Protein Binding	Solubility	Cytochrome P-450 Isozyme	Active Metabolites	Renal Excretion, %
Atorva-	10–80	15–30	80–90	Lipophilic	3A4	Yes	2
Fluva–	20–80	0.5–2.3	>99	Lipophilic	2C9	No	<6
Lova–	20–80	2.9	>95	Lipophilic	3A4	Yes	10
Prava–	10–40	1.3–2.8	43–55	Hydrophilic		No	20
Rosuva–	5–40	19	88	Hydrophilic	2C9	No	10
Simva–	10–80	2–3	94–98	Lipophilic	3A4, 3A5	Yes	13

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEPAT	Transaminitis	Asymptomatic	None	LFTs
MS	Myositis	Myalgia, cramps, aches	Muscle tenderness	Creatinine kinase

Key References: Chan WW, Wong GT, Irwin MG: Perioperative statin therapy, *Expert Opin Pharmocother* 14(7):831–842, 2013; Lewicki M, Ng I, Schneider AG: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass. *Cochrane Database Syst Rev* (3):CD010480, 2015.

Perioperative Implications

- Pts with coronary disease or a coronary disease risk equivalent (DM, symptomatic carotid artery disease, peripheral arterial disease, abd aortic aneurysm, chronic kidney disease, or multiple risk factors that confer a 10-y risk of CHD greater than 20%) should receive chronic statin therapy. Therefore pts on statin therapy should be examined preop for coronary and peripheral vascular disease.
- Concern for statin accumulation and muscular and hepatic side effects among pts receiving major surgery led the ACC/AHA/NHLBI to recommend short-term periop discontinuation of statin administration. Periop observational studies, however, have not assoc statin use with an increased risk of myopathy or rhabdomyolysis, and preoperative cessation of statin therapy (withdrawal) was associated with CV harm in some studies of pts undergoing cardiac and major vascular surgery.
- Some randomized trials and large observational studies suggest beneficial pleiotropic effects of statins administered in the periop period. Trials of statin use in critically ill pts have demonstrated no effect on ARDS, pneumonia, or sepsis.
- In the DECREASE III trial, 497 vascular surgery pts were randomly assigned to either 80 mg of extended-release fluvastatin daily or placebo at least 30 d before the procedure and continued for at least 30 d after surgery. The primary endpoint of myocardial ischemia within 30 d of surgery occurred significantly less often in the fluvastatin group (10.8% vs. 19.0%; hazard ratio 0.55, 95% CI 0.34–0.88). The secondary endpoint of the composite of death from CV