- Midazolam:
  - IV: Peak effect in 2–4 min
  - IM: Peak effect in 30–60 min
- Lorazepam:
  - IV: Peak effect in 5–15 min, painful injection, thrombophlebitis
  - IM: Peak effect in 60–90 min
  - Oral: Peak effect in 2 h
- Diazepam:
  - IV: Peak effect in 1–2 min, painful injection, thrombophlebitis
  - IM: Painful, unpredictable absorption, do not use
  - Oral: Peak effect in 30–60 min, well absorbed; food, aluminum-containing antacids delay absorption
- No clear difference in speed of recovery from diazepam and midazolam drug effect after low dose for sedation in short procedures; differentially shorter clinical recovery times for midazolam after larger dose/prolonged administration.
- Lorazepam provides long duration (>4 h) of sedation and amnesia by any route of administration; do not use in benzodiazepine-naïve pts when rapid recovery from drug effect is desired.
- Prolonged use can lead to tolerance.

Drug Class/Mechanism of Action/Usual Dose

- Anxiolytic, sedative, hypnotic, antispasmodic, antiseizure (DEA Schedule IV).
- Potentiation of GABA–mediated neural inhibition (Ca^{2+} outflow leading to cell hyperpolarization).
- Safe use involves careful titration to the desired effect.
- Usual dosage for premedication and moderate (conscious) sedation
  - Midazolam
    - IV: 0.5–1 mg, repeated; maintenance infusion: 0.04–0.10 mg/kg per h
    - IM: 0.07 mg/kg
    - Oral: 15 mg (0.5 mg/kg in children up to 20 kg)
  - Lorazepam
    - IV: 0.25 mg, repeated
    - IM: 0.05 mg/kg, max 4 mg
    - Oral: 0.5–4 mg
  - Diazepam
    - IV: 1–2 mg, repeated
    - Oral: 5–10 mg

Drug Effects

System	Effect	PE	Test
CV	Decreased systemic vascular resistance and cardiac output	Arterial BP	
RESP	Central respiratory depression Apnea	Respiratory rate	Tidal volume Minute volume, capnography, oximetry
CNS	Anxiolysis Sedation Hypnosis Amnesia Anticonvulsant Decreased cerebral metabolic rate and cerebral blood flow	Slurred speech, drowsiness, ataxia Unresponsiveness	

Key References: Griffin CE, Kaye AM, Bueno FR, et al.: Benzodiazepine pharmacology and central nervous system–mediated effects, *Ochsner J* 13(2):214–223, 2013; Vuyk J, Sitsen E, Reekers M: Intravenous anesthetics. In Miller RD, Eriksson LI, Fleisher LA, et al., editors: *Miller's anesthesia*, ed 8. Philadelphia, 2015, Elsevier, pp 821–863.

Perioperative Implications/Possible Drug Interactions

Preoperative Concerns

- Elderly: Reduce dose up to fivefold (5–10% reduction per decade)
- Cimetidine, ranitidine (microsomal cytochrome P450 inhibitors), and liver cirrhosis decrease clearance; enhanced effect may be seen.
- Smoking and enzyme-inducing drugs increase diazepam clearance.
- Renal failure increases half-life of diazepam.
- Monitor ventilation.

Induction/Maintenance

- Synergistic interaction with anesthesia induction agents and opioids.
- In pts reporting intense pain, consider analgesic titration first before titrating anxiolytic.
- Provide education and instruction for postop care prior to administration of benzodiazepine.

Monitoring

- End-tidal CO_2

Airway

- May require support

Extubation

- Consider benzodiazepine reversal with flumazenil (prior to naloxone) after major surgery for intubated pts who are slow to emerge from general anesthesia, have return of spontaneous ventilation at a normal rate, and received benzodiazepine. Caveat: Increase intensity and duration of postop monitoring.

Regional Anesthesia

- May exacerbate respiratory depression during spinal anesthesia (mechanism unknown).

Postoperative Period

- Additional monitoring time and care required if benzodiazepine reversal agent (flumazenil) administered owing to unequal duration of active and reversal agent.
- Provide written postop education/instructions and/or offer prior to first administration of benzodiazepine, as amnestic effect may last several times the elimination half-life.

Anticipated Problems/Concerns

- Combination with opioids or other CNS depressants may result in severe respiratory depression, apnea, and hypotension.
- Large doses result in prolonged drowsiness and respiratory depression, especially in the elderly; reverse with flumazenil.
- Undesirable intensity/duration of amnesia for some pts.
- Amnesia is anterograde (retrograde amnesia can occur after head injury and ECT but not from administration of benzodiazepine).
- May not be safe to reverse with flumazenil in pts receiving chronic benzodiazepine, particularly as part of an antiseizure regimen.

Beta-Adrenergic Receptor Antagonists (Blockers)

Duminda N. Wijeysundera

Uses

- Available PO and IV.
- Prescribed long term for stable angina, systolic CHF, MI (secondary prevention), Htn, and AFIB (for control of heart rate). No longer considered first-line Rx for essential Htn, especially in elderly pts.
- Long-term Rx must be continued periop (Class I ACC/AHA recommendation).
- Risk-benefit balance of periop (prophylactic) beta-blocker Rx is unclear.
- Periop Rx prevents MI after surgery, but increases risks of CVA and hypotension.
- Periop Rx may be reasonable for selected pts with ischemia on cardiac stress testing or three or more risk factors on the Revised Cardiac Risk Index (Class IIb ACC/AHA recommendation).

Perioperative Risks

- Increases risks of hypotension, bradycardia, and CVA. Risks may be further elevated in the presence of anemia, nonselective beta-blockers, or short duration of preop medication (<5 d).
- Periop beta-blockade should be avoided in pts with CVD.
- Contraindicated in pts with asthma. Nonselective beta-blockers may precipitate bronchospasm in COPD with significant reversible airway obstruction.
- May worsen or precipitate CHF in pts with decreased LV function.

Worry About

- May cause hypotension and CVA, especially in the presence of anemia or nonselective beta-blockers.
- May worsen underlying systolic cardiac dysfunction.
- Can precipitate bronchospasm, especially with nonspecific beta-blockers and COPD with known reversible airway obstruction.

Overview/Pharmacology

- Competitive selective antagonists of beta adrenoreceptors. Binding to receptors is reversible.
- Beta-blockers with intrinsic sympathomimetic activity (e.g., acebutolol) are partial agonists of beta adrenoreceptors that activate the receptors to some extent.
- Partial antagonists cause smaller reductions in HR and CO than beta-blockers without intrinsic sympathomimetic activity.
- Some beta-blockers are also antagonists of alpha$_1$-adrenoreceptors (labetalol, carvedilol) or partial agonists of beta$_2$-adrenoreceptors (nebivolol).
- Selectivity for beta$_1$ adrenoreceptors varies among beta-blockers, with the most selective drugs being nebivolol, followed by bisoprolol, atenolol, and metoprolol.

Drug Class/Mechanism of Action/Usual Dose

- Beta-blockers block interfere with ability of catecholamines and other sympathomimetics to activate beta adrenoreceptors on heart and smooth muscle of airways or blood vessels.
- Chronic administration leads to upregulation of beta adrenoreceptors.
- Routes of clearance include hepatic (metoprolol, carvedilol, propranolol), renal (atenolol, acebutolol), mixed renal and hepatic (bisoprolol, nebivolol), or plasma hydrolysis (esmolol).
- Elimination half-life is specific to individual agents and depends on dose, protein binding, and route of administration (oral vs. IV).

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Decreased HR Decreased CO Decreased contractility Increased CVR Decreased myocardial O_2 consumption	Relief of angina Decreased BP Decreased HR	HR BP	ECG; cardiac stress test
RESP	Increased airway resistance (especially nonselective agents)	Increased wheezing Increased bronchospasm		FEV_1; FEV_1/FVC ratio Increased peak airway pressure
ENDO	Hyperglycemia Hypokalemia			Lab measurements of K^+ and glucose
CNS	Fatigue, lethargy, sleep disturbance, peripheral paresthesia			
OB	Beta-blockers cross placenta and can cause fetal bradycardia, hypotension, or hypoglycemia			

Key References: Frishman WH: β-Adrenergic blockade in cardiovascular disease, *J Cardiovasc Pharmacol Ther* 18(4):310–319, 2013; Wijeysundera DN, Duncan D, Nkonde-Price C, et al.: Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, *Circulation* 130(24):2246–2264, 2014.

Perioperative Implications

Preoperative Concerns

- Long-term beta-blocker Rx must be continued periop (Class I ACC/AHA recommendation).
- May be reasonable for selected pts with ischemia on cardiac stress testing or three or more risk factors on the Revised Cardiac Risk Index (Class IIb ACC/AHA recommendation).
- Abrupt withdrawal results in excess SNS activity within 24–48 h and can lead to unstable coronary syndromes.

Induction/Maintenance

- Beta-blockers may potentiate myocardial depression associated with inhaled or IV anesthetics.

Adjuvants/Regional Anesthesia/Reversal

- Bradycardia can often be reversed with atropine, but life-threatening bradycardia may require a temporary pacemaker.
- Catecholamines (e.g., isoproterenol, dobutamine, epinephrine) can help reverse negative cardiac effects, but very high doses are typically needed. $CaCl_2$ (250–1000 mg in adults) or glucagon (1–5 mg in adults) administered IV can also help reverse myocardial depression.
- In severe overdoses where usual Rx has failed, hyperinsulinemic euglycemia (high-dose insulin with concurrent glucose infusion to maintain euglycemia) may help.

Anticipated Problems/Concerns

- Beta-blocker dose may require temporary adjustment after surgery to account for hemodynamic effects of fluid shifts, epidural analgesia, and other medications. Goal is to avoid hypotension.

Bisphosphonates

Silvia Duong | De Q.H. Tran

Uses

- Oral bisphosphonates:
  - Alendronate (Fosamax), risedronate (Actonel): Prevention and treatment of postmenopausal osteoporosis, prevention and treatment of glucocorticoid-induced osteoporosis, treatment of osteoporosis in men, and Paget disease of bone
  - Etidronate (Didronel): Prevention and treatment of postmenopausal osteoporosis and Paget disease of bone
  - Ibandronate (Boniva) administered PO and IV: Prevention and treatment of postmenopausal osteoporosis
- IV bisphosphonates:
  - Pamidronate (Aredia): Treatment of hypercalcemia of malignancy, osteolysis secondary to bone metastases in breast cancer, osteolytic lesions of multiple myeloma, and Paget disease of bone
  - Zoledronic acid (Zometa): Treatment of hypercalcemia of malignancy, osteolysis secondary to bone metastases in breast cancer, and osteolytic lesions of multiple myeloma
  - Zoledronic acid (Reclast): Prevention and treatment of postmenopausal osteoporosis, prevention and treatment of glucocorticoid-induced osteoporosis, treatment of osteoporosis in men, and Paget disease of bone

Perioperative Risks

- Use of bisphosphonates has been associated with osteonecrosis of the jaw (ONJ) in those undergoing dental surgery. The risk of ONJ is higher (1–12%) among cancer pts receiving higher doses of bisphosphonates. The risk is much lower (1:10,000-100,000) among those who are treated with oral bisphosphonate for osteoporosis.

Overview/Pharmacology

- Oral bisphosphonates are poorly absorbed; bioavailability is only 1–5%.
- After binding to bone surfaces and exerting their effects on osteoclasts, bisphosphonates are retained in the bone for months to years (biologic half-life up to 10 y). Bisphosphonates are gradually and slowly released with the process of bone turnover.
- Bisphosphonates are not metabolized.
- Bisphosphonates are excreted primarily by the kidneys; their elimination decreases linearly with decreased renal function. The use of bisphosphonate is not recommended in individuals with CrCl <30 mL/min.

Mechanism of Action

- Bisphosphonates are analogs of pyrophosphate that adsorb to the surface of bone hydroxyapatite. Bisphosphonates reduce the risk of bone fracture by suppressing osteoclastic bone resorption.
- By interfering with osteoclast-mediated bone resorption, bisphosphonates inhibit calcium release and are used in the management of hypercalcemia.