Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Hypotension Tachycardia	Dizziness, headache	BP, HR	
HEENT	Nasal congestion			
RENAL	Volume expansion		Edema	Ionogram: Na/K

Key References: Grimm RH Jr, Flack JM: Alpha 1 adrenoreceptor antagonists, *J Clin Hypertens (Greenwich)* 13(9):654–657, 2011; Oelke M, Gericke A, Michel MC: Cardiovascular and ocular safety of alpha1-adrenoceptor antagonists in the treatment of male lower urinary tract symptoms, *Expert Opin Drug Saf* 13(9):1187–1197, 2014.

Perioperative Implications

Preoperative Preparation
- Unknown effects in pediatric and pregnant pts.
- Continue until surgery.
- Less responsive to $alpha_1$ agonists.

Monitoring
- Routine; invasive BP for pheochromocytoma surgery

Regional Anesthesia
- Potential for exaggerated hypotensive effect with neuraxial anesthesia

Emergence/Extubation
- No known complications to date

Postoperative Period
- Continue to assess volume status and closely monitor BP.

Alpha$_2$ Adrenergic Agonists

Corey Amlong | Robert Sanders

Uses (Off-Label Uses Included)
- Treatment of hypertensive states (clonidine, guanfacine, guanabenz, alpha methyldopa).
- Sedation of mechanically ventilated pts (dexmedetomidine).
- Adjunct agent in general anesthesia (dexmedetomidine, clonidine, tizanidine).
- Sedation for awake intubation and other minor procedures (dexmedetomidine).
- Management of alcohol, nicotine, benzodiazepine, and cocaine withdrawal symptoms via reduction in cardiosympathetic stimulation. Also used for symptom management during naloxone therapy (dexmedetomidine, clonidine).
- Additive in central neuraxial and peripheral nerve blockade with efficacy possibly from systemic spread (dexmedetomidine, clonidine).
- Reduction in intraocular pressure via decreased aqueous humor secretion (brimonidine, apraclonidine).
- Reduction in postop shivering (clonidine, dexmedetomidine)
- Treatment of myofascial pain, spasticity, and rigidity (tizanidine)
- Treatment of ADHD and impulsivity in children and young adults (clonidine, guanfacine).

Perioperative Risks
- Acute Htn after initiation of use mediated by postsynaptic $alpha_{2B}$-mediated vasoconstriction
- Hypotension and bradycardia mediated by central postsynaptic $alpha_{2A}$ decreases in peripheral sympathetic outflow and peripheral presynaptic $alpha_{2A/2C}$ inhibition of NE/EPI release
- CV collapse in hypovolemic states or other pts dependent on sympathetic tone or SVR for maintenance of BP (e.g., trauma pts, aortic stenosis).

Worry About
- Rebound Htn (>24 h after dexmedetomidine infusion) or any interruption of clonidine (especially after 18 h or in pts taking >1.2 mg daily).
- Xerostomia (may be beneficial in awake intubation).
- Increased half time ("context sensitivity") with prolonged infusions of dexmedetomidine: Half-time of 4 min after a 10-min infusion grows to 250 min after an 8-h infusion.

Overview/Pharmacology
- Dexmedetomidine: This imidazole derivative is highly $alpha_2$-specific (1620/1 $alpha_2$/$alpha_1$ activity), with wide-ranging effects. It binds to postsynaptic $alpha_{2A}$ receptors on inhibitory neurons of the CNS (predominantly in the locus ceruleus), resulting in a unique brand of sedation that simulates natural sleep and preserves respiratory drive. Disinhibition and agitation are observed relatively rarely because sedation is unrelated to the GABA receptor. Agonism at presynaptic peripheral sympathetic nerve terminals inhibits NE release. Central $alpha_{2A}$ postsynaptic agonism leads to inhibition of peripheral sympathetic outflow; agonism at $alpha_{2C}$ autoreceptors in the adrenal medulla leads to inhibition as well. The net result is a reduction in arterial tone, venomotor tone, stroke volume, and heart rate.
- Signal transduction occurs via coupling to G-protein effector systems. Activation of Gi leads to decreases in adenylyl cyclase activity (with resultant reductions in protein kinase activity) as well as increases in hyperpolarizing K^+ currents. Decreases in N-type and L-type Ca^{+2} currents are also seen and may in part be coupled to the activation of Go.
- Amnesia is not reliably seen with $alpha_2$ agonists; however, analgesia is a proven benefit and may occur owing to effects at multiple sites. Direct presynaptic and postsynaptic $alpha_2$ agonism in the substantia gelatinosa may diminish substance P and glutamate release (presynaptic heteroreceptor agonism) and directly inhibit second-order neurons (postsynaptic agonism). Thus ascending nociceptive afferent flow is reduced (in a manner that has minimal cross tolerance with opioids). Supraspinal modulation of ascending input may also occur in the CNS itself.
- Clonidine: This imidazole derivative is less specific for $alpha_2$ receptors (220/1 $alpha_2$/$alpha_1$ activity). Effects on the vascular system are more pronounced than those of dexmedetomidine, whereas its sedative effects are less significant. Nonetheless clonidine has been used to reduce anesthetic requirements in people undergoing general anesthesia and has been successful as an additive in central neuraxial and peripheral nerve blockade in both extending the duration and enhancing the quality of sensory neural blockade while avoiding side effects seen with neuraxial opioids used for the same purpose.
- Dexmedetomidine undergoes extensive hepatic metabolism whereas clonidine is approx 50% hepatically metabolized and 50% excreted unchanged in urine.

Drug Class/Mechanism of Action/Usual Dose
- $Alpha_2$ adrenergic agonists have varying specificity for the different $alpha_2$ receptors.
- Dexmedetomidine: This imidazole derivative is given by IV infusion. An ampule of 200 µg/2 mL is diluted in 48 mL saline with resulting concentration 4 µg/mL. A loading dose of 1 µg/kg is given over 10–15 min followed by an infusion of 0.2–0.7 µg/kg per hour. Loading doses may be given over longer periods (20–30 min) in pts undergoing awake FOI so that response and airway patency may be continually evaluated. Cardiovascular side effects are generally rare and dose-dependent. Rates may need to be reduced in infusions over 24 hr as half-life increases markedly with prolonged infusion. Elimination half-life 2–3 h. The drug's effect can be reversed with atipamezole.
- Clonidine: This imidazoline derivative is given in dosages of 100–300 µg orally 1–4 times daily or via a transdermal patch. Its elimination half-life of 6–10 h limits its utility as sedative.
- Tizanidine: This imidazoline derivative is an antispasmodic used in the treatment of cerebral and spinal spasticity. It has also been used as a premedication adjunct to general anesthesia. It is supplied in 2-, 4-, and 6-mg tablets or capsules; dosing regimens vary by indication.
- Guanfacine and guanabenz: These phenylguanidine derivatives have relatively long half-lives (12–24 h and 4–6 h, respectively). They are functional antihypertensives and are rarely utilized currently.
- Alpha methyldopa: This drug is given in divided doses of 1– 2 g daily. It acts via its central $alpha_2$ agonist metabolite alpha methylnorepinephrine and may cause a positive Coombs test or hemolytic anemia. It has a safe historic record for use as an antihypertensive in pregnancy.
- Brimonidine and apraclonidine: These ophthalmologic agents are used topically in the treatment of glaucoma.

Drug Effects

System	Effect	Assessment by Hx	PE	Test
CV	Increased SVR (with initiation) Decreased SVR Decreased inotropy Decreased chronotropy	Headache, palpitations, dizziness, diaphoresis, abdominal pain	Pulse, BP, skin temperature and turgor	ECG PA cath TEE
RESP	Usually minimally reduced Minute ventilation and preserved CO_2 Responsivity		Hypopnea, apnea, cyanosis	Spirometry Pulse oximetry Capnogram
CNS	Sedation Amnesia Analgesia Reduced CBF	Ramsay sedation scale Recall Pain	Somnolence	BIS Blood glucose
OTHER	Xerostomia/antisialagogue Plt aggregation Lipolysis inhibition Insulin secretion inhibition	Dry mouth/nasal decongestion		

Key References: Carollo DS, Nossaman BD, Ramadhyani U: Dexmedetomidine: a review of clinical applications, *Curr Opin Anaesthesiol* 21(4)457–461, 2008; Giovannitti JA Jr, Thoms SM, Crawford JJ: Alpha-2 adrenergic receptor agonists: a review of current clinical applications, *Anesth Prog* 62(1):31–39, 2015.

Perioperative Implications

Preoperative Preparation

- Pts who do not take their dose of clonidine on the morning of surgery commonly develop rebound hypertension. Pts on clonidine often take it for refractory Htn; labile BP should be anticipated. Baroreceptor sensitivity is generally preserved.
- Clonidine has shown some effectiveness for myocardial protection in CV surgery and can be considered in pts who would benefit from but have a contraindication to periop beta blockade.
- When $alpha_2$ agonists are used for sedation during awake FOI, consider adding low-dose (30–70 μg/kg) midazolam if definitive amnesia is desired.
- Concomitant use of inhibitors of cytochrome P450 enzymes (i.e., cimetidine, some fluoroquinolones, verapamil) may lead to increased serum levels of clonidine and tizanidine.

Induction/Maintenance

- Slow, controlled induction is preferred when not contraindicated. Decreases in SVR and inotropy may be exaggerated in pts receiving $alpha_2$ agonists.
- Pts on clonidine and dexmedetomidine can have significant reductions in MAC requirements (30–50% in some studies but wide ranges seen). Titration to hemodynamic variables or BIS may be useful.

Postoperative Period

- Pts already taking clonidine should continue it to avoid rebound Htn.
- Rebound Htn is unlikely with dexmedetomidine infusions of <24 h duration.
- Dexmedetomidine infusion has been used in the immediate postop setting to reduce narcotic requirements in certain populations where narcotic use is undesirable (e.g., morbidly obese).

Anticipated Problems/Concerns

- Treatment of hypotension and dysrhythmias such as symptomatic bradycardia and AV block may become necessary. Treatment of hypotensive bradycardia with anticholinergics alone (esp. in those in whom coronary perfusion is SVR-dependent) may precipitate myocardial ischemia in pts with low SVR (altered supply/demand ratio).

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Amphetamines

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Uses

- Attention deficit hyperactivity disorder
- Weight loss
- Narcolepsy
- Recreational

Perioperative Risks

- Possible increased requirement for volatile anesthetic with acute use
- Possible decreased requirement for volatile anesthetic with chronic use (CNS depression)
- Catecholamine depletion with chronic use
- Increases in temperature with acute intoxication
- Increases in blood pressure and heart rate with acute intoxication
- Altered mentation, dysphoria, and euphoria with acute intoxication
- Acute intoxication can mimic preeclampsia or eclampsia in parturient pt

Worry About

- Severe Htn, palpitations, confusion, dizziness, and vasomotor disturbances especially in pts with ischemic heart disease, Htn, rhabdomyolysis, and hyperthyroidism

Overview/Pharmacology

- Consumed enterally, inhaled (i.e., smoked), snorted, or administered IV
- Psychoactive substance with CNS stimulation and mood-altering properties; several amphetamine derivatives used for illicit purposes (i.e., meth, Ecstasy).
- Consumption of amphetamine-producing plants occurs in some geographical areas (i.e., East Africa).
- Endogenous (i.e., beta-phenethylamine) amines may have amphetamine-like effects
  - Found in trace quantities in the peripheral nervous system and CNS.
  - Metabolized rapidly by monoamine oxidase.
- Elimination half-life ranges between 6–12 h (renal and hepatic clearance); urine alkalization prolongs half-life, so abusers may ingest HCO_3 to prolong half-life.
- Cardiotoxic manifestations include stress cardiomyopathy, MI, and arrhythmias.

Drug Class/Mechanism of Action/Usual Dose

- Amphetamine
- Complicated mechanism of action likely involves
  - Downregulation of monoamine transporters at synaptic cleft
  - Competitive inhibition of monoamine reuptake at synaptic cleft
  - Stimulation of monoamines at nerve terminals
- Dose variable depending on indication