Drug Effects

Class	Name	Abbrev	Special Indication	Adverse Effects
Nitrogen Mustards				
Mechlorethamine	Mustargen	HN_2	LM	N/V, phlebitis, hyperuricemia, potent vesicant
Cyclophosphamide	Cytoxan	CTX	LM, Brt, Bl, Lu, Ov	Decreases pseudo-ChE; myocardial toxicity, hemorrhagic cystitis
Ifosfamide	Ifex		LM, Ov, Te, Sa	Hemorrhagic cystitis, N/V, CNS toxicity, metabolic acidosis
L-Phenylalanine	Alkeran (melphalan)	L-PAM	MM	Mild N/V
Chlorambucil	Leukeran	CLR	CLL, LM	N/V, seizures
Ethyleneamines				
Triethylene-thiophosphoramide	Thiotepa	T-TEPA	BMT	Can lower pseudo-ChE, prolongs succinylcholine action
Alkyl Sulfonates				
Busulfan	Myleran	MYL	CML	Pulm toxicity, N/V, seizures, mucositis, hyperbilirubinemia
Nitrosoureas				
Chloroethyl-cyclohexyl-nitrosourea	Lomustine	CCNU	LM, Brn	N/V, hepatic toxicity, pulm toxicity, renal toxicity
Bis-chloroethyl-nitrosourea	Carmustine	BCNU	LM, Brn	N/V, phlebitis, pulm toxicity
Streptozocin	Zanosar	STZ	Pa	N/V, dose-related renal toxicity
Triazenes				
Dimethyltriazenoimidazole carboxamide	Dacarbazine	DTIC	HD, Sa, Me	N/V, anaphylaxis, phlebitis, hepatotoxicity

Bl, bladder; *BMT*, bone marrow transplant; *Brn*, brain; *Brt*, breast; *CLL*, *CML*, leukemias; *HD*, Hodgkin disease; *LM*, lymphoma; *Lu*, lung; *Me*, melanoma; *MM*, multiple myeloma; *Ov*, ovarian; *Pa*, pancreatic; *Sa*, sarcoma; *Te*, testicular.

Key References: Cytotoxic agents. In Brunton LL, Chabner BA, Knollmann BC *Goodman & Gilman's the pharmacological basis of therapeutics*, ed 12, New York, 2011, McGraw-Hill; Huettemann E, Sakka SG: Anaesthesia and anti-cancer chemotherapeutic drugs. *Curr Opin Anaesthesiol* 18:307–314, 2005.

Perioperative Implications

Preoperative Preparation
- Full-stomach precautions.
- Risk of infection secondary to leukopenia.
- Adequate hydration to prevent additional nephrotoxicity.
- Check CBC due to myelosuppression.
- Consider PFTs (busulfan, cyclophosphamide).
- Consider ECHO or MUGA (if concern for cyclophosphamide-induced pericarditis/myocarditis).

Intraoperative Considerations
- Risk of aspiration during induction.
- Prolonged bleeding.
- Consider RBC transfusion.
- Maintain UO.
- Reduced dose of succinylcholine (CTX, thiotepa).

Postoperative Period
- Risk of N/V (most agents).
- Continued fluid hydration.
- Monitor for cardiac or pulm dysfunction.
- Monitor renal and hepatic function.

Alpha$_1$ Antagonists

Patrick F. Wouters

Uses
- First-line drug treatment for male lower urinary tract symptoms
- Treatment of primary hypertension (not as first-line therapy)
- Preop treatment of pheochromocytoma
- Emerging role in treatment of autonomic dysreflexia
- Occasionally used in treatment of Raynaud phenomenon
- Less commonly used in congenital heart surgery to reduce SVR and correct systemic-to-pulmonary blood flow ratio
- Less commonly used to achieve controlled hypotension intraop
- Being explored as a potential treatment of posttraumatic stress disorder

Perioperative Risks
- Intraop hypotension with attenuated response to the effect of alpha$_1$-agonist therapy
- Intraop floppy iris syndrome: Inhibition of iris dilator muscle contraction and tendency of iris to protrude through surgical incision

Worry About
- Orthostatic hypotension, syncope (less with α_{1A}-selective blockers; more when combined with antihypertensive medication
- Reflex tachycardia (less with selective alpha$_1$ blockers)
- Volume expansion of interstitium and plasma (secondary hyperaldosteronism)
- Priapism, urinary incontinence
- Other adverse events: Asthenia, nasal congestion, headache, dizziness

Overview/Pharmacology
- Also known as α_1-adrenoceptor antagonists (α_1-blockers)
- Mechanism of action: reversible competitive antagonism of postsynaptic alpha$_1$-adrenergic receptors
- Primarily active in tissues that sustain high levels of alpha-adrenergic sympathetic tone (resistance arteries, capacitance veins, urinary bladder outflow tract)
- Effect proportional to baseline sympathetic tone
- Nonselective (alpha$_1$ and alpha$_2$) adrenergic blockers: Phenoxybenzamine (irreversible) and phentolamine
- Selective alpha$_1$-adrenergic blockers: Prazosin (highest affinity), doxazosin, terazosin, silodosin, tamsulosin, bunazosin, alfuzosin
- Mixed alpha$_1$ and beta-adrenergic blocker: Labetalol
- Mixed alpha$_1$-adrenergic and 5-HT1A blocker: Urapidil

Usual Dose
- Treatment of hypertension: Prazosin 1–20 mg 2–3x/d; terazosin 1–20 mg 1–2x/d; doxazosin 1–16 mg 1x/d
- Treatment of benign prostatic hypertrophy: Alfuzosin 5 mg 1–2x/d; silodosin 4–8 mg 1x/d; tamsulosin 0.4 mg 1x/d; terazosin 1–10 mg 1x/d

Toxicity
- Safety unknown during pregnancy; many pass through breast milk
- No safety studies in children

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.