Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Orthostatic hypotension, Htn	Dizziness, vision changes	BP, HR	Orthostatic BP, HR
GI	Hepatotoxicity, constipation	Jaundice		LFTs
CNS	Agitation, seizures			EEG

Key Reference: Tjan J, Malhotra V: *Yao and Artusio's anesthesiology: problem-oriented patient management*, ed 6, Philadelphia, 2008, Lippincott Williams & Wilkins, pp 641–645.

Perioperative Implications

Preoperative Concerns
- Avoid coadministration of MAOIs and SSRIs within 6 wk to avoid serotonin syndrome.
- Check LFTs, because hepatotoxicity and/or hepatic enzyme inhibition may exaggerate depressant effects of opioids, benzodiazepines, barbiturates, antihistamines, and anticholinergics.
- Controversy persists regarding discontinuation prior to elective surgery. Previous recommendations were cessation 2–3 wk prior to surgery, but recent reviews show no increased periop adverse hemodynamic effects.
- Effective anxiolysis to avoid sympathetic hyperactivity.

Induction/Maintenance
- Consider arterial cannula for close monitoring of BP.
- Phenelzine can prolong the duration of succinylcholine by inhibiting pseudocholinesterase.
- Interaction with opioids, particularly phenylpiperidine opioids including meperidine, methadone and tramadol, can lead to serotonin syndrome.
- Fentanyl and fentanyl analogues have also been implicated in other case studies as contributing to the serotonin syndrome.
- Consider regional techniques to avoid opioids; morphine or hydromorphone is preferred if necessary. Make sure that local anesthetic preparations are epinephrine-free.
- N_2O and volatile agents are acceptable.
- Hyperactive response to vasopressors and sympathetic stimulation can occur; direct-acting vasopressors of short duration at a reduced dose are preferred (such as phenylephrine at a reduced dose).
- Avoid drugs that increase sympathetic activity, such as ketamine, pancuronium, cocaine, and epinephrine (in local anesthetics).

Postoperative Period
- Judicious opioid use if needed. Analgesia is important to prevent Htn; use appropriate therapy to avoid serotonin syndrome.
- Use adrenergic alpha or beta antagonists or direct-acting vasodilators for Htn and use short-acting direct alpha agonism at a reduced dose for likely hypotension.
- Discuss timing and dosing of MAOI resumption with psychiatric consultants.

Naltrexone

Chris J. Curatolo

Uses
- Reverse the effects of opioid-agonist overdose (although IV therapy is preferred).
- Prevent relapse in pts (including physicians) addicted to alcohol and/or opioids.
  - Oral route is most common and popular.
  - Newer formulations (e.g., Vivitrol [naltrexone for extended-release injectable suspension]) are once-monthly forms that release the drug over a long period so that pts (1) do not feel the effects of opioids if they try to abuse and (2) cannot stop taking naltrexone during the treatment window.
- Treatment of intrathecal opioid-induced pruritus and nausea.
- Included in the formulation of "tamper-resistant" extended-release opioids (e.g., morphine extended release + sequestered naltrexone) so as to discourage alteration (e.g., crushing) of these long-acting formulations.
- Rapid detoxification of opioid dependence (performed under general anesthesia).

Perioperative Risks
- May precipitate acute opioid withdrawal in pts with chronic opioid use.
- Pts on chronic naltrexone therapy may be more sensitive to dangerous side effects due to receptor upregulation and hypersensitivity.

Worry About
- Pts may be refractory to the effects of opioid agonists.

Overview/Pharmacology
- Antagonist at μ-, δ-, and κ-type opioid receptors (with strongest affinity for μ-receptor)
- Longer-acting ($T_{½}$ 4 h) than its IV counterpart naloxone ($T_{½}$ 0.5–1.5 h, but has an active metabolite, 6-beta-naltrexol, with a $T_{½}$ of 13 h).

Usual Dose
- 50 mg/d oral, with higher doses once tolerated.
- IM injection of 380 mg once monthly for extended-release preparations.
- Toxicity: Generally considered safe without major adverse effects in most pts.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Syncope	Syncopal episodes	Potential markers of trauma from syncopal episodes	None usually indicated
GI	Nausea/vomiting Loss of appetite	Dyspepsia Anorexia	Usually none Weight loss	None usually indicated Weight
HEPAT	Transaminitis (supratherapeutic doses)	Usually no symptoms	Usually none	AST/ALT
MS	Increased CPK activity	Minimal typically, but may include pain	Myalgias or arthralgias	Plasma CPK
ENDO	Augments endogenous release of cortisol and catecholamines	Minimal	Minimal	Plasma cortisol
CNS	Mild dysphoria	Mild depressive symptoms	Minimal	Mood disorder inventory

Key References: Kleber HD: Naltrexone, *J Subst Abuse Treat* 2(2):117–122, 1985; Bryson EO: The perioperative management of patients maintained on medications used to manage opioid addiction, *Curr Opin Anaesthesiol* 27(3):359–364, 2014.

Perioperative Implications

Preoperative Concerns
- Pts on oral naltrexone therapy should discontinue approximately 3–7 d prior to surgery since chronic naltrexone therapy makes it more difficult to control pain.
- Pts on newer, extended-release formulations (such as once-monthly injectable naltrexone) should be at the end of their 30-d dosing window when having elective surgery.
- Pts may have an altered response to opioid agonists and may be entirely refractory to their effects while simultaneously more sensitive to dangerous side effects due to receptor upregulation and hypersensitivity.

Monitoring
- Routine
- If used in the setting of rapid detoxification under general anesthesia, monitor for signs of sympathetic hyperstimulation (e.g., increased catecholamine release and subsequent cardiovascular stimulation).

Regional Anesthesia
- Naltrexone may reduce pruritus and N/V following intrathecal opioid administration, but may also reduce the analgesic duration of the intrathecal opioid.
- RA is the preferred periop analgesic modality in pts on naltrexone therapy who are unable to discontinue prior to surgery.

Emergence/Extubation
- No known complications to date

Postoperative Period
- Increased risk of relapse to alcohol or opioid abuse postop in pts who discontinued chronic naltrexone use prior to surgery.
- Difficult to treat periop pain due to opioid receptor blockade by naltrexone.
- Maximize use of regional anesthesia and nonopioid medications to control pain.

Nicotine Replacement Therapies

Susan M. Lee

Uses
- NRTs are USA FDA-approved devices that are effective in helping treat tobacco dependence, acting on nicotinic acetylcholine receptors to mimic or replace the effects of nicotine, the highly addictive chemical from tobacco products.
- NRTs are available OTC (e.g., gum, transdermal patch, sublingual lozenge/tablet) and by prescription (e.g., nasal spray, inhaler).
- NRTs provide only nicotine; they do not contain the carcinogens and toxic gases that are found in cigarette smoke.

Perioperative Risks
- Pts who smoke cigarettes are at increased risk of periop complications, including respiratory, cardiac, and wound-healing complications. Preop smoking cessation can reduce these risks, particularly when abstinent for at least 3–4 wk before surgery.
- NRT is effective for increasing smoking cessation in both periop and nonperiop settings.
- Nicotine via NRTs is safer than cigarette smoking, since exposure to toxic combustion products is averted. Starting NRT as early as possible preop is advised to increase the duration of preop cessation. There is no evidence that short-term cessation increases complications. Smoking cessation at any time periop may lead to long-term cessation.
- Some preclinical evidence that nicotine in higher doses than produced by NRT decreases viability of skin flaps. However, no human studies have shown increased risk of cardiovascular or wound-healing complications caused by NRT.

Worry About
- During MRI procedures, transdermal nicotine patches that have metallic components can cause cutaneous burns if a pt wears them during the scan.
- Nicotine gum or sublingual lozenges/tablets can cause hiccups, nausea, and heartburn; this could potentially increase aspiration risk for pts undergoing general anesthesia.
- NRTs can cause irritation to the skin or inside of the mouth.
- A fatal nicotine dose for adults is more than 60 mg. Individual cigarettes contain 1–3 mg of nicotine. Serious overdose with standard NRT dosages is unlikely, although concomitant smoking could place the user at risk. Increased skin blood flow with inhalation agents could increase absorption from skin depot or patch.
- Nicotine toxicity manifests as nausea, salivation, abd cramps, vertigo, mental confusion, difficulty breathing, increased heart rate, skeletal muscle weakness, and seizures.
- Nicotine withdrawal can create a negative emotional state, anxiety and irritability, perception of increased stress, difficulty concentrating, increased appetite, headache, and insomnia.

Overview/Pharmacology
- Nicotine from NRTs is absorbed from the skin, the resp tract, or buccal mucous membranes. These methods deliver nicotine to the bloodstream more slowly than smoking.
- Nicotine's half-life is approximately 2 h. It is metabolized primarily by the liver and eliminated by the kidneys and in breast milk. Cotinine, which can be a urinary marker of nicotine exposure, is the principle metabolite.
- Nicotine can cause the induction of liver microsomal enzymes, resulting in faster metabolism of some anesthetics, analgesics, and sedatives.

Drug Class/Mechanism of Action/Usual Dose
- Nicotine is a highly addictive alkaloid. It is a sympathomimetic drug that stimulates autonomic ganglia and acts as a central nicotinic cholinergic agonist, thereby facilitating neurotransmitter release (i.e., dopamine, norepinephrine, serotonin, glutamate, GABA).
- A typical pack-per-day smoker absorbs 20–40 mg/d. The dose of NRTs is variable: transdermal patches (5–22 mg/24 h); gum, lozenges, tablets (1–4 mg each); inhaler (cartridge contains 10 mg); nasal spray (0.5 mg/spray). A typical 8–10 wk course of transdermal NRT for a smoker of >10 cigarettes/d is 21 mg/d patch × 6 wk, 14 mg/d × 2 wk, 7 mg/d × 2 wk. For <10 cigarettes/d: 14 mg/d × 6 wk, 7 mg/d × 2 wk.
- There is evidence that combining a nicotine patch with a rapid delivery form of NRT (e.g. gum, lozenge, inhaler, spray) is more effective than using a single type of NRT.
- Nicotine can have unpredictable effects, initially acting as a stimulant and then as a depressant.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Increased HR, BP, cardiac contractility; coronary and peripheral vasoconstriction	Palpitations, chest pain	Cardiac exam, heart sounds	Vital signs
RESP	Increased ventilation (stim of aortic and carotid body chemoreceptors)	Increased respiratory rate	Respiratory exam, breath sounds	O_2 sat, respiratory rate
GI	Vomiting, diarrhea, heartburn, initial ↑ salivary secretions	Dyspepsia, nausea		
CNS	Stimulation	Initially tremor		
ENDO	Decreased insulin sensitivity; may aggravate or precipitate diabetes			Blood sugar; HbA_{1c}
IMMUNE	May be a tumor promoter through angiogenesis, increased cell proliferation, and decreased apoptosis			

Key References: Stead LF, Perera R, Bullen C, et al.: Nicotine replacement therapy for smoking cessation, *Cochrane Database Syst Rev* 11:CD000146, 2012; Nolan MB, Warner DO: Safety and efficacy of nicotine replacement therapy in the perioperative period: a narrative review, *Mayo Clin Proc* 90(11):1553–1561, 2015.

Perioperative Implications

Preoperative Concerns
- The longer the duration of preop abstinence from smoking, the better.
- Pts may experience anxiety, irritability, increased stress, and/or headache from nicotine withdrawal; consider maintenance of nicotine supplementation via transdermal patch in medically stable pts.
- Behavioral support (brief advice and referral for individual, group, or telephone counseling) should be offered along with NRT to further increase the odds of successful smoking cessation.

Induction/Maintenance
- Pts who are smokers or receiving NRTs may experience resistance to some anesthetic or analgesic agents as a result of increased metabolism from induced hepatic enzymes.
- Nicotine is a sympathomimetic agent and also has effects on autonomic ganglia. Smokers receiving nicotine patches preop have been observed to show exaggerated increases in heart rate after tracheal intubation. NRTs may have hemodynamic effects that may need to be addressed in the periop period.
- While NRTs are safe in medically stable pts, the data are limited for critically ill pts or in pts undergoing