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

cardiopulmonary bypass surgery. NRT has been successfully used in nonoperative pts after acute coronary syndrome.

Postoperative Period

- Smoking contributes to acute physiologic effects such as increased sympathetic tone, lung inflammation, and tissue hypoxia, as well as long-term pathophysiologic changes such as atherosclerosis and COPD, placing these pts at higher risk for postop complications.
- Nicotine withdrawal should be considered as a cause of postop agitation or anxiety.

Anticipated Problems/Concerns

- NRTs have proven to be both safe and effective in treating tobacco dependence in medically stable pts, even in those with smoking-related diseases. NRTs can be valuable tools to manage tobacco dependence in the periop period.
- Use of NRTs in the periop period is far preferable to continued smoking, per most experts in the field.

Acknowledgment

The author wishes to acknowledge the contribution of Dr. Esther Sung to this chapter in the previous edition.

Nitric Oxide, Inhaled

Warren M. Zapol

Uses

- Children: Acute or chronic pulm Htn associated with persistent pulmonary Htn of newborn (PPHN), meconium aspiration, CHD, and congenital diaphragmatic hernia
- Adults: Acute or pulm Htn associated with ARDS, pulm embolism, placement of a LVAD, and cardiac surgery

Perioperative Risks

- Methemoglobinemia (especially breathing >80 ppm NO)
- NO_2 and peroxynitrite formation

Worry About

- Methemoglobinemia; measure metHb, especially in infants, within 6 h and then every 24 h.
- Measure inhaled NO and NO_2 levels continuously.
- Do not give if high NO_2 levels (>2 ppm).
- Do not allow NO to stagnate in ventilator or breathing circuits; it slowly converts to toxic NO_2 gas.
- High inhaled NO levels may inhibit platelet aggregation.
- In severe heart failure, reducing PVR with NO may raise left atrial pressure.
- Rebound pulm Htn during acute NO withdrawal.

Overview/Pharmacology

- Inhaled NO activates guanylate cyclase in lung vessels and airways and increases levels of cGMP, causing selective pulm vasodilation.
- Very rapid and avid binding with RBCs. Hgb inactivates NO and thereby prevents systemic vasodilation.
- NO is metabolized to nitrate and excreted in urine.
- Supplied as stock gas of ≤1000 ppm by volume of NO in nitrogen or other inert gas.
- Inhaled NO is mixed with O_2-containing gas immediately before administration via intratracheal cath, ventilator, mask, or nasal prongs.

Drug Class/Mechanism of Action/Usual Dose

- NO is a free radical with a short $T_{½}$ in aqueous solutions (~17 sec)
- It combines with ferrous-heme ring of guanylate cyclase and thereby stimulates the conversion of GTP to cGMP; cGMP reduces intracellular Ca^{2+}, causing smooth muscle relaxation, and modulates other cell functions by regulating gene expression; cGMP is broken down by phosphodiesterases.
- Usual inhaled NO dose is 1-40 ppm by volume.

Assessment Points

System	Effect	PE	Test
RESP	Decreased PVR		Decreased PAP Increased CO
	Increased gas exchange	Skin color	Increased PaO_2 Increased SaO_2 Decreased $PacO_2$

Key References: Abman SH: Inhaled nitric oxide for the treatment of pulmonary arterial hypertension, *Handb Exp Pharmacol* 218:257–276, 2013; Rossaint R, Lewandowski K, Zapol WM: Our paper 20 years later: inhaled nitric oxide for the acute respiratory distress syndrome—discovery, current understanding, and focused targets of future applications, *Intensive Care Med* 40(11):1649–1658, 2014.

Perioperative Implications

Preoperative Concerns

- Check for heart failure; do not use in severe heart failure (e.g., PCWP >25 mm Hg) or with pulm venous disease (e.g., pulm vein stenosis, pulm venoocclusive disease). Use of inhaled NO in these settings can cause severe pulm edema with hypoxemia and decreased lung compliance. Some pts with mild left heart dysfunction (diastolic dysfunction) may also develop worsening pulm edema with iNO.

Monitoring

- Must monitor: Inhaled NO, NO_2 levels; metHb levels
- Consider monitoring: PA pressure; RV ECHO; ABGs, SpO_2

Induction/Maintenance

- For inhalation, 1–40 ppm in pts with ARDS (usual dose: 5–15 ppm). Initiate therapy with a higher dose (usually 40 ppm) in the setting of ARDS with moderate or severe pulm Htn and lower doses (5–10 ppm) to reduce intrapulmonary shunt (e.g., ARDS).
- In PPHN, begin therapy at 20 ppm and progressively reduce the dose to 5 ppm or less with improved oxygenation (e.g., FiO_2 <0.60) and PAP by ECHO. Inhaled NO therapy should not be initiated without first optimizing lung volume, ventilation, cardiac performance, and systemic BP.
- Ideal doses need better definition, but lower doses are most effective for improving oxygenation by matching ventilation and perfusion and higher doses to treat pulm Htn. Failure to respond in term infants with PPHN may reflect underlying lung developmental abnormality or structural (anatomic) heart disease.
- Give as little NO as possible to reduce oxidant burden of lung.

Adjuvants

- Phosphodiesterase inhibitors (e.g., sildenafil) increase sensitivity and duration of the dilatory effect of inhaled NO but must be used with caution as they can cause systemic hypotension.

Postoperative Period

- Slowly wean from NO over hours if possible watching for abrupt worsening of oxygenation or pulm Htn with the D/C of NO ("rebound" effect).

Anticipated Problems/Concerns

- Beware rapid D/C of iNO; reactive pulm vasoconstriction and hypoxemia leading to RHF may ensue. These effects may not be seen while doses are being reduced but can be dramatic with D/C of iNO therapy and can even occur after D/C low doses of NO.
- Do not allow NO stock tanks to deplete.
- Provide NO freshly mixed in O_2-containing gas for manual ventilation even when briefly disconnecting from ventilator for suctioning or moving pt.
- If iNO does not reverse hypoxemia despite mechanical ventilation with PEEP, high-frequency oscillatory ventilation, and so on, ECMO may be required.