due to the fear of metformin-associated lactic acidosis. It is unproven whether metformin causes the lactic acidosis or whether it is the diabetes that causes it.

Pharmacokinetics/Pharmacodynamics

- Oral bioavailability 50–60%
- Absorbed from the small intestine
- Binding to plasma proteins is negligible
- Not metabolized
- Excreted unchanged in the urine
- Half-life is approx 6 h; however, antihyperglycemic effects last >24 h.

Drug Class/Mechanism of Action/Usual Dose

- Biguanide oral antihyperglycemic agent
- Decreases hepatic glucose production.
- Decreases intestinal absorption of glucose.
- Improves insulin sensitivity by increasing peripheral glucose uptake and utilization.
- Usually dosed 500-1000 mg twice daily.
- Maximum recommended daily dose is 2550 mg.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
ENDO	Hypoglycemia	Use of other oral antihyperglycemic, decreased intake by mouth, alcohol consumption Elderly, debilitated, or malnourished pts, and those with adrenal or pituitary insufficiency more susceptible	Irritability, seizures, bradycardia, hypotension, respiratory failure	Serum glucose (72 mg/dL [4.0 mmol/L])
METAB	Lactic acidosis	Presence of predisposing conditions: Disease states that increase production of lactic acid (CHF, hypoxic states, shock, septicemia) or decrease removal of lactic acid (severe liver disease, alcohol)	Nonspecific Hypotension and respiratory failure have been reported	Serum lactate, serum bicarbonate, ABG, metformin levels
GI	Diarrhea, N/V, flatulence, indigestion, abdominal discomfort			
CNS	Headache			
OTHER	Asthenia, megaloblastic anemia			

Key References: Dhatariya K, Levy N, Flanagan D, et al.; for the Joint British Diabetes Societies: Management of adults with diabetes undergoing surgery and elective procedures: improving standards. Revised March 2016. www.diabetologists-abcd.org.uk/JBDS/Surgical_guidelines_2015_full_FINAL_amended_Mar_2016.pdf (Accessed February 21, 2017); Holstein A, Stumvoll M: Contraindications can damage your health—is metformin a case in point? *Diabetologia* 48(12):2454–2459, 2005.

Perioperative Implications

Perioperative Use of Metformin

- Although the summary of product characteristics states that metformin should be discontinued in the periop period, it is recognized that this strategy will lead either to widespread periop hyperglycemia (with its ensuing complications) or increased use of periop insulin and its ensuing complications. Pragmatic advice from UK suggests that the drug can be continued in the periop period in the absence of preexisting renal dysfunction, prolonged starvation, and periop risk factors for AKI.

Preoperative Concerns

- Renal, hepatic, and cardiac function should be assessed preop.
- Length of starvation should be anticipated preop.
- If there is no appreciable risk of AKI, the surgical time is short, and anticipated resumption of normal eating and drinking is rapid, it may be possible to continue metformin in preassessed pts.
- If metformin is stopped, alternative periop hypoglycemic strategies must be employed.

Postoperative Implications

- Metformin should be withheld in pts at risk of AKI.
- Do not resume metformin until the pt is tolerating an oral diet.
- Alternative strategies for maintaining euglycemia must be utilized if metformin is withheld.

Monoamine Oxidase Inhibitors; Reversible Inhibitors of Monoamine Oxidase

Jacob Addison Thomas | Lee A. Fleisher

Uses

- MAOIs are a broad class of psychoactive medications that affect the metabolism of multiple neurotransmitters.
- MAOIs are indicated for many psychiatric conditions including but not limited to atypical depression, refractory depression, depression with prominent anxiety, low psychomotor activity, and severe phobias.
- Other indications include Parkinson disease, narcolepsy, and intractable headache.

Perioperative Risks

- Risks result from accumulation of physiologically active neurotransmitters because of decreased levels of MAO. Best understood as either serotonergic or catecholic.
- Hypertensive crises arise because of excess levels of tyramine from food or norepinephrine with vasoactive drugs. Manifests as dramatically increased sensitivity to adrenergic drugs, especially indirect-acting catecholamine agonists such as ephedrine.
- Serotonin syndrome (central serotonergic hyperactivity) arises because of impaired metabolism and dramatic increase in concentration of serotonin. In pts on chronic MAOI therapy this concentration rarely rises with administration of anesthetic medications with serotonergic effects including but not limited to fentanyl and methadone.

Worry About

- Side effects of chronic MAOI administration include orthostatic hypotension, agitation, tremor, seizures, muscle spasms, urinary retention, dysuria, paresthesias, hepatotoxicity, jaundice, sedation, vision changes, hallucinations, dryness of the mouth, and constipation.
- Hypertensive crises can occur after ingestion of tyramine-containing substances such as red wine, cheeses, liver, beer, chocolate, fava beans, avocados, and pickled herring. Tyramine causes significant catecholamine release, which can lead to headache, tachycardia, nausea, hypertension, dysrhythmias, and stroke. Similarly, anesthetic medications including ephedrine and norepinephrine can precipitate a tyramine crisis. Adrenergic alpha-antagonists such as phentolamine and prazosin are useful in the treatment of tyramine-induced Htn.
- Serotonin syndrome is a well-described poisoning event described in the literature as a rare but potentially fatal reaction occurring following increased synaptic levels of synaptic serotonin. The syndrome manifests as Htn, hyperthermia, muscle rigidity, and agitation; if untreated, toxicity will progress to respiratory depression, seizures, and coma. Serotonin syndrome can be precipitated by periop or intraop coadministration of serotonin releasing medications.

Overview/Pharmacology

- MAO is an endogenous mitochondrial enzyme that inactivates neurotransmitters by deamination.
- MAOIs block oxidative deamination of naturally occurring amines, which permits neurotransmitter accumulation and increased adrenoreceptor activation.
- The two MAO isoenzymes (types A and B) differ in their substrate selectivities.
- MAO A is selective for serotonin, dopamine, and norepinephrine.
- MAO B is selective for tyramine and phenylethylamine; ineffective as antidepressant.
- Nonselective (irreversible MAO A inhibitors) agents include phenelzine, isocarboxazid, and tranylcypromine.
- Nonselective agents may interfere with many other enzymes.
- Selective agents (reversible MAO A inhibitors) include moclobemide, broforamide, lazabemide, toloxatone, and cimoxatone. Notably, reversible MAO A inhibitors are much less susceptible to drug/diet interactions.
- MAO regeneration after irreversible inhibition usually occurs after several wk.

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).