Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	Hypotension Tachycardia (bradycardia with chronic use) Vasodilation Myocardial depression with higher doses Increased myocardial O_2 demand Increased cerebral blood flow (decreased with chronic use)	Recent exposure Duration and amount of use Use of other recreational drugs Tobacco/alcohol use	Vital signs Injected conjunctiva Reduced oculomotor tracking	Urine toxicology screen
RESP	Coughing Decreased O_2-carrying capacity secondary to CO_2 intake with inhalation Bronchial dilation Increased ventilation (decreased with larger doses) Bronchitis Decreased transport of secretions Squamous metaplasia Emphysema			
CNS	Euphoria/dysphoria Lethargy Impairment of coordination Changes in perception Decreased ability to perform complex thoughts or actions Decreased nausea Dizziness Hallucinations Panic reactions Ataxia/dysarthria Confusion Amnesia Anticonvulsant/proconvulsant Schizophreniform symptoms Poor judgment Increasing cognitive impairment with chronic use Depression			
OPHTH	Decreased IOP Possible rebound increase in IOP with cessation Poor oculomotor tracking			
IMMUNE	Decreased resistance to infection Impairment of macrophages			
GU	Urinary retention			
OB	Preterm labor IUGR VSD in fetus Delay in cognitive development			

Key References: Whiting PF, Wolff RF, Deshpande S, et al.: Cannabinoids for medical use—a systematic review and meta-analysis, *J Am Med Assoc* 313(24):2456–2473, 2015; Kumar RN, Chambers WA, Pertwee RG: Pharmacological actions and therapeutic uses of cannabis and cannabinoids. *Anaesthesia* 56(11):1059–1068, 2001.

Perioperative Implications

Preoperative Concerns

- Chronic use can lead to prolonged intoxication, lasting several days, secondary to storage in adipose tissue and reuptake of active metabolites in the gut.
- Pts may be sedated or have signs and symptoms of bronchitis and asthma.
- Marijuana may increase opioid effects on ventilation.

Induction/Maintenance

- May interact with medications that affect heart rate
- Reduces the MAC and may cause pronounced myocardial depression with potent inhaled anesthetics.
- Anesthesiologists should anticipate interactions with anticholinergics, barbiturates, and depressants.

Postoperative Period

- Increased postop agitation and confusion.
- Motor function and coordination may be reduced for a longer period than anticipated.
- Some pts may experience withdrawal. Signs include restlessness, irritation, agitation, nausea, and cramping.

Anticipated Problems/Concerns

- Increased risk of having respiratory complications during anesthesia.
- Periop agitation.
- Recent use may impair pt's ability to give consent. Chronic use may lead to difficulty following postop instructions.
- Interactions with the effects of chronotropic medications.
- Cannabinoids have prolonged action in older pts and those with liver disease.
- Anesthesiologists should encourage preop discontinuance of the drug for elective cases and consider delaying elective cases with recent use.

Acknowledgment

The authors would like to acknowledge the contributions of Drs. Joshua W. Sappenfield and Christopher T. Stephens to this chapter in the previous edition.

Metformin (Glucophage)

Ketan Dhatariya | Nicholas A. Levy

Uses

- Treatment of type 2 DM, particularly in overweight pts, when dietary management and exercise alone do not result in adequate glycemic control.
- A reduction of diabetic complications has been shown in overweight type 2 diabetic pts treated with metformin as first-line therapy after diet failure.

Side Effects

Very common: Nausea, vomiting, abdominal pain
Common: Taste disturbance
Very rare: Lactic acidosis

Perioperative Risks

- Hypoglycemia (rare)
- Metformin-associated lactic acidosis: The summary of product characteristics states that "Metformin hydrochloride should be discontinued 48 h before elective surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 h following surgery or resumption of oral nutrition and only if normal renal function has been established." This is

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.