

The rank of 293 indicates that based on the Top 300 Prescription Drugs of 2017, epinephrine formulations are relatively uncommon prescription medications. However, it is of note that the true per annum use of epinephrine is far greater, i.e., epinephrine is underrepresented in the database because local anesthetic (LA) formulations containing epinephrine and epinephrine as an emergency drug administered by healthcare providers are not counted in the database.

Most epinephrine formulations are prescribed primary by physicians. Oral healthcare providers administer epinephrine to patients as an adjuvant in local anesthetic formulations as a matter of standard practice in association with perioperative pain management. Furthermore, in rare instances, oral healthcare providers are called upon to administer epinephrine formulations during the course of managing acute severe Type 1 allergic reactions, i.e., anaphylaxis.

When oral healthcare providers are administering epinephrine-containing drug formulations, minimum competency must reflect knowledge in relation to the pharmacology of epinephrine in the following eight areas: (1) drug name (brand/generic), (2) mechanisms of action, (3) drug kinetics, (4) indications for use, (5) dosing, (6) familiarity with potential ADRs and monitoring parameters, (7) contraindications, and (8) the use of reliable informational resources.

[DailyMed](#), a useful online resource, is the official repository for FDA-approved package inserts, i.e., for individual drug-related, clinically

relevant data.³ The posted information is the most recent submitted to the FDA by pharmaceutical companies and includes strengthened warnings undergoing FDA review. The information is accurate; whenever possible it is based on human experience; and does not contain promotional or misleading information such as implied claims.

Epinephrine Formulations in the Top 300

DrugStats uses generic drug synonyms and salts to aggregate all epinephrine formulations.² Predicated on the delivery systems of these formulations, the drugs were prescribed for “self-administration” by patients (or caretakers) in ambulatory settings (Table 1). The majority of epinephrine formulations in the 2014 database were auto-injectors indicated for intramuscular (IM) administration in the emergency treatment of Type I allergic reactions, i.e., anaphylaxis.

Some of the drugs (Bronkaid Mist, Primatene Mist, and Sus-phrine Sulfite Free) were formulated for delivery by metered-dose inhalers (MDIs) intended for the treatment of mild, intermittent asthma and as rescue medication in the treatment of acute asthma. However, in 2012, the FDA began to phase out MDIs with chlorofluorocarbon (CFC)-based propellants, a substance that harms public health and the environment by destroying the ozone in the upper atmosphere.⁴

Epinephrine formulations in MDIs that were available in 2014 for the symptomatic treatment of acute asthma and COPD are no longer available commercially in the United States.⁴ Today, albuterol in MDIs, (a

Table 1. Epinephrine-containing Prescription-formulations in the Top 300 Prescription Drugs of 2017.²

Generic Drug Synonyms and Salts*	Mechanisms of Action	Indications
Epinephrine Epinephrine hydrochloride Epinephrine bitartrate	Alpha (α)- and beta (β)-adrenoceptor agonism	Type I allergic reactions Mild, intermittent asthma Reversible bronchospasm associated with chronic obstructive pulmonary disease (COPD)

*Brand names in the original data (MEPS) included Adrenaclick, Adrenalin, Auvi-q, Bronkaid Mist, Epi E Z Pen Jr, Epi E Z Pen, Epipen Jr., Epipen, Primatene Mist, Sus-phrine Sulfite Free, Twinject 0.15, and Twinject 0.3 - some of these products are no longer marketed or are very infrequently prescribed.

non-catecholamine, orally inhaled, short-acting, strongly β_2 -adrenoceptor-selective agonist) is the cornerstone of treatment of mild, intermittent asthma and as rescue medication in the treatment of acute exacerbations of asthma and COPD.^{5,6}

Physiological Basis of Adrenergic Pharmacology

The nervous system has two major components (Figure 1): the peripheral nervous system (PNS) and the central nervous system (CNS).⁷ Its functions include sensory input, integration of data, and motor output. The PNS is divided into sensory and motor divisions. The sensory division conducts information from the PNS to the CNS. The motor division conducts signals from the CNS to the PNS and is divided into the somatic (SNS) and autonomic nervous systems (ANS).⁷

The autonomic division of the PNS, i.e., the autonomic nervous system (ANS), controls involuntary responses through the coordinated actions of its sympathetic (adrenergic) and

parasympathetic (cholinergic) branches.⁷ The parasympathetic branch of the ANS is responsible for conserving energy by regulating “rest and digest” responses. The sympathetic branch of the ANS mobilizes body systems to provide energy for “fight or flight” responses.

The sympathetic branch of the ANS is the major source of endogenous catecholamines, i.e., dopamine, norepinephrine, and epinephrine.⁸ Norepinephrine is synthesized primarily at sympathetic nerve endings and epinephrine is synthesized primarily in chromaffin cells of the adrenal medulla by sequential modification of tyrosine (Figure 2).⁸ Activation of the sympathetic branch and subsequent release of catecholamine is initiated by signals originating in the CNS.⁸

The conversion of tyrosine to DOPA and of DOPA to dopamine occurs within the cytoplasm of neuronal cells. Dopamine is transported into synaptic vesicles where it is converted to norepinephrine. In adrenal medullary chromaffin

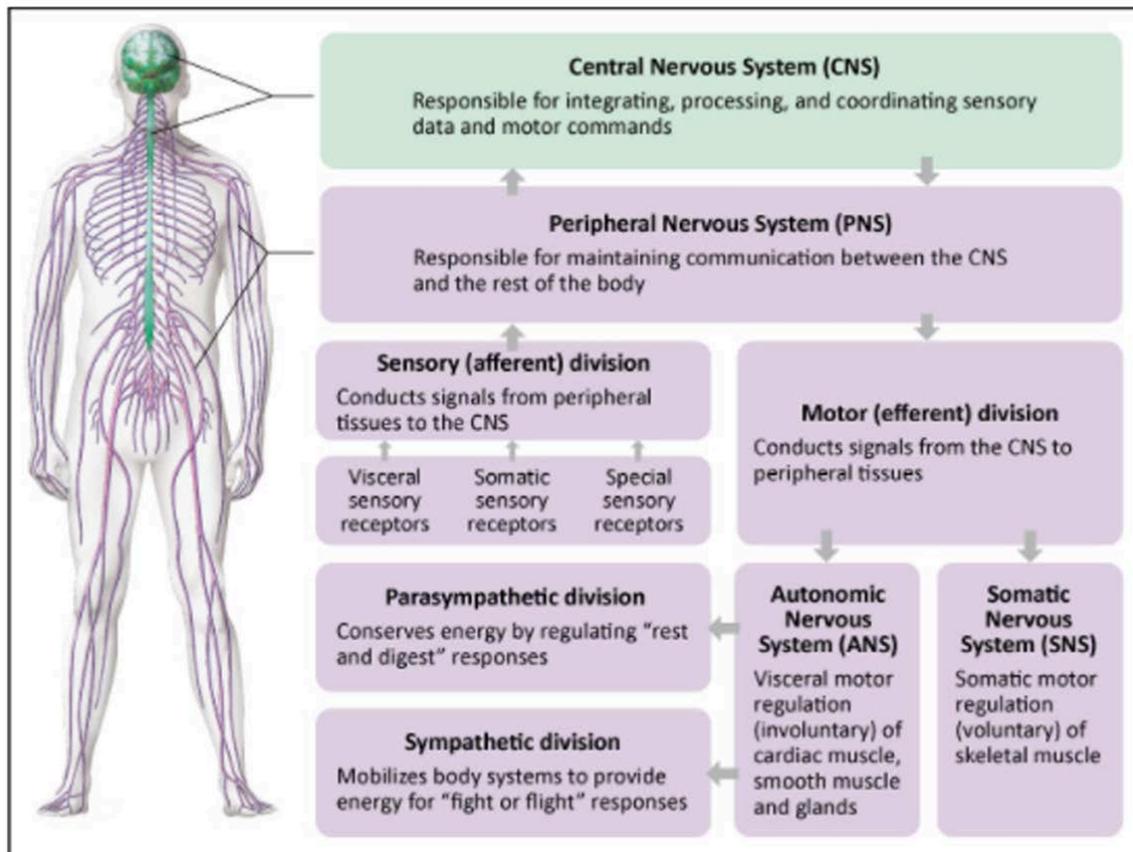


Figure 1. The Nervous System.

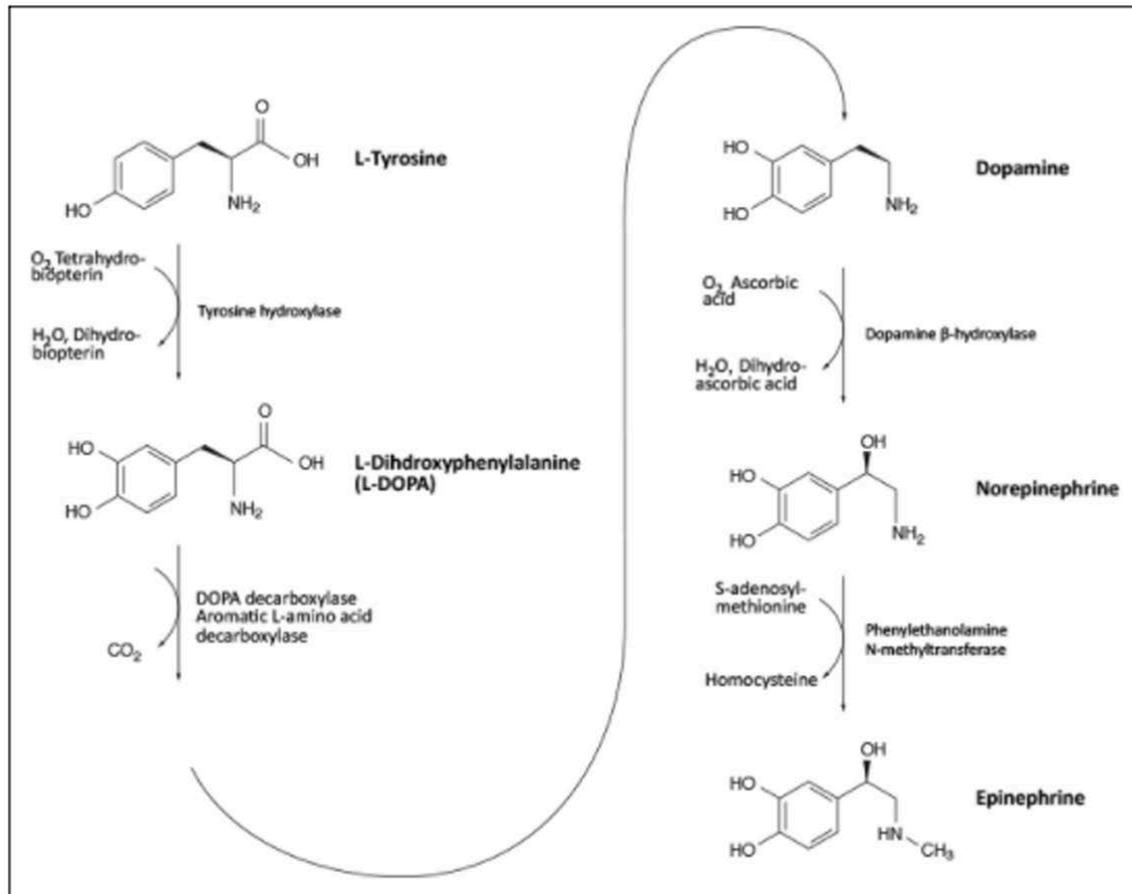


Figure 2. The Synthesis of Catecholamines: Dopamine, Norepinephrine, and Epinephrine.

cells, norepinephrine is transported or diffuses back into the cytoplasm where, under the influence of cortisol, it is converted to epinephrine. Epinephrine is then transported back into vesicles for storage until it is released by exocytosis.

Unlike sympathetic neurons, which synthesize and release norepinephrine at synapses on specific target organs, neuroendocrine (chromaffin) cells of the adrenal medulla synthesize epinephrine and release it directly into the bloodstream to be transported to target organs.⁸ In either case, to produce a biological/physiological effect, both norepinephrine and epinephrine must interact with adrenergic receptors (adrenoceptors), which have an organ-specific distribution.⁷⁻⁹

Adrenoceptors are selective for norepinephrine and epinephrine and are divided into three main classes, each of which has three subtypes; α_1

(α_{1A} , α_{1B} , and α_{1D}), α_2 (α_{2A} , α_{2B} , and α_{2C}), and β (β_1 , β_2 , and β_3).^{8,9} Each of the adrenoceptor subtype is a member of the G protein-coupled receptor family (i.e., transmembrane receptors coupled to intracellular G proteins), so called because they bind guanine nucleotides, i.e., guanosine diphosphate (GDP) and triphosphate (GTP).^{8,9}

G proteins are composed of α - and $\beta\gamma$ -subunits. The binding of an agonist to a G protein-coupled adrenoceptor causes the exchange of GTP for GDP on the α -subunit.^{8,9} The α -GTP subunit dissociates from the $\beta\gamma$ -subunit and interacts with effector proteins such as adenylate cyclase (Figure 3), phospholipase C, ion channels, and other proteins. Depending on the subtype of the adrenoceptor and the G_o isoform, G_o can stimulate or inhibit the activities of target organs.

Major G_o isoforms include: G_{os} (G_o stimulatory isoform), G_{oi} (G_o inhibitory isoform), G_{oq} (generally

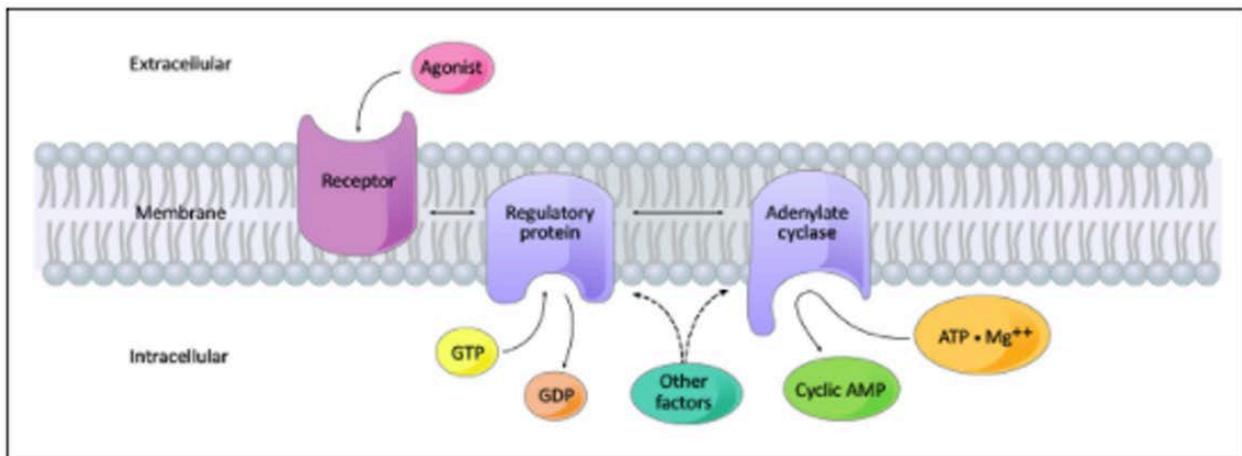


Figure 3. Schematic Representation of Agonist- G_s Regulatory Protein Interaction.

G_a stimulatory isoform), and $G_{\alpha_{12/13}}$ (a G_a isoform that interacts with diverse ion channels).^{8,9} Clearly, adrenoceptor subtypes bound to G_a isoforms activate different signaling pathways and have unique effects on target tissues (Table 2). G protein-mediated signals are terminated by the hydrolysis of GTP to GDP, catalyzed by α -subunit GTPase activity.^{8,9}

Prototypical signaling mechanism of α_1 -adrenoceptors primarily involves G_{α_q} , a stimulatory G_a isoform. G_{α_q} activates phospholipase C and increases intracellular Ca^{2+} ion concentrations.^{8,9} Increased Ca^{2+} ion concentrations activate diverse regulatory proteins that mediate physiological responses in various tissues. Alpha₁-adrenoceptors are expressed primarily in vascular smooth muscle, genitourinary smooth muscle, gastrointestinal smooth muscle, heart, liver, and brain.^{8,9}

Prototypical signaling mechanism of α_2 -adrenoceptors primarily involves G_{α_i} , an inhibitory G_a isoform. G_{α_i} activation includes inhibition of adenylate cyclase that blocks the synthesis cAMP.^{8,9} Blocking cAMP synthesis decreases neuronal Ca^{2+} ion concentrations and neurotransmitter release from target neurons. Alpha₂-adrenoceptors are expressed primarily in pancreatic β -cells, platelets, vascular smooth muscles, and at various sites in the CNS.^{8,9}

Prototypical signaling mechanism of β -adrenoceptors primarily activate G_{α_s} , a stimulatory G_a isoform.^{8,9} G_{α_s} activates adenylate cyclase catalyzing the synthesis

of cAMP. Increased cAMP activates protein kinases affecting a variety of intracellular proteins, including ion channels.^{8,9} Beta₁-adrenoceptors are expressed primarily in the kidney and heart; β_2 -adrenoceptors in smooth muscle, skeletal muscle, liver, and heart; and β_3 -adrenoceptors in adipose tissue.^{8,9}

Pharmacokinetics of Epinephrine

Epinephrine is well absorbed and has rapid onset of action following parenteral administration, e.g., when injected in combination with LAs or when administered IM into the vastus lateralis muscle (i.e., anterolateral aspect of the thigh) using an auto-injector.⁴ Following administration with LAs, epinephrine reaches peak plasma concentrations in 5-10 minutes; when using an auto-injector, it reaches peak plasma concentrations in 8 ± 2 minutes.^{4,10-13}

Epinephrine is distributed to most tissues: it crosses the placenta, it is secreted into milk, but it does not cross the blood-brain barrier.⁴ Epinephrine is rapidly cleared from the extracellular fluid by uptake into sympathetic postganglionic neurons, where it is mainly stored; and by uptake into liver cells, where it is inactivated primarily by catechol-O-methyltransferase and monoamine oxidase and excreted in the urine.⁴ The elimination half-life of epinephrine is ≈ 2 minutes.¹⁴

Therapeutic Use of Epinephrine

The sympathetic nervous system has an organ-specific distribution of adrenoceptor

Table 2. Actions of adrenoceptor and G α signaling mediators.^{8,9}

Adrenoceptor Subtype	Signaling Mediators	Tissue	Effects
α_1	G _{12q} /G _{q1}	Vascular smooth muscle	Contraction
		Genitourinary tract smooth muscle	Contraction
		Gastrointestinal smooth muscle	Relaxation
		Heart	Increases inotropy and chronotropy
		Liver	Glycogenolysis and gluconeogenesis
α_2	G _{o1}	Pancreatic β -cells	Inhibits insulin secretion
		Neurons	Decreases norepinephrine release Feedback inhibition of sympathetic transmission
		Vascular smooth muscle	Contraction
		Platelet	Aggregation
β_1	G _{s1}	Sinoatrial (SA) node	Increases heart rate (chronotropy)
		Atrioventricular (AV) node	Increases conduction velocity
		Cardiac muscle	Increases contraction (inotropy)
		Kidney (juxtaglomerular cells)	Renin release
		Adipose tissue	Increases lipolysis
β_2	G _{12q} /G _{q1}	Bronchial smooth muscle	Relaxes bronchioles
		Skeletal muscle	Glycogenolysis
		Gastrointestinal smooth muscle	Constricts the sphincters Relaxes the gut
		Vascular smooth muscle	Vasodilation
		Uterus	Relaxes uterine wall
		Bladder	Relaxes bladder
		Pancreatic β -cells	Increases insulin release
		Liver	Glycogenolysis and gluconeogenesis
β_3	G _{s1}	Adipose tissue	Increases lipolysis

subtypes and there are many prescription drugs that modulate their activities. For example, β_1 -adrenoceptor antagonists, such as metoprolol, can selectively decrease heart rate and contractility; while β_2 -adrenoceptor agonists, such as albuterol, can selectively dilate bronchioles.^{15,16} Other sympathetic agonists/antagonists are used to treat gastrointestinal and genitourinary problems.¹⁶

Here, further discussion is limited to the therapeutic uses of epinephrine in auto-injectors to treat anaphylaxis and the use of epinephrine and levonordefrine adjuvants in some LA formulations intended to decrease LA's rate of vascular absorption, thereby, localizing and prolonging LA's duration of action and, potentially, reducing LA's systemic toxicity; and, with infiltration anesthesia, to control superficial bleeding from arterioles and capillaries.⁴

Treatment of Anaphylaxis

Epinephrine is the drug of choice for the emergency treatment of Type 1 allergic reactions to stinging and biting insects (e.g., bees, wasps, hornets, yellow jackets, fire ants, mosquitoes, and triatoma); idiopathic or exercise-induced anaphylaxis; foods; immunobiologicals, contrast media, and other drugs; and various other allergens (e.g., latex).^{3,4}

No absolute contraindications exist to the use of epinephrine in the emergency treatment of acute anaphylactic reactions.^{3,4}

It is of note that in 2016, the FDA changed its labeling standards for all single-entity epinephrine preparations such as those used in the treatment of anaphylaxis.⁴ Dosage strengths must now only be expressed in mg/mL. The labeling change was prompted by numerous reports of serious medication errors caused by confusion with ratio expressions (e.g., 1:1000, 1:2000, etc.). Pre-filled, single-use, epinephrine auto-injectors are available in convenient strengths and include:^{3,4}

- EpiPen Jr[®]
 - 0.15 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector (green label – Figure 4)³

- EpiPen[®]
 - 0.3 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector (yellow label – Figure 5)³
- Auvi-Q[®]
 - 0.1 mg/0.1 mL epinephrine injection, USP, pre-filled auto-injector (white and lavender outer case – Figure 6)³
 - 0.15 mg/0.15 mL epinephrine injection, USP, pre-filled auto-injector (blue outer case – Figure 7)³
 - 0.3 mg/0.3 mL epinephrine injection, USP, pre-filled auto-injector (red outer case – Figure 8)³

FDA-approved generic epinephrine injection formulations are also available in pre-filled, single-use, auto-injectors capable of delivering one dose of either 0.15 mg/0.15 mL or 0.3 mg/0.3 mL of epinephrine injection, USP (Figure 9).³ In 2017, the FDA also approved Symjepi[®], a pre-filled, single-use syringe for manual injection containing 0.3 mg/0.3 mL of epinephrine, USP.³

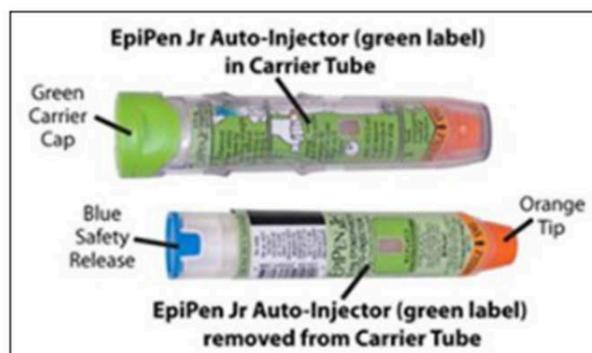


Figure 4. EpiPen Jr[®], 1.5 mg of epinephrine.

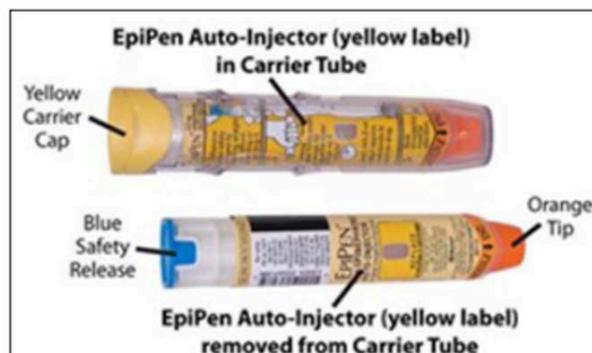


Figure 5. EpiPen[®], 0.3 mg of epinephrine.



Figure 6. Auvi-Q, 0.1 mg of epinephrine.



Figure 7. Auvi-Q, 0.15 mg of epinephrine.



Figure 8. Auvi-Q, 0.3 mg of epinephrine.



Figure 9. Generic epinephrine auto-injectors: 0.15 mg and 0.3 mg.

Some manufacturers of epinephrine auto-injectors supply an auto-injector trainer device (e.g., EpiPen Trainer Device - Figure 10; and AUVI-Q Trainer - Figure 11).³ The devices contain neither a needle nor epinephrine. It is prudent to practice with a trainer to ensure the safe use of the real auto-injector before an emergency occurs. **Reliable information on the use of these trainer devices is available in the FDA-approved package insert of each product.**³

An anaphylactic reaction may occur within minutes after reexposure (previous sensitization is a prerequisite) to a specific allergen and consists of urticaria, pruritus, angioedema (e.g., swelling of the lips, eyelids, and tongue), wheezing, dyspnea, and hypotension.^{4,10,17} Although patients susceptible to anaphylaxis are instructed to always carry their epinephrine auto-injector with them, it should always be available in various fixed-dose formulations in every emergency kit.

The safe and effective use of epinephrine auto-injectors in the treatment of anaphylaxis in oral healthcare setting is predicated on familiarity with FDA-approved, individual drug-related, clinically relevant data and include the following general information:^{3,4}

Step 1 - Select an auto-injector with the appropriate dosage strength predicated on the patient's body weight:

- Patients 7.5 to 15 kg (16.5 to 33 pounds)
 - 0.1 mg; with severe persistent anaphylaxis, repeat injection with an additional dose may be necessary in 15-20 minutes
- Patients 15 to 30 kg (33 to 66 pounds)
 - 0.15 mg; with severe persistent anaphylaxis, repeat injection with an additional dose may be necessary in 15-20 minutes
- Patients ≥30 kg (≥66 pounds)
 - 0.3 mg; with severe persistent anaphylaxis, repeat injection with an additional dose may be necessary in 15-20 minutes



Figure 10. EpiPen Trainer Device.



Figure 11. AUVI-Q Trainer.

Step 2 - Remove the auto-injector from its protective case.

- Check to make sure the expiration date has not passed.
- Confirm that the liquid inside the auto-injector is not discolored (i.e., not pinkish or brownish), cloudy, and is free of particles.

Step 3 - Grasp the auto-injector in the dominant hand, with thumb closest to the safety cap; and, with the other hand, remove the cap.

Step 4 - Hold the patient's leg to keep it steady while injecting.

- Place (jab) the needle end of the auto-injector at right angle against the anterolateral aspect of the thigh.
- The needle is designed to go through clothing.

Step 5 - Press on the auto-injector firmly to release the needle and inject the epinephrine.

- Keep auto-injector in place for ≈5 seconds.
- Do not be alarmed if liquid is left in the auto-injector, the auto-injector is designed to release the proper dose.

Step 6 - Remove the auto-injector and massage the injection site for 10 seconds.

- Some auto-injectors have a needle that retracts back into the case after use.
- If the needle remains exposed, insert the injector (needle first) back into its case.

Step 7 - **Immediately following the administration of epinephrine, the patient must be referred for additional medical care - Call 911.**

- Tell the dispatcher you just administered epinephrine to a patient to treat a suspected anaphylactic reaction.

Step 8 - With severe persistent anaphylaxis a repeat injection of epinephrine, with an additional auto-injector, may be necessary in 15-20 minutes.

- **More than two sequential doses of epinephrine should not be administered without direct medical supervision of the patient.**

Step 9 - Do not discard the auto-injector.

- Identify the site of injection and surrendered the auto-injector to EMS personnel.

ADRs may occur with the administration of therapeutic doses of epinephrine.^{4,10,17} Signs and symptoms, which usually subside rapidly with rest and recumbency, include restlessness, tremor, palpitations, tachycardia, sweating, nausea and vomiting, pallor, headache, dizziness, feelings of panic or anxiety, and respiratory difficulties. These signs and symptoms are more likely to occur in patients with high blood pressure (BP) and those with uncontrolled hyperthyroidism.^{4,10,17}

Overdosage (and even therapeutic doses) of epinephrine may precipitate angina pectoris and/or produce ventricular arrhythmias in patients with heart disease (i.e., cardiac arrhythmias, coronary artery or organic heart disease), high BP, hyperthyroidism, and in patients who are on drugs that may sensitize the heart to the effects of epinephrine.^{3,4,17} While waiting for EMS, prepare to begin cardiopulmonary resuscitation (CPR) and automated external defibrillation.

Epinephrine in Local Anesthetic Agents

The use of local anesthetic agents is standard practice in dentistry. Some of the LA formulations in delivery systems intended for use in oral healthcare settings (i.e., cartridges) include epinephrine or levonordefrin for vasoconstriction.¹⁸⁻²⁰ These adjuvants decrease the rate of LAs' systemic absorption; prolong LAs' duration of action; reduce the risk of LAs' systemic toxicity; and with infiltration anesthesia, they may reduce bleeding in the operative field.¹⁸⁻²⁰

The 2016 change in labeling standards mandated by the FDA for all single-entity epinephrine formulations does not apply to multiple-entity formulations containing epinephrine. However, to minimize medication errors, it may be prudent to think of dosage strengths of epinephrine in LAs in mg/mL rather than ratio expressions (e.g., 1:100,000) as well.⁴ It is of note that mepivacaine and prilocaine have no intrinsic vasodilating effect and are available without a vasoconstrictor.¹⁸

LAs available with vasoconstrictors (Table 3) include 2% lidocaine w/epinephrine 1:100,000 (i.e., 0.01 mg/mL) and w/epinephrine 1:50,000 (i.e., 0.02 mg/mL); 4% prilocaine w/epinephrine 1:200,000 (i.e., 0.005 mg/mL); 4% articaine w/epinephrine 1:100,000 (i.e., 0.01 mg/mL) and w/epinephrine 1:200,000 (i.e., 0.005 mg/mL); 0.5% bupivacaine w/epinephrine 1:200,000 (i.e., 0.005 mg/mL), and 2% mepivacaine w/levonordefrin 1:20,000 (i.e., 0.05 mg/mL).^{3,18-20}

Levonordefrin is a derivative of norepinephrine.²¹ It activates peripheral α_2 -adrenoceptors in vascular smooth muscles and produces vasoconstriction. It also activates α_2 -adrenoceptors in the cardiovascular control

center of the CNS, suppresses sympathetic output from the brain and lowers BP. Levonordefrin, 0.05 mg, is bioequivalent to epinephrine, 0.01 mg. Levonordefrin is less likely than epinephrine to cause cardiac arrhythmias but it may cause reflex bradycardia.

In general, the maximum recommended dose (MRD) of epinephrine in LA formulations for healthy adults is 0.2 mg per visit.¹⁸ Based on this recommendation, the maximum safe dose of 2% lidocaine w/epinephrine 1:100,000 (0.01 mg/mL) is 20 mL and w/epinephrine 1:50,000 (0.02 mg/mL) it is 10 mL. Consequently, with these LA formulations, the MRD of epinephrine (0.2 mg) is reached before the MRD of 2% lidocaine, which is 500 mg or 25 mL of LA (Table 3).³

Mepivacaine 2% is available w/levonordefrin 1:20,000 (0.05 mg/mL). Levonordefrin, 0.05 mg, is bioequivalent to epinephrine, 0.01 mg; consequently, the MRD of levonordefrin is 1 mg. Based on this recommendation, the maximum safe dose of 2% mepivacaine w/levonordefrin 1:20,000 (0.05 mg/mL) is 20 mL. With 2% mepivacaine formulation, the MRD of levonordefrin (1 mg) and the MRD of mepivacaine (400 mg) are both reached with 20mL of LA (Table 3).

Prilocaine 4% is available w/epinephrine 1:200,000. The MRD of epinephrine (0.2 gm) is reached with 40 mL of LA, but based on the MRD of prilocaine (600 mg), the safe dose of 4% prilocaine is 15 mL (Table 3). Articaine 4% is available w/epinephrine 1:100,000 and 1:200,000. The MRD of epinephrine is reached with 20 mL and 40 mL of LA, respectively; however, based on the MRD of articaine (500 mg), the safe dose of 4% articaine is 12.5 mL (Table 3).

Epinephrine has a relatively narrow therapeutic window. Common adverse effects may occur even with the administration of recommended therapeutic doses and include restlessness, agitation, anxiety, tremulousness, headache, dizziness, pallor, palpitation, and tachycardia.^{3,17-20} In patients with Parkinson's disease it may increase tremor and rigidity. Since epinephrine does not cross the blood-brain barrier, these ADRs are the result of peripheral effects.

Table 3. Dosage strengths of local anesthetic agents in mg/mL of LA and epinephrine in mg/mL in LA and maximum safe doses in mL of LA.³

LA Formulations		MRD of LA In mg	LA In mg/mL	500 mg of LA In mL of LA	MRD of EPI In mg	EPI In mg/mL	0.2 mg of EPI in mL of LA
Lidocaine 2%	w/ epinephrine 1:100,000	500	20	25	0.2	0.01	20*
	w/epinephrine 1:50,000	500	20	25	0.2	0.02	10*
Mepivacaine 2%	w/levonordefrin 1:20,000	400	20	20*	1.0	0.05	20*
					(levonordefrin)		
Prilocaine 4%	w/epinephrine 1:200,000	600	40	15*	0.2	0.005	40
Articaine 4%	w/epinephrine 1:100,000	500	40	12.5*	0.2	0.01	20
	w/epinephrine 1:200,000	500	40	12.5*	0.2	0/005	40
Bupivacaine 0.5%	w/epinephrine 1:200,000	90	5	18*	0.2	0.005	40

*Maximum safe dose of LAs in mL per visit predicated on the MRD of LA or MRD of epinephrine (levonordefrin).

Particularly vulnerable populations to the effects of therapeutic doses of epinephrine include the young and the old; those with high BP, severe cardiovascular disease (i.e., unstable angina pectoris, recent myocardial infarction (MI), decompensated heart failure, severe valvular disease, supraventricular arrhythmias with uncontrolled ventricular rate, and symptomatic ventricular arrhythmias); patients with uncontrolled hyperthyroidism; and those taking certain drugs.^{3,17-20}

Epinephrine should be used with caution in patients on other sympathomimetic agents because of additivity.^{4,17-22} Epinephrine should be used with caution in patients on nonselective β -adrenoceptor antagonists, which

block β_2 -adrenoceptor-mediated vasodilation resulting in unopposed α -adrenoceptor-induced vasoconstriction and high BP.^{4,17-22} Epinephrine should be avoided in patients on cocaine, it inhibits the reuptake of epinephrine increasing HR and BP.²²

Epinephrine should be used with caution in patients under the influence of general anesthetics (e.g., halothane and cyclopropane) that sensitize the myocardium to epinephrine causing ventricular arrhythmias (premature ventricular contractions, tachycardia, or fibrillation).^{4,19-22} Levonordefrin should be avoided in patients on tricyclic antidepressants (e.g., amitriptyline) that inhibit the reuptake of norepinephrine increasing HR.^{4,19-22}

Epinephrine should be used with caution in patients with supraphysiological thyroid levels (i.e., thyroid overdose or hyperthyroidism) that upregulate β -adrenoceptors in vascular smooth muscles sensitizing the myocardium to β -adrenergic effects of epinephrine increasing HR and BP.^{4,22} Caution is also recommended when patients are on digoxin and diuretics, which may increase cardiosensitivity and potentiate the arrhythmogenic effects of epinephrine, respectively.⁴

In high-risk populations, the therapeutic benefits of epinephrine must outweigh possible risks and a lower maximum dose of 0.02 to 0.05 mg is recommended.¹⁸ Since the main physiologic stimulus to epinephrine secretion is exercise, to establish the safe dose of epinephrine determine the patient's functional capacity.²³ Functional capacity (FC) reflects a person's functional reserve to meet physiological demand for oxygen and is expressed in metabolic equivalents (METs).

One MET is defined as the FC required of a 70-kg, 40-year-old man at rest, sitting quietly in a chair, to meet metabolic demand for oxygen. Work at 1 MET requires a capacity to deliver 3.5 mL of O_2 /kg/min.²⁴ Work at 2 METs requires twice the resting capacity, the individual must meet metabolic demand for 7 mL of O_2 /kg/min, work at 3 METs requires three times the resting capacity, the individual must meet metabolic demand for 10.5 mL of O_2 /kg/min, etc.

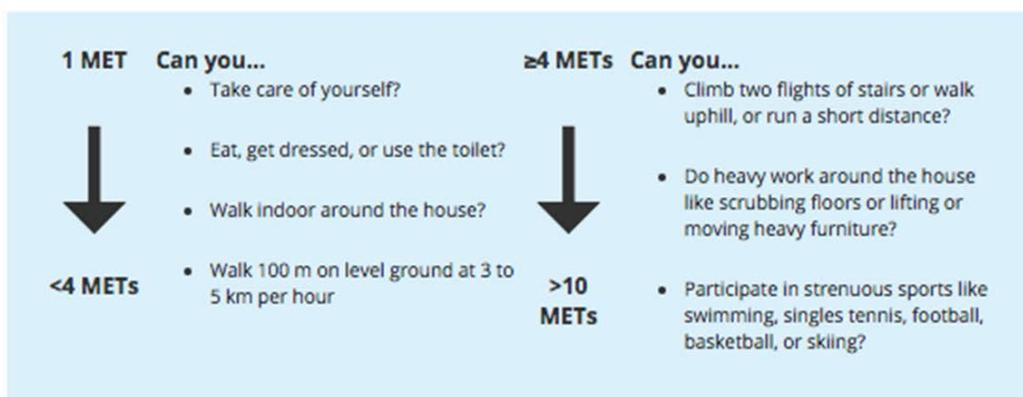
FC is reflected in a person's ability to participate in and complete common daily activities (Box 1).²⁴⁻²⁷ FC is poor if the patient cannot

perform to completion activities requiring ≥ 2 METs. FC is moderate if the patient can perform to completion activities requiring ≥ 2 METs but < 5 METs. FC is good if the patient can perform to completion activities requiring ≥ 5 METs but < 7 METs. FC is excellent if the patient can perform to completion activities requiring > 7 METs.

A FC of < 4 METs is indicative of increased perioperative and long-term cardiac risk.²³ Other clues indicative of increased cardiac risk include the physical findings of tremor, anxiety, cyanosis, pallor, diaphoresis, dyspnea, tightness and/or pain in the chest with minimal activity, and peripheral edema.¹ Critically, the HR (normal: 60 to 100 beats per minute - bpm) and BP (normal: $< 120/80$ mm Hg) of the patient must also be determined as part of risk assessment.¹

The hemodynamic effects (determined by echocardiography) of infiltration anesthesia with 0.045 mg of epinephrine (i.e., 4.5 mL of 2% lidocaine w/epinephrine 1:100,000) in normotensive and hypertensive patients was reported to be less than those produced by ergometric stress testing at 4 METs.²⁸ Consequently, from a mean resting (supine) metabolic state, 0.045 mg of epinephrine produces an approximate 4-fold transient increase in mean plasma epinephrine concentration.

Based on other studies conducted in oral healthcare settings, investigators reported mean resting (supine) plasma epinephrine concentrations of 27 ± 4 pg/mL ($n=11$, mean age 24 ± 3 years) and 28 ± 8 pg/mL ($n=14$, mean age



Box 1. Estimated Energy Requirement for a Spectrum of Common Daily Activities.²⁴⁻²⁷

33±4 years).^{11,12} These mean resting (supine) plasma epinephrine concentrations compare favorably to 34±18 pg/mL (n=60) reported by other investigators, and overlap the lower half of the reported mean resting (supine) range of <10-70 pg/mL.^{29,30}

In one study, a randomized double-blind crossover design, nerve block anesthesia was obtained either with 1.8 mL of 2% lidocaine without epinephrine or w/epinephrine 1:100,000 (0.018 mg) in normotensive patients.¹¹ To determine patient-response to nerve blocks, heart rate (HR), mean arterial pressure (MAP), plasma epinephrine and norepinephrine concentrations were quantified at two baselines (-30 and -20 minutes) and at 1, 2, 4, 8, 16, 30, and 60 minutes post-injection.

Lidocaine alone did not alter plasma catecholamine levels, HR, or MAP over the study period. Lidocaine with 0.018 mg of epinephrine resulted in ≈3.5-fold transient elevation of mean plasma epinephrine values from 27±4 pg/mL (baseline) to peak plasma levels of 94±13 pg/mL at 8 minutes post-injection. HR increased by a few beats, but MAP and norepinephrine values were unaffected. Clearly, the transient rise in epinephrine levels was due to the epinephrine in the LA.

In the other study, nerve block anesthesia with 1.8 mL of 2% lidocaine w/epinephrine 1:100,000 (0.018 mg) was obtained in normotensive patients requiring class II amalgam restoration of posterior teeth.¹² HR, MAP, and plasma epinephrine and norepinephrine concentrations were determined at 11 time-points, including two baselines (-30 and -20 minutes), 5 and 10 minutes post-injection, and 10 minutes post-treatment during procedures lasting 62±4 minutes.

Lidocaine with 0.018 mg of epinephrine resulted in a transient ≈3.5-fold elevation of mean plasma epinephrine concentration from 28±8 pg/mL (baseline) to peak plasma levels of 105±28 pg/mL at 10 minutes post-injection. HR increased by 3-4 bpm at 5 and 10 minutes post-injection. MAP and mean plasma norepinephrine concentrations were unaffected. Once again, the transient rise in epinephrine levels was due to the epinephrine in the LA and not procedure-related.

The hemodynamic effects of 5.4 mL of 2% lidocaine w/epinephrine 1:100:000 (i.e., 0.054 mg) were evaluated in 21 patients undergoing third molar extractions.¹³ Mean plasma epinephrine concentration (semi-supine) rose 5-fold from 60±41 pg/mL (pre-operative baseline) to peak plasma levels of 269±140 pg/mL 5 minutes post-injection with increases in HR (64±8 to 80±20 bpm), systolic BP (114±15 to 130±25 mm Hg), and cardiac output (6.0±1.6 to 8.2±2.2 L/min).

It is instructive to note that mean plasma epinephrine concentrations were also reported to increase from mean resting (supine) values of 34±18 pg/mL nearly 2-fold (≈50 pg/mL) during quite standing; nearly 3-fold during cigarette smoking (≈100 pg/mL); and from 2 to 13-fold during mild to heavy exercise (≈75 to 425 pg/mL); and nearly 7-fold to peak plasma levels of 230 pg/mL in response to a decrement in plasma glucose levels from 95 to 60 mg/mL.^{29,30}

Note as well that threshold epinephrine values for hemodynamic and metabolic effects begin at or are slightly above normal values (range: <10 to 70 pg/mL).^{29,30} Based on graded infusion studies, plasma epinephrine threshold for increments in HR is 50-100 pg/mL, i.e., chronotropic effects occur at only 2 to 3-fold basal levels; and plasma epinephrine threshold for increments in systolic BP is 75-125 pg/mL and for decrements in diastolic BP it is 150-200 pg/mL.^{29,30}

Data from graded infusion studies also showed that as mean plasma epinephrine values rose from 24 to 1,020 pg/mL, baseline HR rose by nearly 30 bpm, systolic BP rose by slightly more than 20 mm Hg, and diastolic BP decreased by about 20 mm Hg. Transient mean plasma epinephrine concentration of 1,024 pg/mL would require administering ≈0.17 to 0.21 mg of epinephrine (MRD in healthy adults: 0.2 mg) or ≈17 to 21 mL of LA w/epinephrine 1:100,000.¹¹⁻¹³

Note that, in general, ADRs with therapeutic doses of epinephrine subside rapidly with rest and recumbency. Not only does epinephrine have a short half-life (≈2 minutes), it accelerates its own metabolic clearance.^{29,30} The reported mean plasma metabolic clearance rate of epinephrine in young men at steady-state plasma concentrations between 24-74 pg/mL is

52±4 mL/kg/min; at steady-state values between 90-1020 pg/mL it is 89±6 mL/kg/min (a 79% increase in clearance).

Epinephrine appears to regulate its metabolic clearance through β -adrenergic mechanisms. In normal subject, propranolol, a β -adrenoceptor blocking agent, reduced the stimulated clearance rate of epinephrine by more than 75%, i.e., to more than 50% below the basal clearance rate.^{29,30} The reduction in epinephrine clearance appears to be due to vasoconstriction and decreased delivery of epinephrine to the liver and other tissues critical in epinephrine clearance.^{29,30}

Rarely, overdosage with epinephrine in oral healthcare settings may result from intravascular injection; administration of suprathreshold doses, especially to high-risk patients; concomitant therapy with other drugs, which may potentiate adverse sympathetic effects; and additivity of epinephrine administered with the LA and endogenous epinephrine released in response to surgical stress, i.e., procedure-related stress mediated by the sympathoadrenal system.

The magnitude of surgical stress depends on the extent of procedure-related tissue trauma, duration of the procedure, volume of blood loss, fluid shifts in the body, and changes in core body temperature.³¹ For example, the mean plasma epinephrine concentration rose nearly 7-fold from baseline during elective cholecystectomy to >200 pg/mL.²⁹ Plasma epinephrine at these levels can precipitate tachycardia, hypertension, and increase myocardial oxygen demand.

Surgical stress can also cause alterations in the balance between prothrombotic and fibrinolytic factors, resulting in hypercoagulability and possible coronary thrombosis (elevation of fibrinogen and other coagulation factors, increased platelet activation and aggregation, and reduced fibrinolysis).³¹ The extent of these responses is also proportional to the degree and duration of procedure-related surgical stress and contribute to myocardial ischemia and heart failure.

Cardiac risk, defined as myocardial infarction or cardiac death within 30 days of non-cardiac procedures, has been assessed.³² It was concluded that non-cardiac procedures may be associated

with high, intermediate, or low cardiac-risk. Breast surgery, eye surgery, and dental procedures under local anesthesia were identified as low cardiac-risk procedures, i.e., the risk of a cardiac event is negligible unless, as noted earlier, strong patient-specific risk factors are present.³²

Data from clinical trials that define perioperative cardiac risk for various dental procedures is limited.¹¹⁻¹³ However, based on evidence from a retrospective analysis of EMS data in Seattle and King Counties, WA, with a combined population 1.5 million, over a seven year period only six major cardiac events (i.e., nonfatal MI, heart failure, or sudden cardiac death) were confirmed in community-based dental practices (<0.002/practice/year).³³

Low cardiac-risk with dental procedures is further supported by data from two independent prospective surveys.³⁴ Over a 10-year period, 4,309 dentists documented 30,602 medical emergencies, i.e., 0.5 emergencies per practice (not dentist) per year. Cardiovascular events included postural hypotension (17.8%), angina pectoris (4.6%), MI (1.4%), and cardiac arrest (1.1%) at an annual rate of 0.08, 0.02, 0.007, and 0.005 per dental practice per year, respectively.

The minimum lethal dose of epinephrine, based on data for subcutaneous injection, is estimated to be 4 mg.³⁵ Autopsy findings in patients who died of epinephrine overdosage include evidence of circulatory collapse and congestion of most organs with blood (e.g. pulmonary edema).¹⁹

The treatment of acute epinephrine toxicity is mainly supportive - Call 911. While waiting for EMS, prepare to begin CPR and automated external defibrillation.

Summary

When used in recommended dosages and administered by the intended route of the formulation, epinephrine is the clinician's best friend. In fixed-dose auto-injectors it is the drug of choice for the treatment of anaphylactic reactions in oral healthcare settings, but immediately following the administration of epinephrine, the patient must be referred for additional medical care. Call 911 and while waiting for the EMS, prepare to initiate CPR and automated cardiac defibrillation.

The use of epinephrine with LAs is standard dental practice. The question to ask is not whether epinephrine should be used – the question to ask is how much epinephrine can be used safely. To minimize serious medication errors, think of dosage strengths of epinephrine in mg/mL of LA rather than ratio expressions (e.g., 1:100,000). In general, the MRD of epinephrine with LAs for healthy adults is 0.2 mg per visit; in high-risk populations, 0.02 to 0.05 mg is recommended.

Toxicity associated with epinephrine overdose is characterized by increased HR and force of myocardial contraction, which may lead to angina pectoris, MI, fatal arrhythmias, heart failure, and cardiac arrest. Increased cardiac stimulation and peripheral vascular resistance may also lead to rapid rise in BP, which may lead to pulmonary edema and respiratory failure. Call 911 and while waiting for the EMS, prepare to initiate CPR and automated cardiac defibrillation.

Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to: www.dentalcare.com/en-us/professional-education/ce-courses/ce547/start-test

- 1. All of the following statements related to the ClinCalc DrugStats database are correct EXCEPT which one?**
 - a. ClinCalc DrugStats provides prescription drug utilization data estimates based on the annual Medical Expenditure Panel Survey.
 - b. The list of the Top Prescription Drugs of 2017 reflects data collected in 2017.
 - c. The Top 200 Prescription Drugs of 2017 represent 40% of the available 500 active ingredients and comprise 90% of all prescription drugs.
 - d. The Top 300 Prescription Drugs of 2017 represent 60% of the available 500 active ingredients and comprise 97% of all prescription drugs.

- 2. Which of the following statement related to the DailyMed website is correct?**
 - a. DailyMed, a useful online resource, is the official repository for FDA-approved package inserts, i.e., for individual drug-related, clinically relevant data.
 - b. The information on DailyMed is the most recent submitted to the FDA by pharmaceutical companies and includes warnings undergoing FDA review.
 - c. The information is accurate; when possible it is based on human experience; and does not contain promotional or misleading information (e.g., implied claims).
 - d. All of the above.

- 3. Which of the following statement related to the Top 300 Drugs of 2017 is correct?**
 - a. The majority of epinephrine formulations were prescribed for "self-administration" by patients (or caretakers) in ambulatory settings.
 - b. Epinephrine in auto-injectors are indicated for intramuscular (IM) administration in the emergency treatment of Type I allergic reactions, i.e., anaphylaxis.
 - c. Epinephrine formulations in MDIs that were available in 2014 are no longer available commercially in the United States.
 - d. All of the above.

- 4. All of the following statements related to the peripheral nervous system (PNS) are correct EXCEPT which one?**
 - a. The PNS is divided into sensory and motor divisions.
 - b. The sensory (afferent) and motor (efferent) neurons, conduct signals from peripheral tissues to the CNS and from the CNS to peripheral tissues, respectively.
 - c. The somatic nervous system, a component of the motor division of the PNS regulates involuntary skeletal muscle responses.
 - d. The sympathetic branch of the ANS mobilizes body systems to provide energy for "fight or flight" responses.

- 5. All of the following statements related the sympathetic branch of the ANS are correct EXCEPT which one?**
 - a. Activation of the sympathetic branch and subsequent release of catecholamine is initiated by signals originating in the PNS.
 - b. Norepinephrine is synthesized primarily at sympathetic nerve endings and is released at synapses on specific target organs.
 - c. Epinephrine is synthesized by neuroendocrine (chromaffin) cells of the adrenal medulla and it is released into the bloodstream to be transported to target organs.
 - d. To produce an effect, both norepinephrine and epinephrine must interact with adrenergic receptors (adrenoceptors), which have an organ-specific distribution.

- 6. All of the following statements related to adrenoceptors are correct EXCEPT which one?**
- Epinephrine interacts with adrenoceptors which are divided into three classes; α_1 (α_{1A} , α_{1B} and α_{1D}), α_2 (α_{2A} , α_{2B} and α_{2C}), and β (β_1 , β_2 , and β_3).
 - Each of the adrenoceptor subtype is a member of the G protein-coupled receptor family (i.e., transmembrane receptors coupled to intracellular G proteins).
 - The binding of epinephrine to a G protein-coupled adrenoceptor invariably increases, i.e., stimulates the target organ.
 - G proteins are composed of α - and $\beta\gamma$ -subunits, the binding of an agonist to a G protein-coupled adrenoceptor causes the exchange of GTP for GDP on the α -subunit, the α -GTP subunit dissociates from the $\beta\gamma$ -subunit and interacts with effector proteins.
- 7. All of the following statements related to signaling mechanisms of adrenoceptors are correct EXCEPT which one?**
- Prototypical signaling mechanism of α_1 -adrenoceptors primarily involves G_{α_q} , resulting in increased sympathetic activity.
 - Prototypical signaling mechanism of α_2 -adrenoceptors primarily involves G_{α_i} , resulting in increased cAMP, which activates protein kinases affecting a variety of intracellular proteins, including ion channels.
 - α_2 -adrenoceptors are expressed primarily in pancreatic β -cells, platelets, vascular smooth muscles, and at various sites in the CNS.
 - Prototypical signaling mechanism of β -adrenoceptors primarily involves G_{α_s} , resulting in increased sympathetic activity.
- 8. All of the following statements related to the pharmacokinetics of epinephrine are correct EXCEPT which one?**
- Epinephrine is well absorbed and has rapid onset of action following parenteral administration, e.g., in combination with LAs or when administered IM.
 - Epinephrine in LAs reaches peak plasma concentrations in 5-10 minutes; following IM injection it reaches peak plasma concentrations in 8 ± 2 min.
 - Epinephrine is distributed to most tissues: it crosses the placenta, it is secreted into milk, and it crosses the blood-brain barrier.
 - Epinephrine is inactivated primarily by catechol-O-methyltransferase and monoamine oxidase and excreted in the urine (elimination half-life: ≈ 2 minutes).
- 9. All of the following statements related to the use of epinephrine in the treatment of anaphylaxis are correct EXCEPT which one?**
- Epinephrine is the drug of choice for the emergency treatment of severe Type 1 allergic reactions, i.e. anaphylaxis.
 - No absolute contraindications exist to the use of epinephrine in the emergency treatment of acute anaphylactic reactions.
 - Because of serious medication errors with epinephrine, dosage strengths on single-entity preparations must be expressed as ratios (e.g., 1:1000, 1:2000, etc.).
 - Pre-filled, single-use, auto-injectors are available in convenient dosage strengths such as 0.1 mg/0.1 mL, 0.15 mg/0.15 mL, 0.15 mg/0.3 mL, and 0.3 mg/0.3 mL.

- 10. Which of the following statement related to anaphylaxis is correct?**
- An anaphylactic reaction may occur within minutes after reexposure (previous sensitization is a prerequisite) to a specific allergen.
 - Anaphylaxis consists of urticaria, pruritus, angioedema (e.g., swelling of the lips, eyelids, and tongue), wheezing, dyspnea, and hypotension.
 - Epinephrine auto-injectors should always be available in various fixed-dose formulations in every office emergency kit.
 - All of the above.
- 11. All of the following statements related to the treatment of anaphylaxis in oral healthcare setting are correct EXCEPT which one?**
- When treating anaphylaxis, select an auto-injector with the appropriate dosage strength predicated on the patient's body weight.
 - Immediately following the administration of epinephrine, the patient must be referred for additional medical care - Call 911.
 - With severe persistent anaphylaxis a repeat injection of epinephrine, with an additional auto-injector, may be necessary in 15-20 minutes.
 - More than two sequential doses of epinephrine should only be administered under direct medical supervision of the patient by the dentist.
- 12. All of the following statements related to the consequences of treating anaphylaxis are correct EXCEPT which one?**
- ADRs are not likely to occur with the administration of therapeutic doses of epinephrine.
 - ADRs usually subside rapidly with rest and recumbency.
 - Signs and symptoms of ADRs include restlessness, tremor, palpitations, tachycardia, sweating, nausea and vomiting, pallor, headache, dizziness, feelings of panic or anxiety, and respiratory difficulties.
 - Overdosage (and even therapeutic doses in some patients) of epinephrine may precipitate angina pectoris and/or produce ventricular arrhythmias.
- 13. All of the following statements related to the rationale for including a vasoconstrictor in LA formulations are correct EXCEPT which one?**
- Decrease the rate of LAs' systemic absorption.
 - Prolong LAs' duration of action.
 - With block anesthesia, reduce bleeding in the operative field.
 - Reduce the risk of LAs' systemic toxicity.
- 14. All of the following statements related levonordefrin are correct EXCEPT which one?**
- 2% mepivacaine is available w/levonordefrin 1:20,000 (i.e., 0.05 mg/mL) which is bioequivalent to epinephrine 1:100,000 (i.e., 0.01 mg/mL).
 - Levonordefrin is a derivative of norepinephrine and activates peripheral α_2 -adrenoceptors in vascular smooth muscles and produces vasoconstriction.
 - Levonordefrin is more likely than epinephrine to cause cardiac arrhythmias.
 - Levonordefrin activates α_2 -adrenoceptors in the cardiovascular control center of the CNS, suppresses sympathetic output from the brain and lowers BP.

- 15. All of the following statements related to the available 2% lidocaine formulations w/ epinephrine are correct EXCEPT which one?**
- In general, the maximum recommended dose (MRD) of epinephrine in LA formulations for healthy adults is 0.2 mg per visit.
 - The maximum safe dose of 2% lidocaine w/epinephrine 1:100,000 (0.01 mg/mL) is 20 mL.
 - The maximum safe dose of 2% lidocaine w/epinephrine 1:50,000 (0.02 mg/mL) is 10 mL.
 - The MRD of 2% lidocaine is reached before the MRD of epinephrine 1:100,000 (0.01 mg/mL) or epinephrine 1:50,000 (0.02 mg/mL).
- 16. All of the following statements related to mepivacaine 2% w/levonordefrin 1:20,000 (0.05 mg/mL) are correct EXCEPT which one?**
- Levonordefrin, 0.05 mg, is bioequivalent to epinephrine, 0.05 mg.
 - The MRD of levonordefrin is 1 mg.
 - The maximum safe dose of 2% mepivacaine w/levonordefrin 1:20,000 (0.05 mg/mL) is 20 mL.
 - With 2% mepivacaine formulation, the MRD of levonordefrin (1 mg) and the MRD of mepivacaine (400 mg) are both reached with 20mL of LA.
- 17. All of the following statements related to various available LA formulations are correct EXCEPT which one?**
- Based on the MRD of prilocaine (600 mg), the MRD of epinephrine 1:200,000 in prilocaine is reached after the MRD of 4% prilocaine.
 - Based on the MRD of articaine (500 mg), the MRD of epinephrine 1:100,000 in articaine is reached before the MDR of 4% articaine.
 - Based on the MRD of articaine (500 mg), the MRD of epinephrine 1:200,000 in articaine is reached after the MDR of 4% articaine.
 - Based on the MRD of bupivacaine (90 mg), the MDR of epinephrine 1:200,000 in bupivacaine is reached after the MDR of 0.5% bupivacaine.
- 18. All of the following statements related to epinephrine are correct EXCEPT which one?**
- Epinephrine has a relatively narrow therapeutic window.
 - Since epinephrine crosses the blood-brain barrier, epinephrine-associated ADRs are the result of CNS effects.
 - Common adverse effects may occur even with the administration of recommended therapeutic doses and include restlessness, agitation, anxiety, tremulousness, headache, dizziness, pallor, palpitation, and tachycardia.
 - In patients with Parkinson's disease epinephrine may increase tremor and rigidity.
- 19. Particularly vulnerable populations to the effects of therapeutic doses of epinephrine include all of the following EXCEPT which one?**
- Patients with uncontrolled hypothyroidism.
 - The young and the old.
 - Those with high BP and severe cardiovascular diseases (i.e., unstable angina pectoris, recent myocardial infarction (MI), decompensated heart failure.
 - Patients with severe valvular disease, supraventricular arrhythmias with uncontrolled ventricular rate, and symptomatic ventricular arrhythmias).

20. **Epinephrine should be _____.**
- used with caution in patients on other sympathomimetic agents and in patients on nonselective β -adrenoceptor antagonists
 - avoided in patients on cocaine
 - used with caution in patients with supraphysiological thyroid levels (i.e., excess thyroid medication or hyperthyroidism)
 - All of the above.
21. **All of the following statements related to epinephrine dosing in high-risk populations are correct EXCEPT which one?**
- In high-risk populations, the therapeutic benefits of epinephrine must outweigh possible risks and a lower maximum dose of 0.02 to 0.05 mg is recommended.
 - Since the main physiologic stimulus to epinephrine secretion is exercise, to establish the safe dose of epinephrine determine the patient's functional capacity.
 - Functional capacity is expressed in metabolic equivalents (METs) and reflects a person's functional reserve to meet physiological demand for oxygen.
 - Work at 1 MET requires a capacity to deliver 7 mL of O_2 /kg/min.
22. **All of the statements related to the relationship between cardiac risk, metabolic equivalents, plasma epinephrine levels, and stress testing are correct EXCEPT which one?**
- A functional capacity of <2 METs is indicative of increased perioperative and long-term cardiac risk.
 - Clues indicative of increased cardiac risk include the physical findings of tremor, anxiety, cyanosis, pallor, diaphoresis, dyspnea, tightness and/or pain in the chest with minimal activity, and peripheral edema.
 - The hemodynamic effects of infiltration anesthesia with 0.045 mg of epinephrine, was reported to be less than those produced by stress testing at 4 METs.
 - From a mean resting (supine) metabolic state, 0.045 mg of epinephrine produces about a 4-fold transient increase in mean plasma epinephrine concentration.
23. **All of the following statements related to transient increases in mean plasma epinephrine levels are correct EXCEPT which one?**
- Significant transient elevation in mean plasma epinephrine levels was reported w/ nerve block anesthesia with 1.8 mL of 2% lidocaine without epinephrine.
 - Transient \approx 3.5-fold elevation of mean plasma epinephrine level was reported w/ nerve block anesthesia with 1.8 mL of 2% lidocaine w/0.018 mg of epinephrine.
 - Transient \approx 3.5-fold elevation of mean plasma epinephrine level was reported w/ restorative procedures under 1.8 mL of 2% lidocaine w/0.018 mg of epinephrine.
 - Transient \approx 5-fold elevation of mean plasma epinephrine level was reported w/ third molar extractions under 5.4 mL of 2% lidocaine w/ 0.054 mg of epinephrine.
24. **All of the statements related to transient elevation of mean plasma epinephrine levels are correct except which one? Mean resting (supine) values rise from mean resting (supine) values nearly _____.**
- 2-fold during quiet standing.
 - 3-fold during cigarette smoking.
 - 7-fold in response to an increment in plasma glucose levels from 60 to 95 mg/mL.
 - 2 to 13-fold during mild to heavy exercise.

- 25. All of the statements related to threshold epinephrine values for hemodynamic and metabolic effects are correct EXCEPT which one?**
- Threshold epinephrine values for hemodynamic and metabolic effects begin at or are slightly above normal values (range: <10 to 70 pg/mL).
 - Plasma epinephrine threshold for increments in HR is 50 - 100 pg/mL, i.e., chronotropic effects occur at only 2 to 3-fold basal levels.
 - Plasma epinephrine threshold for increments in systolic BP is 75 - 125 pg/mL and for decrements in diastolic BP it is 150 - 200 pg/mL.
 - Plasma epinephrine threshold for increments in diastolic BP is 150 - 200 pg/mL.
- 26. All of the statements related to rises in mean plasma epinephrine values from a baseline of 24 pg/mL to peak plasma concentration of $1,020$ pg/mL are correct EXCEPT which one?**
- Baseline HR rises by nearly 30 bpm.
 - Baseline systolic BP rises by slightly more than 20 mm Hg.
 - Baseline diastolic BP rises by about 20 mm Hg.
 - Transient mean plasma epinephrine concentration of $1,024$ pg/mL would require ≈ 0.17 to 0.21 mg of epinephrine (MRD in healthy adults: 0.2 mg).
- 27. All of the statements related to the clearance of epinephrine are correct EXCEPT which one?**
- In general, ADRs with therapeutic doses of epinephrine subside rapidly with rest and recumbency.
 - Epinephrine has a half-life of about 2 hours; but it accelerates its own metabolic clearance through α -adrenergic mechanisms.
 - Mean plasma metabolic clearance rate of epinephrine in young men at steady-state plasma concentrations between 24 - 74 pg/mL is 52 ± 4 mL/kg/min.
 - Mean plasma metabolic clearance rate of epinephrine in young men at steady-state plasma concentrations between 90 - 1020 pg/mL is 89 ± 6 mL/kg/min.
- 28. Rarely, overdose with epinephrine in oral healthcare settings may result from _____.**
- intravascular injection and/or the administration of suprathreshold doses, especially to high-risk patients
 - concomitant therapy with other drugs, which may potentiate adverse sympathetic effects
 - additivity of epinephrine administered with the LA and endogenous epinephrine released in response to surgical stress
 - All of the above.
- 29. The magnitude of surgical (procedure-related) stress depends on _____.**
- the extent of tissue trauma and duration of the procedure
 - volume of blood loss, fluid shifts in the body
 - changes in core body temperature
 - All of the above.
- 30. All of the statements related to epinephrine-induced cardiac risk are correct EXCEPT which one?**
- Cardiac risk is defined as myocardial infarction or cardiac death within 30 days of a non-cardiac procedure.
 - Dental procedures under local anesthesia are low cardiac-risk procedures, i.e., cardiac-risk is negligible unless strong patient-specific risk factors are present.
 - The minimum lethal dose of epinephrine, based on data for subcutaneous injection, is estimated to be 0.4 mg.
 - Autopsy findings in patients who died of epinephrine overdose include evidence of circulatory collapse and congestion of most organs with blood.

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