

# SYMPATHOMIMETICS

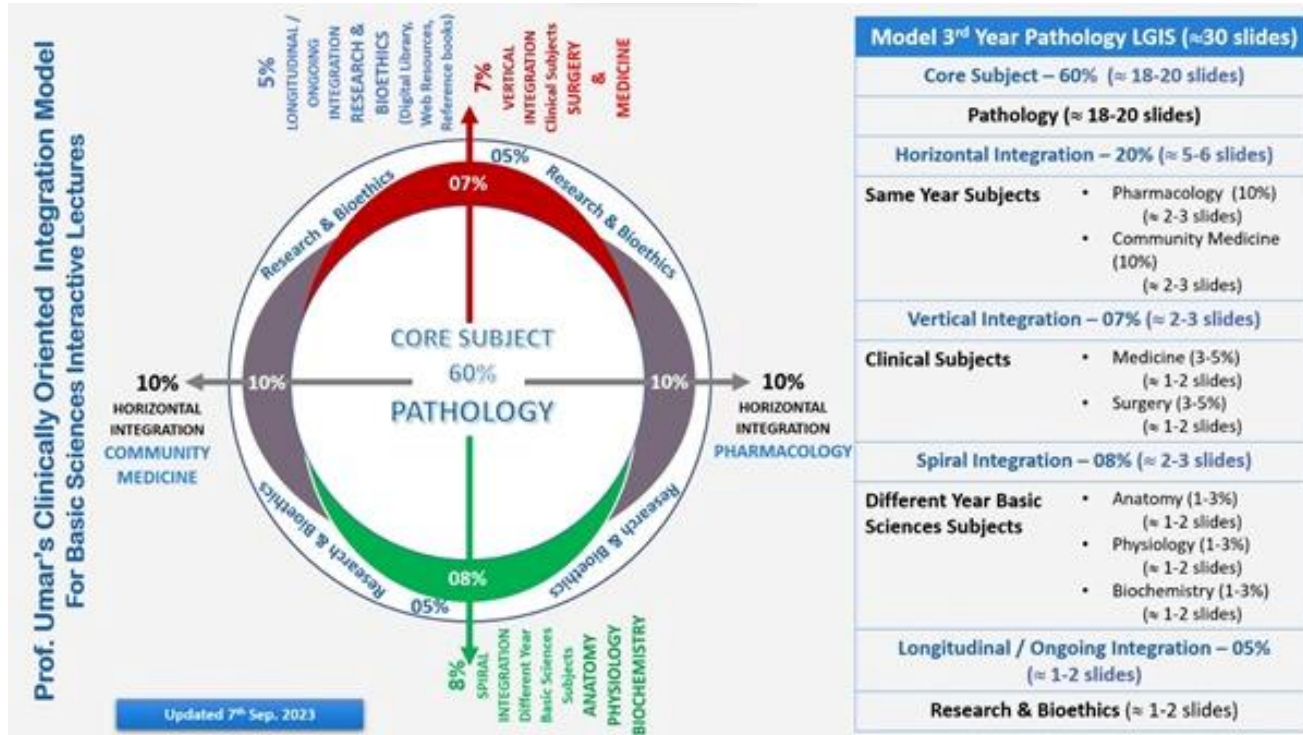
- **Katzung's Basic & Clinical Pharmacology, 16<sup>th</sup> Edition**
- **Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13<sup>th</sup> Edition**

# MOTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine



# UMAR'S MODEL OF INTEGRATION



# PROF. UMAR'S MODEL OF TEACHING STRATEGY

- Self Directed Learning Assessment Program
- **Objectives** :To cultivate critical thinking, analytical reasoning, and problem-solving competencies.
- To instill a culture of self-directed learning, fostering lifelong learning habits and autonomy.
- **How to Assess?**
- Ten randomly selected students will be evaluated within the **first 10 minutes of the lecture** through 10 multiple-choice questions (MCQs) based on the PowerPoint presentation shared on Students Official WhatsApp group, one day before the teaching session.
- The number of MCQs from the components of the lecture will follow the guidelines outlined in the Prof. Umar model of Integrated Lecture.

Component of LGIS	Core Knowledge	Horizontal Integration	Vertical Integration	Spiral Integration
No of MCQs	6-7	1-2	1	1

# PRELECTURE ASSESSMENT

A 55-year-old woman suffering from postural hypotension started a treatment with an  $\alpha_1$ -adrenergic drug. Which of the following is a body site where autonomic receptors are primarily  $\alpha_1$  adrenergic?

- A. Bronchial muscle
- B. Sphincter muscle of the iris
- C. Atrioventricular node
- D. Purkinje fibers
- E. Skin vessels

A 34-year-old woman was at the dentist for an endodontic procedure. Before starting the procedure, the dentist injected a solution of lidocaine plus epinephrine near the tooth in order to provide local anesthesia. The epinephrine-induced increased duration of the lidocaine effect was most likely mediated by the activation of which of the following adrenoceptors?

- A.  $\beta_1$
- B.  $\beta_2$
- C.  $\beta_3$
- D.  $\alpha_1$
- E.  $\alpha_2$

# PRE-LECTURE ASSESSMENT

Which of the following is a characteristic of catecholamines?

- A. They are used for local bronchodilation
- B. They have a common basic chemical structure
- C. They are used for systemic vasodilation
- D. They are not destroyed by digestive enzymes
- E. They can be given orally

Which of the following structural modifications generally enhance the potency of sympathomimetic drugs?

- A) Addition of a bulky group at the para position of the aromatic ring
- B) Increasing the length of the side chain between the aromatic ring and the amino group
- C) Replacement of the hydroxyl group on the aromatic ring with a methoxy group
- D) Introduction of a methyl group on the amine nitrogen
- E) Removal of the hydroxyl group on the beta carbon of the side chain

# PRE-LECTURE ASSESSMENT

A hypotensive patient in the critical care unit is given an intravenous infusion of an alpha-adrenergic agonist that lacks beta-adrenergic activity. The cardiovascular effects of this drug are:

- A. Increased vascular resistance
- B. Decrease heart rate
- C. Decrease conduction velocity
- D. Decrease force of contraction
- E. Decrease vascular resistance

A 20-year-old man has been self-treating his nasal congestion with a nonprescription alpha agonist nasal spray for 2 weeks. When he stopped using it he found that he experienced:

- A) Increased nasal congestion
- B) Decreased nasal discharge
- C) Improvement in breathing
- D) Reduction in headache
- E) Enhanced sense of smell

# PRE-LECTURE ASSESSMENT

A 3-year-old child presents to the emergency department with acute asthma. He is given a nebulized bronchodilator that relaxes bronchial smooth muscle through direct action on adrenergic receptors. This drug acts via:

- A. Nuclear receptors
- B. G protein coupled receptors
- C. Voltage gated ion channels
- D. Enzyme linked channels
- E. Cytoplasmic receptors

The sympathomimetic which may promote diuresis by a direct effect on the kidney is

- A. Isoproterenol
- B. dobutamine
- C. norepinephrine
- D. dopamine
- E. epinephrine



Which of the following direct-acting drugs is a relatively pure alfa agonist, an effective mydriatic and decongestant and can be used to raise blood pressure?

- A. Epinephrine
- B. Norepinephrine
- C. Phenylephrine
- D. Ephedrine
- E. Dopamine

A 65-year-old patient is prescribed a drug to treat hypotension. The drug is known to have a rapid onset of action and is metabolized quickly by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).

Which of the following drugs is most likely being prescribed?

- A) Epinephrine
- B) Phenylephrine
- C) Albuterol
- D) Isoproterenol
- E) Dopamine

At the end of the lecture, students of 3<sup>rd</sup> Year MBBS will be able to ;



## Learning Objectives

- ▶ **Classify sympathomimetic drugs**
- ▶ **Identify the dose dependent effect of epinephrine on adrenergic receptors**
- ▶ **Discuss the organ system effects of epinephrine**
- ▶ **Describe valid clinical uses of epinephrine**
- ▶ **Recognize the adverse effects of epinephrine**



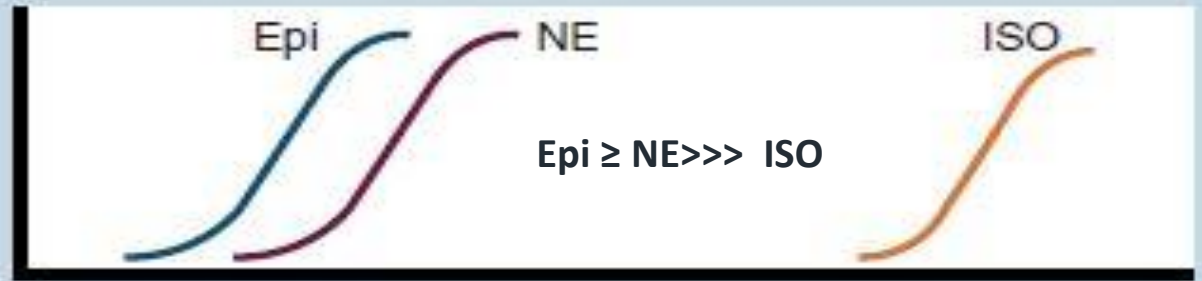
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# **Receptor Selectivity**

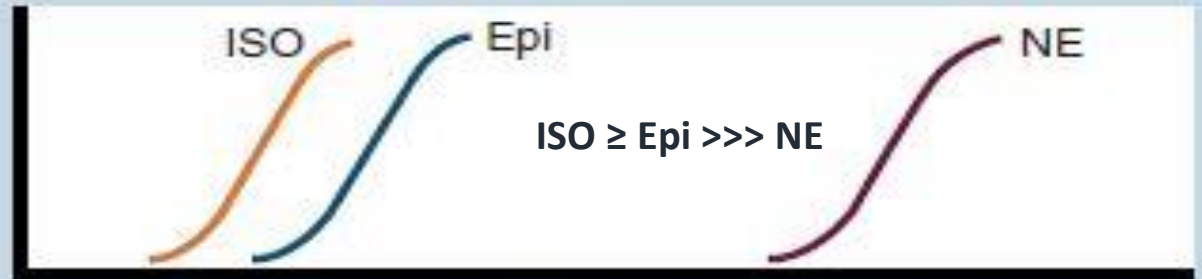
# Receptor selectivity

	Relative Receptor Affinities
<b>Alpha agonists</b>	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>> \beta$
<b>Mixed alpha and beta agonists</b>	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
<b>Beta agonists</b>	
Dobutamine <sup>1</sup>	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
<b>Dopamine agonists</b>	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

Contraction of  
arterial strips  
( $\alpha_1$  receptor)



Relaxation of  
bronchial  
smooth muscle  
( $\beta_2$  receptor)



Augmented  
contraction of  
heart  
( $\beta_1$  receptor)



Log concentration of catecholamine

## $\alpha$ Adrenoceptors

Epinephrine



Norepinephrine



Isoproterenol



## $\beta$ Adrenoceptors

Isoproterenol



Epinephrine



Norepinephrine



High affinity

Low affinity



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# Therapeutic Classification

# Therapeutic uses/Clinical Applications

- Central nervous system (CNS)
  1. **ADHD(Attention deficit hyper activity disorder)**  
Clonidine, Methylphenidate
  2. **Narcolepsy**  
Modafinil , Methamphetamine (abused drug)
  3. **Withdrawal(smoking, alcohol, narcotic analgesics)**  
Clonidine
  4. **Anorexic agents in obesity**  
Phenmetrazine, Amphetamine, Methylphenidate & Pemoline
  5. **Sedation in ICU**  
Dexmedetomidine
  6. **Premedication before GA**  
Clonidine





# Therapeutic uses/Clinical Applications



- Ophthalmic Uses

1. **Mydriatic**

Phenylephrine , Oxymetazoline , Tetrahydrozoline

2. **Open angle glaucoma**

Apraclonidine, Brimonidine , Dipivefrin, Epinephrine

3. **Localization of lesion of horner's syndrome**

Hydroxyamphetamine

- Nasal decongestants

Naphazoline, Oxymetazoline, Xylometazoline,  
Pseudoephedrine Phenylpropanolamine, Phenylephrine

# Therapeutic uses/Clinical Applications

- Cardiovascular system(CVS)

1. **Shock**

- a) **Hypovolemic shock** (dopamine)
- b) **Cardiogenic shock** (dopamine, dobutamine)
- c) **Anaphylactic shock** (epinephrine)

2. **Cardiac arrest** (epinephrine)

3. **Heart failure CCF** (dobutamine)

4. **Hypotension**

- a) **Acute hypotension** (Norepinephrine , Phenylephrine, Methoxamine)
- b) **Chronic orthostatic hypotension** (Midodrine, Ephedrine, Phenylephrine, Droxidopa)

5. **Hypertension** (clonidine)

6. **Hemostatic agents** (epinephrine, phenylephrine)

7. **Prolong effect of local anesthetic** (epinephrine, phenylephrine )



# Therapeutic uses/Clinical Applications

- Pulmonary (bronchodilators)

1. **Asthma**

- a)  **$\beta_2$  Selective Agonists:** Salbutamol (Albuterol), Terbutaline , Metaproterenol , Pirbuterol , Salmeterol , Formoterol
- b)  **$\beta_1$  &  $\beta_2$  Agonists:** Isoprenaline, Orciprenaline
- c) **Both  $\alpha$  &  $\beta$  Agonists:** Epinephrine (status asthmaticus)

- Genitourinary system

1. **Premature Labor**

Salbutamol, Ritodrine, Isoxsuprine

2. **Stress incontinence**

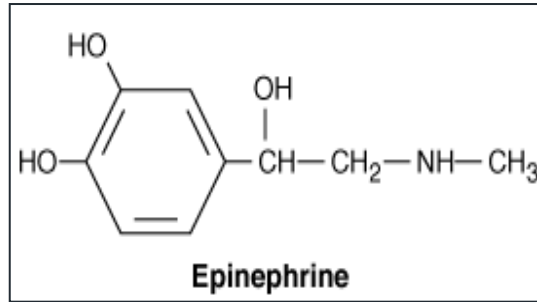
Ephedrine



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# **Directly Acting Sympathomimetics**

# Epinephrine



- Catecholamine
- Naturally produced in adrenal medulla, some areas of brain
- Directly acting on adrenoceptors

$$\alpha_1 = \alpha_2 ; \beta_1 = \beta_2$$

- |                 |                       |
|-----------------|-----------------------|
| • At low doses  | $\beta$ predominates  |
| • At high doses | $\alpha$ predominates |

# Organ system effects

## Pharmacological actions depend on

- i. Receptor selectivity
- ii. Intrinsic activity
- iii. Predominance of receptors
- iv. Other reflexes modulating effects of these drugs

- Apprehension, restlessness and anxious

- Decrease peripheral glucose utilization
- Increase glycogenolysis ( $\beta$ )
- Decrease insulin
- Increase lipolysis

- Bronchodilation ( $\beta_2$ )**
- BV ( $\alpha_1$ ) constricted---decongestion
- $\downarrow$  release of mediators from mast cells
- Smooth muscle relaxed

$\beta$  directly,  $\alpha_2$  presynaptic receptors  
Stomach relaxed,  $\downarrow$  amplitude & tone of contractions

- Contraction of sphincters ( $\alpha_1$ )

#### ❖ Bladder:

- Detrusor muscle relaxed ( $\beta_2$  &  $\beta_3$ )
- Bladder base, urethral sphincter ( $\alpha_1$ )

- Renin secretion**  
(stimulated by  $\beta_1$ , Inhibited by  $\alpha_2$ )
- Increase secretion of Epinephrine

- Mydriasis  
( $\alpha_1$  mediated dilation of dilator pupillae)
- Increase outflow of aqueous humor
- Pallor of conjunctiva—  
( $\alpha_1$  mediated blood vessel constriction)

#### **Sinoatrial (SA) node**

- Increase rate of depolarization
- Increase heart rate

#### **Atrioventricular (AV) node**

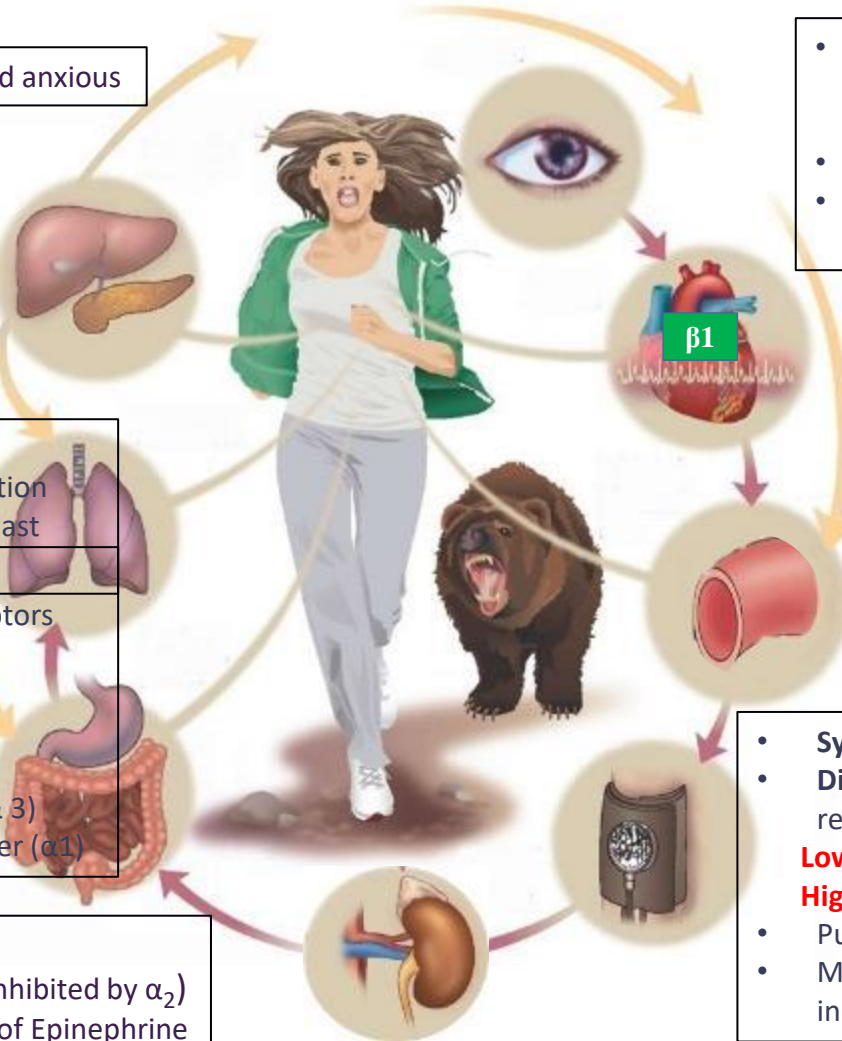
- Increase in conduction velocity

#### **Cardiac myocytes**

- Increase force of contraction

- Alpha 1 : vasoconstriction
- Beta 2: vasodilation

- Systolic BP**----- HR & CO ( $\beta_1$ )
- Diastolic BP**-----  
relative stimulation of  $\alpha_1$ - &  $\beta_2$  receptors
- Low dose ----- $\beta_2$  (vasodilation)**
- High dose----- $\alpha_1$  (vasoconstriction)**
- Pulse pressure-----widened
- Mean arterial pressure-----slightly increased



# Therapeutic uses of Epinephrine

- Anaphylaxis – 0.3-0.5mg (0.3-0.5ml 1:1000 epinephrine solution)
- Prolongation of local anesthetic action (1:100,000)
- Cardiac resuscitation (restore cardiac rhythm)
- Control of capillary bleeding (topical hemostatic agent) – epistaxis, gingival bleeding
- Glaucoma
- Bronchial asthma
- Hyperkalemia





# Adverse effects of Epinephrine

## CNS

Can not cross BBB

- Somatic manifestations of restlessness, nervousness, anxiety, fear
- Throbbing headache
- Cerebral hemorrhage (sudden rise in BP)

## CVS

- Tachycardia, palpitations, arrhythmia
- Tissue necrosis
- Precipitation of angina in pts with coronary disease

## Contraindications

- Hypertensive, hyperthyroid and pts with IHD
- Pheochromocytoma

# Pheochromocytoma

A rare tumor of the adrenal medulla that results in excessive production of epinephrine, leading to hypertension, sweating, headaches, and palpitations.

# RESEARCH

**Ippolito M, Benovic JL. Biased agonism at  $\beta$ -adrenergic receptors. Cell Signal. 2021 Apr;80:109905. doi: 10.1016/j.cellsig.2020.109905. Epub 2020 Dec 29. PMID: 33385503; PMCID: PMC7878421.**

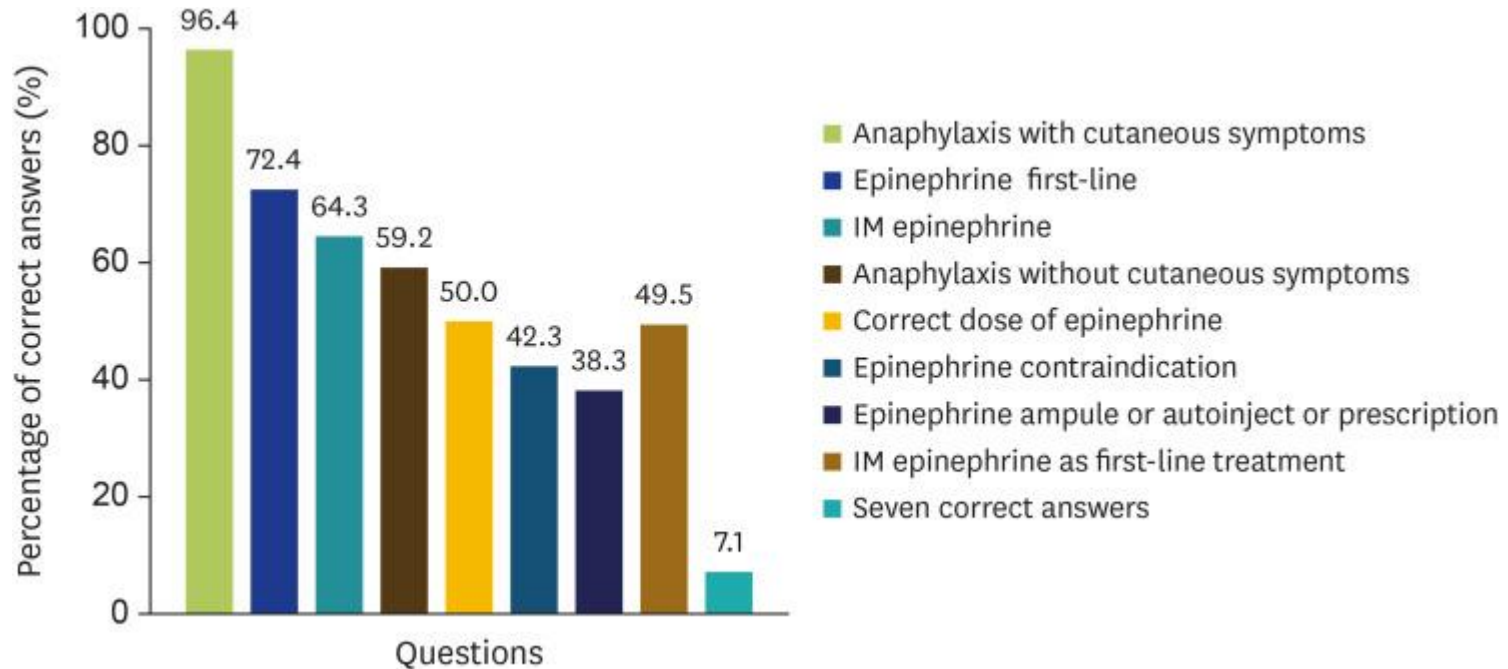
# ARTIFICIAL INTELLIGENCE

**Shahrokhi Z, Sohrabi MR, Nik SM. The application of artificial intelligence system and regression methods based on the spectrophotometric method for fast simultaneous determination of naphazoline and antazoline in ophthalmic formulation. Optik. 2020 Feb 1;203:164010.**

# BIOETHICS

Suissa, K., Schneeweiss, S., Kim, D.W. and Patorno, E., 2021. Prescribing trends and clinical characteristics of patients starting antiobesity drugs in the United States. *Diabetes, Obesity and Metabolism*, 23(7), pp.1542-1551.

# FAMILY MEDICINE



Pimentel-Hayashi JA, Navarrete-Rodriguez EM, Moreno-Laflor OI, Del Rio-Navarro BE. Physicians' knowledge regarding epinephrine underuse in anaphylaxis. *Asia Pac Allergy*. 2020 Oct 22;10(4):e40. doi: 10.5415/apallergy.2020.10.e40. PMID: 33178565; PMCID: PMC7610080.

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JAZAKALLAHU  
KHAIIR