IN THE NAME OF ALLAH

THE MOST BENEFICIENT
THE MOST MERCIFUL

MOTTO 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

TOLERANCE AND TACHYPHYLAXIS

DR MEMUNA KANWAL

SOURCE :
BERTRAM G.KATZUNG BASIC & CLINICAL PHARMACOLOGY 15TH EDITION
GOOGLE FOR IMAGES & RESEARCH ARTICLE

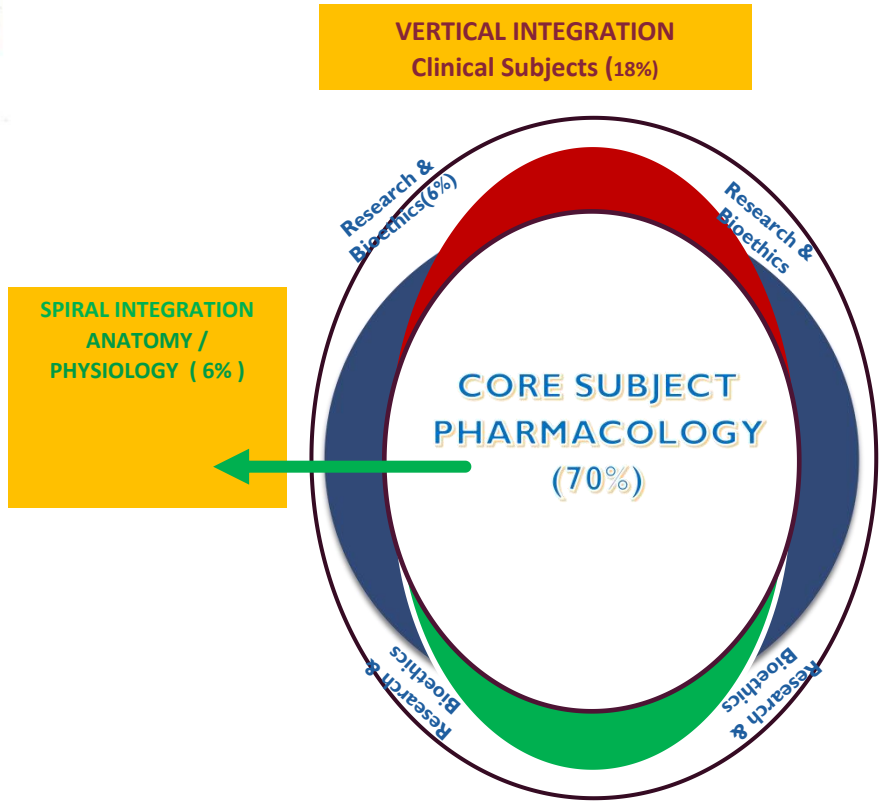
Prof. Umar's Model of Teaching Strategy

- **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

PROFESSOR UMAR'S CLINICALLY ORIENTED INTEGRATION MODEL FOR INTERACTIVE LECTURES



3RD Year Pharmacology LGIS(26 slides)	
Core Subject – 18 slides (69.4%)	
Vertical integration (Clinical Subjects)	• 3 slides (11.5%)
Spiral Integration (basic sciences subjects)	• 1 slide (3.8%)
Spiral integration	• 4 slides (15.3%)

1. Tachyphylaxis differs from tolerance in that it:
A. Requires a higher drug dose to maintain efficacy
B. Occurs rapidly after repeated drug exposure
C. Is caused by increased drug metabolism
D. Is due to upregulation of drug receptors
E. Develops slowly over days to weeks

2. Receptor desensitization is most commonly associated with:
A. Pharmacokinetic tolerance
B. Pharmacodynamic tolerance
C. Drug antagonism
D. Competitive inhibition
E. Drug accumulation

3. Which of the following strategies can help overcome tolerance to opioids?
A. Decreasing the drug dose
B. Administering an enzyme inducer
C. Switching to another opioid
D. Increasing drug metabolism
E. Blocking opioid receptors

4. A 45-year-old hypertensive patient on clonidine for six months suddenly stops the medication. He experiences a rapid increase in blood pressure. Which of the following mechanisms best explains this reaction?
A. Downregulation of α2 receptors
B. Upregulation of α2 receptors
C. Increased drug metabolism
D. Increased renal clearance
E. Competitive inhibition of receptor binding

5. A 60-year-old man with stable angina has been using sublingual nitroglycerin for symptom relief. Over time, he notices that the drug is becoming less effective, requiring more frequent doses. Which of the following best explains this phenomenon?
A. Drug resistance
B. Tachyphylaxis
C. Pharmacokinetic tolerance
D. Pharmacodynamic tolerance
E. Drug hypersensitivity

6. A patient with myasthenia gravis has been receiving pyridostigmine for symptom control. Initially, the drug was effective, but after several weeks, its effectiveness has significantly decreased. What is the most likely cause?
A. Enzyme induction
B. Desensitization of nicotinic receptors
C. Competitive inhibition of acetylcholinesterase
D. Autoimmune destruction of muscarinic receptors
E. Upregulation of acetylcholinesterase

7. A 55-year-old patient with chronic back pain has been on opioid therapy for several months. Despite increasing doses, the pain relief is diminishing. As a family physician, what is the most appropriate next step?
A. Continue increasing the opioid dose
B. Switch to a different opioid or use adjunctive therapies
C. Stop opioid therapy abruptly
D. Advise the patient that tolerance is irreversible
E. Prescribe a sedative to enhance opioid effects

CORE KNOWLEDGE

SDL ASSESSMENT PROGRAM

8. A patient with asthma has been using a β2-agonist inhaler for symptom control. Over time, he finds that he needs more frequent doses for the same relief. As a family physician how will you manage this issue?
A. Switching to a long-acting β2-agonist
B. Increasing the inhaler dose
C. Administering the drug intravenously
D. Adding a corticosteroid
E. Using a short drug holiday

SPIRAL INTEGRATION

HORIZONTAL INTEGRATION

9. A long-term heroin user is found deceased from an overdose. Toxicology reports indicate a dose similar to their usual intake but administered in an unfamiliar environment. Which phenomenon explains this outcome?
A. Reverse tolerance
B. Conditioned tolerance failure
C. Enzyme inhibition
D. Psychological dependence
E. Post-mortem redistribution

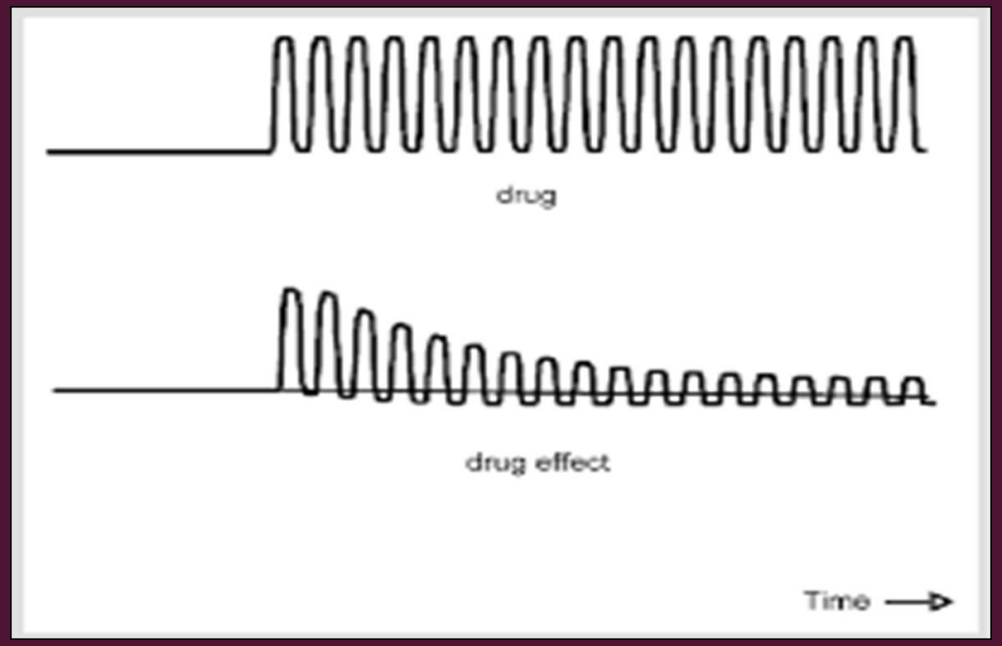
10. A patient with chronic pain has been on opioids for several months and now requires higher doses for pain relief. What cellular adaptation underlies this form of tolerance?
A. Increased neurotransmitter release
B. Upregulation of opioid receptors
C. Downregulation of opioid receptors
D. Inhibition of neurotransmitter reuptake E. Decreased hepatic metabolism of the drug

HORIZONTAL INTEGRATION

LEARNING OBJECTIVES

- •Define tolerance & tachyphylaxis with clinical examples
- •Differentiate between tolerance and tachyphylaxis
- •Discuss different types and mechanism of drug tolerance
- • Identify strategies to minimize or prevent the development of tolerance and tachyphylaxis in clinical practice
- •Discuss the clinical implications of tolerance and tachyphylaxis

TOLERANCE



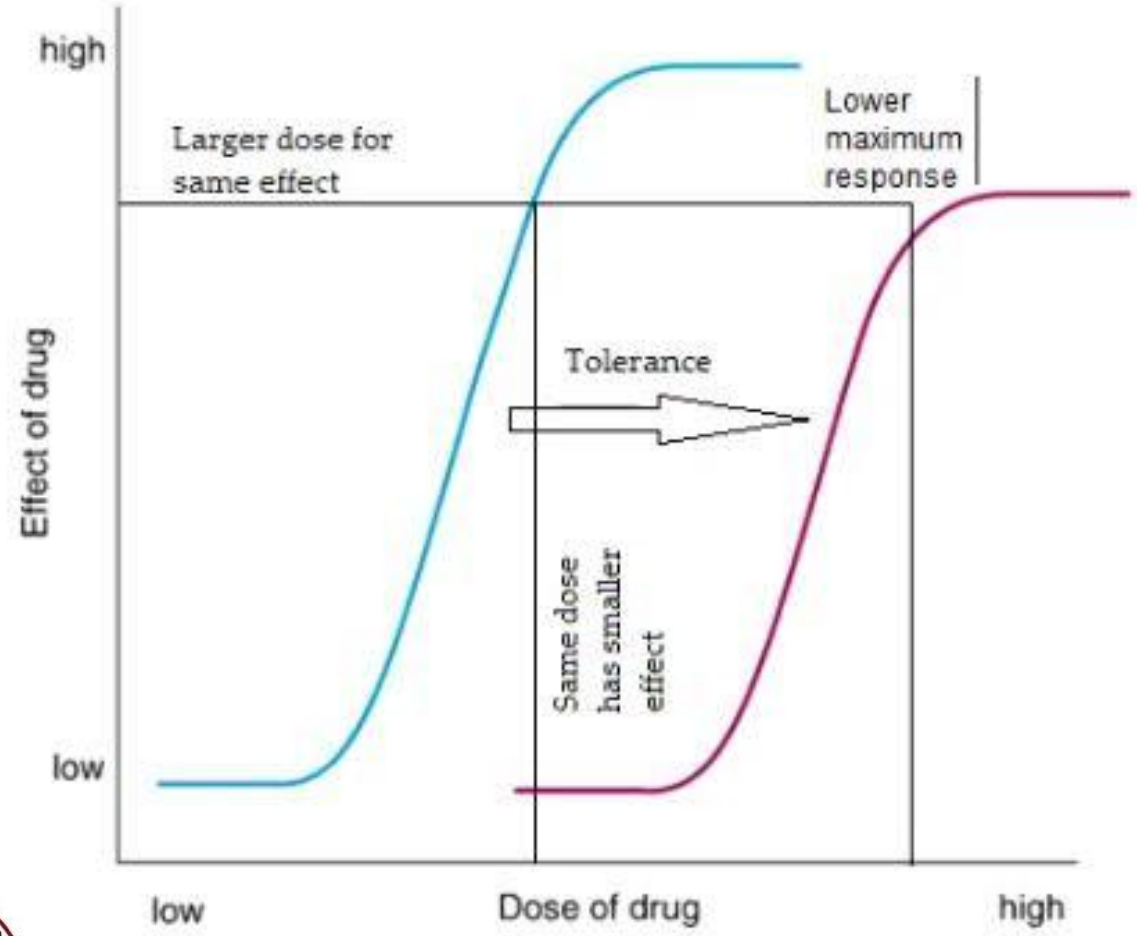
- Progressively diminished pharmacological response to drug at a certain dose following repeated or prolonged exposure, and requiring increasing dosages to achieve the desired effect on subsequent administrations

CHARACTERISTICS OF TOLERANCE

- Reversible
- Takes days to week to develop tolerance
- Dependent on the dose and frequency of drug exposure
- Variable time course and extent of tolerance development between different drugs.
- Not all drug effects develop the same amount of tolerance

DOSE RESPONSE CURVE

- Shifts to right
- In tolerant individual
  - The same dose has less effect
  - A greater dose is required to produce same effect



CORE SUBJECT

TYPES OF TOLERANCE

- Natural tolerance
- Acquired tolerance
- Learned tolerance

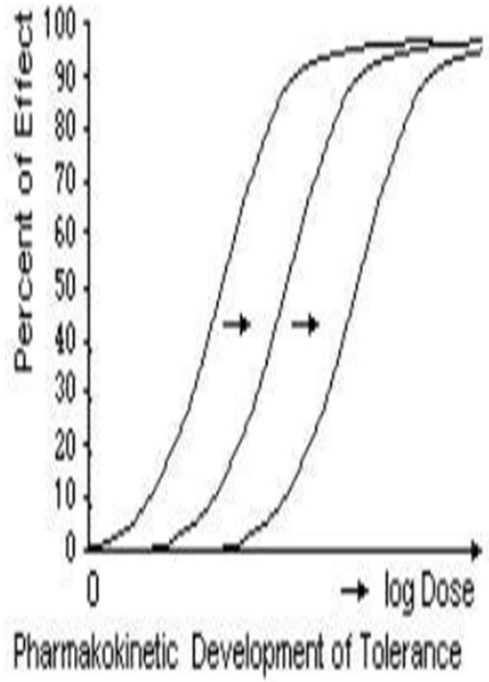
NATURAL TOLERANCE

- The species/individual is inherently less sensitive to drug
- Black races are tolerant to Mydriatics
- Rabbits are tolerant to Atropine
- Certain individuals are less responsive to certain drugs i.e beta blockers

ACQUIRED TOLERANCE

- Develops after repeated use of a dug in an individual who was initially responsive to it.
  - Pharmacokinetic tolerance
  - Pharmacodynamic tolerance
  - Learned tolerance

PHARMACOKINETIC TOLERANCE



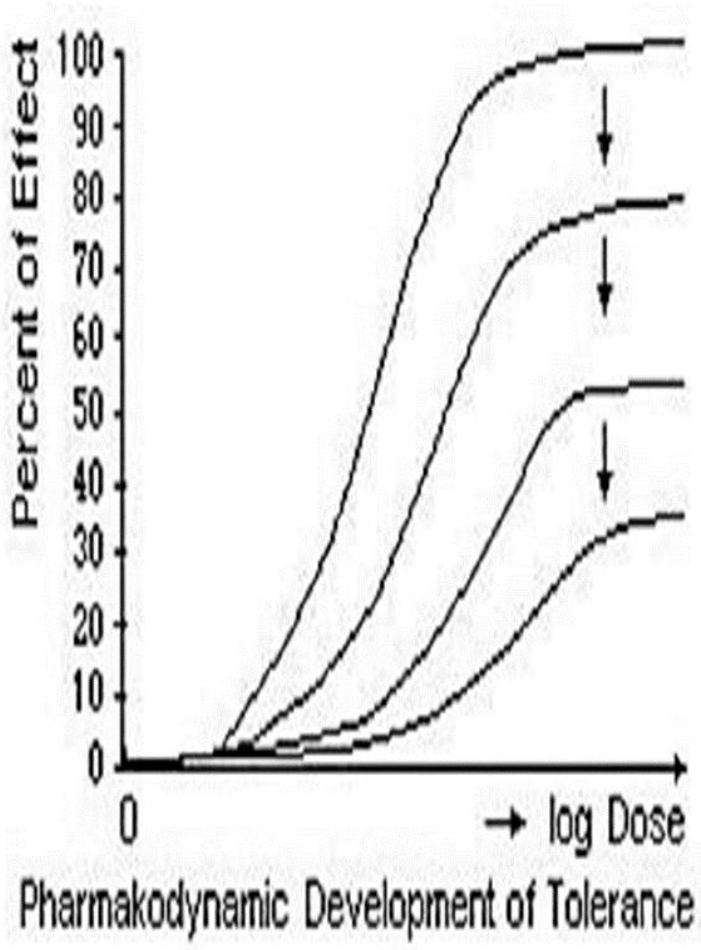
Pharmakokinetic Development of Tolerance

- Occurs when repeated use of a drug changes its pharmacokinetic properties & reduces the amount of the drug available at the target site
- Enzyme induction, e.g. Carbamazepine, Barbiturates
- Increased urinary excretion e.g. Amphetamine, Lithium Therapy

CORE SUBJECT

PHARMACODYNAMIC TOLERANCE

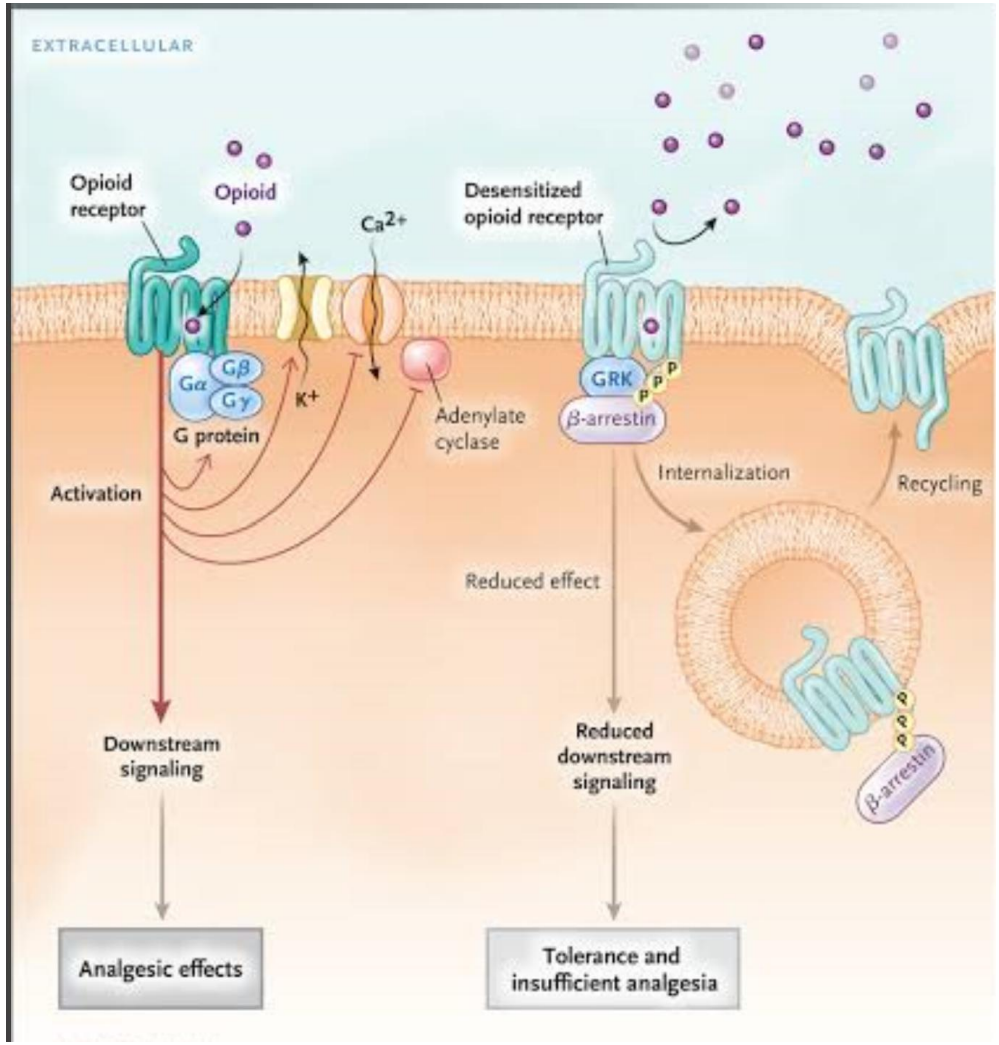
- •Occurs when repeated use produces adaptive changes within systems so that response to a given concentration of the drug is reduced



CORE SUBJECT

MECHANISM OF PHARMACODYNAMIC TOLERANCE

- **Desensitization of receptors**
- Desensitization is characterized by either a change in coupling of signal transduction pathways to receptors or by internalization of receptors into the cell
- e.g. Morphine



CORE SUBJECT+SPIRAL INTEGRATION

MECHANISM OF PHARMACODYNAMIC TOLERANCE

- **Downregulation of receptors**
- Downregulation of receptors reduces the number of functional receptors on the cell surface.
- e.g. Salbutamol

LEARNED TOLERANCE

- Reduction in the effects of a drug due to compensatory mechanisms that are acquired by past experiences
  - Behavioral tolerance
  - Conditioned tolerance

LEARNED TOLERANCE

- **Behavioral tolerance:**
- The skills that can be developed through repeated experiences with attempting to function despite a state of mild to moderate intoxication.
- At higher levels of intoxication, behavioral tolerance is overcome, and the behavioral deficits are obvious.
- Learning to walk a straight line despite the motor impairment produced by alcohol intoxication.

LEARNED TOLERANCE

- **Conditioned tolerance** (situation/context specific tolerance):
- Develops when repeated drug use reduces its effect in the environment where it is typically administered, but not in other environments.
- Opioid tolerance, Ethanol tolerance
- Caffeine tolerance, Heroin tolerance, Benzodiazepine tolerance
- What is the risk associated with it?

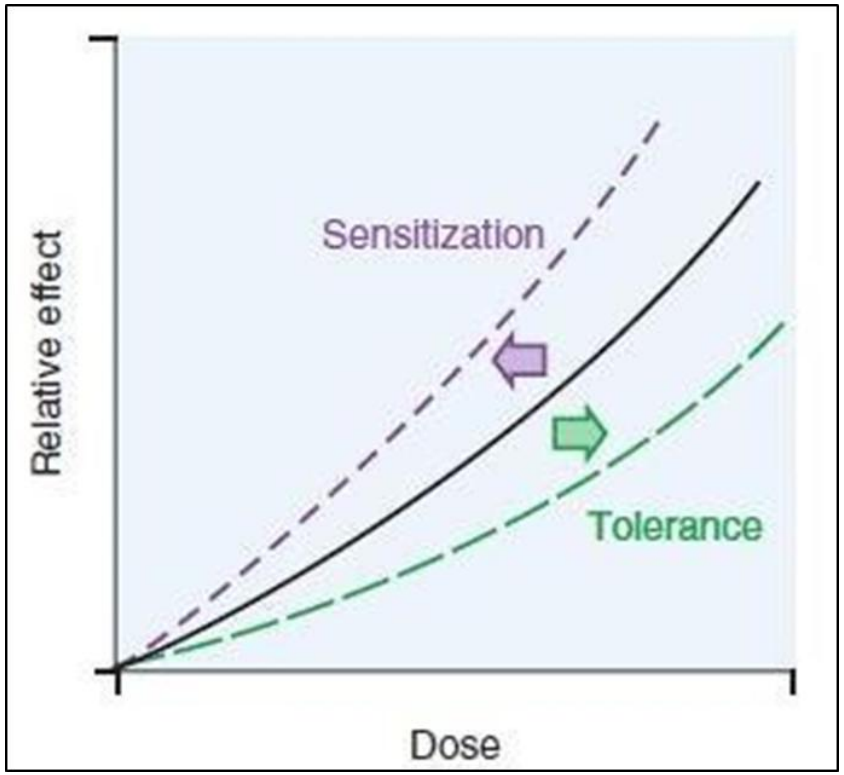
OTHER TYPES OF TOLERANCE

- Cross tolerance
- Reverse tolerance
- Tachyphylaxis
- Pseudotolerance

CROSS TOLERANCE

- When tolerance to one drug diminishes the effect of another drug
- Generally occurs between drugs of the same class
- **Opioids:** Morphine, Methadone
- Can occur between drugs with similar pharmacological effects
- **CNS depressants:** Morphine & Barbiturates
- Useful in medical management of drug dependence/detoxification
- Heroin addict is given methadone.

REVERSE TOLERANCE



- Also called SENSITIZATION
- An increase in response with repetition of the same dose of the drug.
- Shift to the left of the dose-response curve
- e.g. cocaine or amphetamine

CORE SUBJECT

TACHYPHYLAXIS

- It is rapidly developing reduction in response when same doses of some drugs are repeatedly given over short intervals
- Acute tolerance
- Rapid tolerance developing with repeated use on a single occasion, such as in a "binge."
- e.g. cocaine, ephedrine

TACHYPHYLAXIS

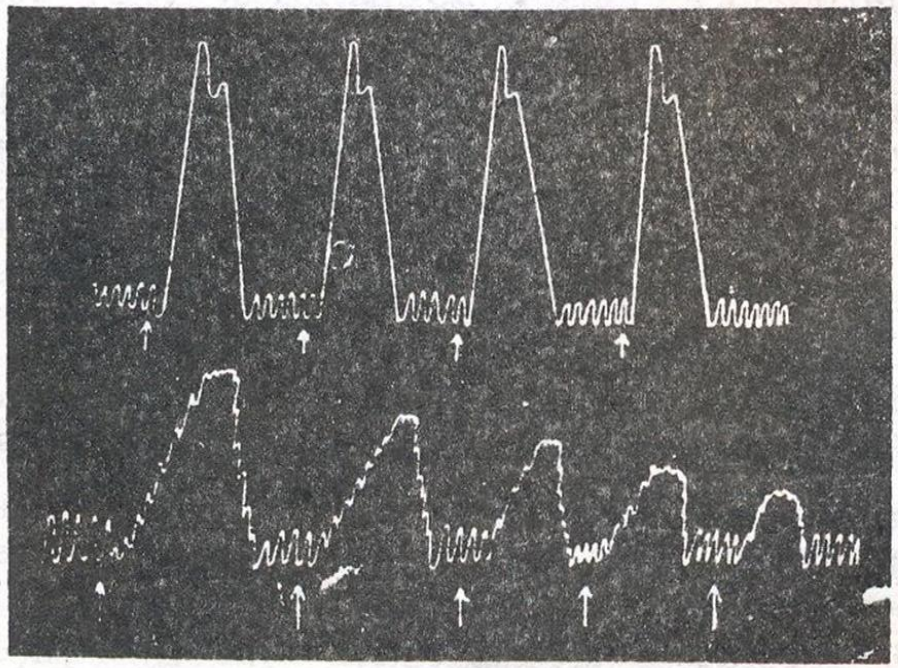
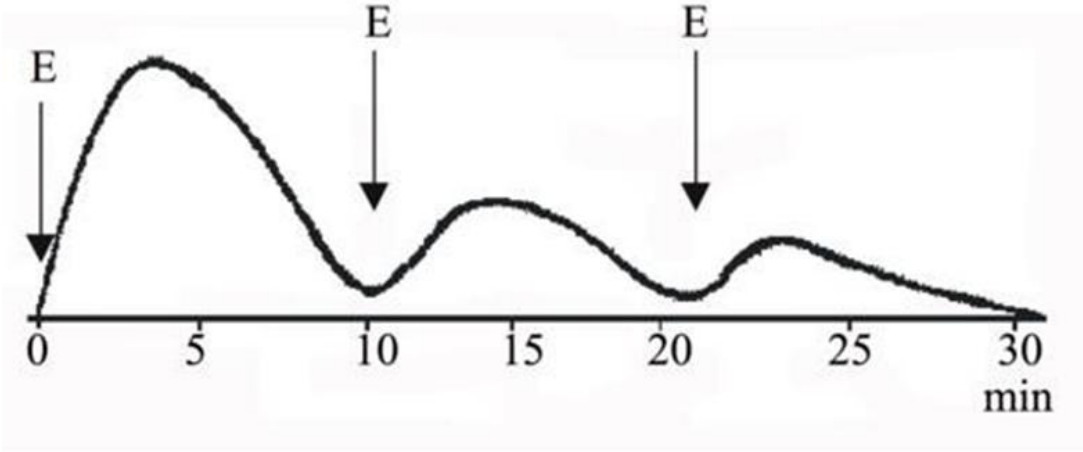


Figure 1-16. Effect of repeated doses of adrenaline (upper graph) and ephedrine (lower graph) on blood pressure in anaesthetised dog. Arrows denote administration of the same doses.

Effect of repeated doses of adrenaline is similar. It does not show tachyphylaxis. Exphedrine, an indirectly acting drug, shows tachyphylaxis as effect of repeated doses is progressively decreased.

Tachyphylaxis after repeted ephedrine administration (decrease ineffect on blood pressure)



E = ephedrine administration

VERTICAL INTEGRATION

TACHYPHYLAXIS

- **Mechanism:** Depletion of stores of mediators
- **Example:** Indirectly acting sympathomimetics
- Tyramine , Amphetamine , Ephedrine.
- Nitrate tolerance
- **Tachyphylaxis can be overcome by:** Increasing the interval between doses

TOLERANCE VS TACHYPHYLAXIS

	TOLERANCE	TACHYPHYLAXIS
Onset	Develops slowly	Develops rapidly
Dose dependency	Yes, high doses cause tolerance	Not dose dependant
How to overcome	Increase the dose Add adjunctive therapy Switch to other medications	Increase the dose interval
Example	Salbutamol, Benzodiazepines	Ephedrine, Nitrates

CLINICAL IMPLICATIONS

- Opioid use as analgesics
- Beta 2 agonists in asthma
- Beta blockers use as antihypertensives
- Antiepileptic drugs
- CNS depressants

VERTICAL INTEGRATION

CLINICAL IMPLICATIONS

- Monday disease?
- Drug Holiday?
- When drug holidays are not advisable?
- Opioids due to withdrawal symptoms
- Antidepressants and antiepileptics due to risk of relapse
- Beta-blockers due to risk of rebound hypertension

VERTICAL INTEGRATION

BIOETHICS

- Risk of overuse and dependence
- Monitoring foe side effects
- Avoid inappropriate polypharmacy
- Informed consent: explain tolerance and tachyphylaxis, alternative treatment strategies
- Limit unnecessary prescriptions
- Special consideration for vulnerable populations
- Prevent overprescription

SPIRAL INTEGRATION

ROLE OF FAMILY PHYSICIAN

- Early identification and prevention of tolerance and tachyphylaxis
- Explain drug tolerance to patients
- Adjust treatment plans (shift from benzodiazepines to behavioral therapy)
- Monitor polypharmacy
- Long term follow up
- Adress addiction risk

SPIRAL INTEGRATION

HOW TO ACCESS DIGITAL LIBRARY

1. Go to the website of HEC National Digital Library.
2. On Home Page, click on the INSTITUTES.
3. A page will appear showing the universities from Public and Private Sector and other Institutes which have access to HEC National Digital Library HNDL.
4. Select your desired Institute.
5. A page will appear showing the resources of the institution
6. Journals and Researches will appear
7. You can find a Journal by clicking on JOURNALS AND DATABASE and enter a keyword to search for your desired journal.

FURTHER READING

- Svensson CK. Attenuation of response to repeated drug administration: A proposal for differentiating tachyphylaxis and tolerance. The Journal of Pharmacology and Experimental Therapeutics. 2022 Apr 1;381(1):22-32.
- Bowen AJ, Huang TL, Nowacki AS, Trask D, Kaltenbach J, Taliercio R, Benninger MS, Milstein CF, Bryson PC. Tachyphylaxis and dependence in pharmacotherapy for unexplained chronic cough. Otolaryngology–Head and Neck Surgery. 2018 Oct;159(4):705-11.

SPIRAL INTEGRATION


Thank
you!