





Tolerance and Tachyphylaxis

- Dr Ayesha Jamil



Define Tolerance

Define Cross Tolerance

Define Reverse
Tolerance

Define Innate Tolerance

Define Tachyphylaxis

Define Drug Resistance

Define Drug Holiday

Describe The Mechanism
Of Tolerance &
Tachyphylaxis

Tolerance

Diminished response of same dose of drug given for prolonged period of time.

Need of larger dose of drug to produce the desired response which was initially produced with the smaller dose of the same drug.

Decreased response to a drug that necessitates larger dose to achieve the same effect.

Tolerance

Tolerance develops after a longer time, say weeks or months.

Types of Tolerance

**Natural/innate
Tolerance**

**Genetically determined
reduced/lack of response to a
drug**

Species specific

Racial Tolerance

Acquired Tolerance

**Develops due to
repeated exposure to
drug for a prolonged
period of time**

Innate Tolerance

Innate tolerance refers to the genetically determined reduced sensitivity (or lack of sensitivity) to a drug that is observed the first time that the drug is administered.

Species Tolerance

Some species are tolerant to certain drugs genetically.

Example;

Rabbits can tolerate large doses of atropine, doses that can produce toxic effects in humans.

Racial Tolerance

Some races show tolerance to certain drugs

Example

Blacks are tolerant to mydratics.

Acquired Tolerance

It develops due to repeated exposure to a drug.

Sometimes tolerance develops to certain effects of drug,

Example

Repeated use of morphine leads to tolerance to euphoric effects but not to meiotic effects and constipation.

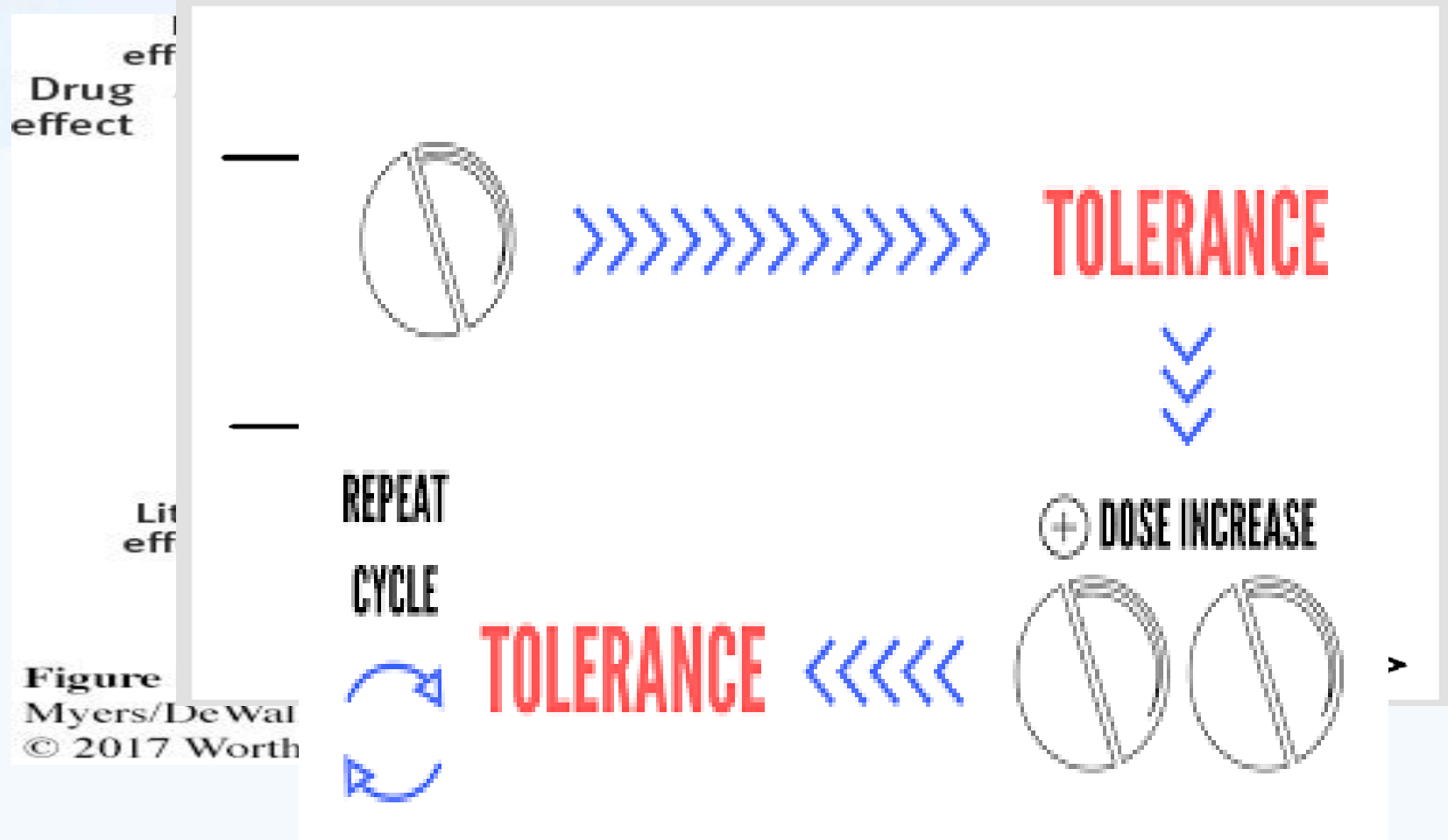


Figure
Myers/DeWal
© 2017 Worth

Mechanism of development of Tolerance

Pharmacokinetic Causes
(Dispositional Tolerance)

Pharmacodynamic
Causes
(Functional Tolerance)

Physiological Adaptation

Mechanism of development of Tolerance

Pharmacokinetic Causes
(Dispositional Tolerance)



Decreased concentration of
drug at the target site



Decreased absorption


Increased metabolism

Increased excretion

Mechanism of development of Tolerance

Pharmacodynamic Causes (Functional Tolerance)

Decrease in the number of
receptors
(Down Regulation)



Prolonged use of agonist result in gradual decrease in the surface receptors due to internalization of the receptors. This internalization occurs by *endocytosis* of patches of membrane, a process dependent upon phosphorylation.


Example

Isoprenaline causes decrease in adrenoreceptors.

Mechanism of development of Tolerance

Pharmacodynamic Causes (Functional Tolerance)

Decrease in receptor –
coupled signal transduction



Phosphorylation of intracellular region of
receptor protein, leads to tolerance.

Mechanism of development of Tolerance

Physiological Adaptation

Diminution of a drug's effect may occur because it is nullified by a homeostatic response.

Example :

B-P lowering effect of **Thiazide diuretic** is limited due to gradual activation of renin angiotensin system.

Cross Tolerance

Cross-tolerance is a phenomenon that occurs when tolerance to the effects of one drug produces tolerance to another drug.

It often happens between two drugs with structural similarity or similar functions or effects—for example, acting on the same cell receptor or affecting the transmission of certain neurotransmitters.

Ethanol & Benzodiazepines
(functional similarity)

Among different types of nitrates
Among different types of opioids.
(structural and functional similarity)

Tachyphylaxis

Also called acute tolerance.

DEFINATION

Repeated use of certain drug at short intervals may result in rapid decrease in pharmacological response is called **tachyphylaxis**.

Tachyphylaxis

Causes

Down regulation of receptors due to receptor phosphorylation

Change in receptors due to phosphorylation.

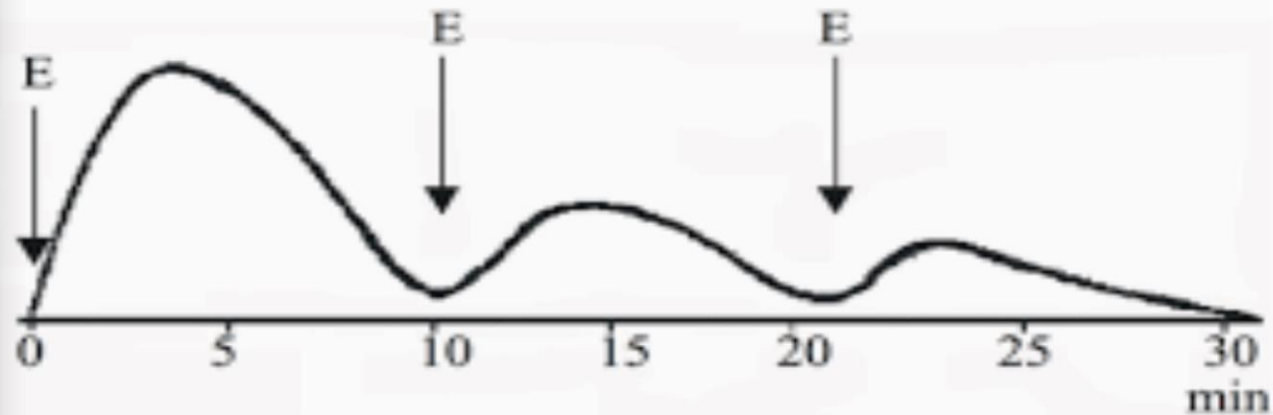
Exhaustion of Neurotransmitters.

Tachyphylaxis

Example

Ephedrine
Amphetamine

Tachyphylaxis after repeated ephedrine administration
(decrease in effect on blood pressure)



E = ephedrine administration

Reverse Tolerance



Drug sensitization

It is defined as an amplification in the response **(positive or negative)** of a drug resulting from repeated administration at a given dose.

Alcoholics initially develop **tolerance** to ethanol and require heavy drinking to produce effect.

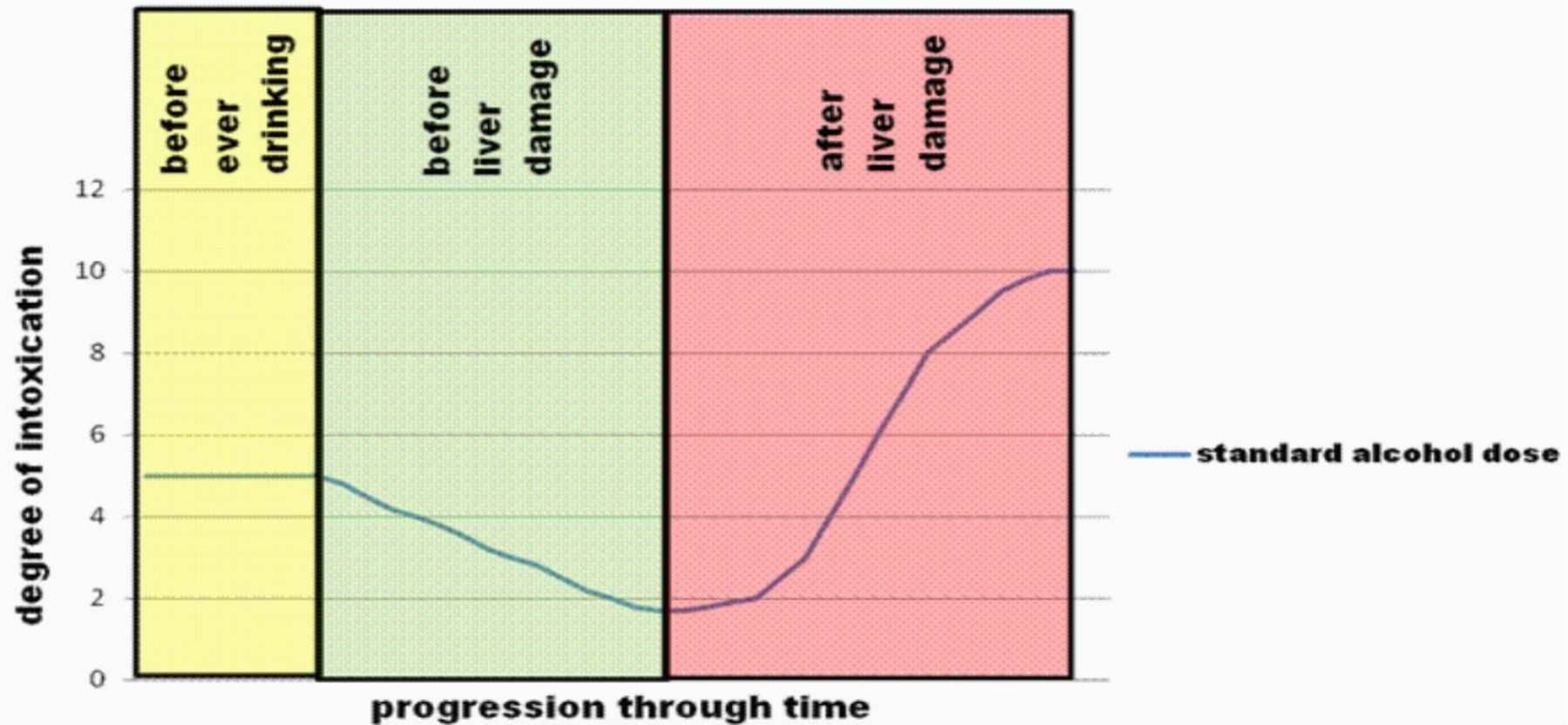
Heavy drinking often damage the liver.

Such people with damaged liver are at risk of intoxication now, even with smaller dose of ethanol.

Therefore---Smaller dose ----Amplified Response.

Reverse Tolerance

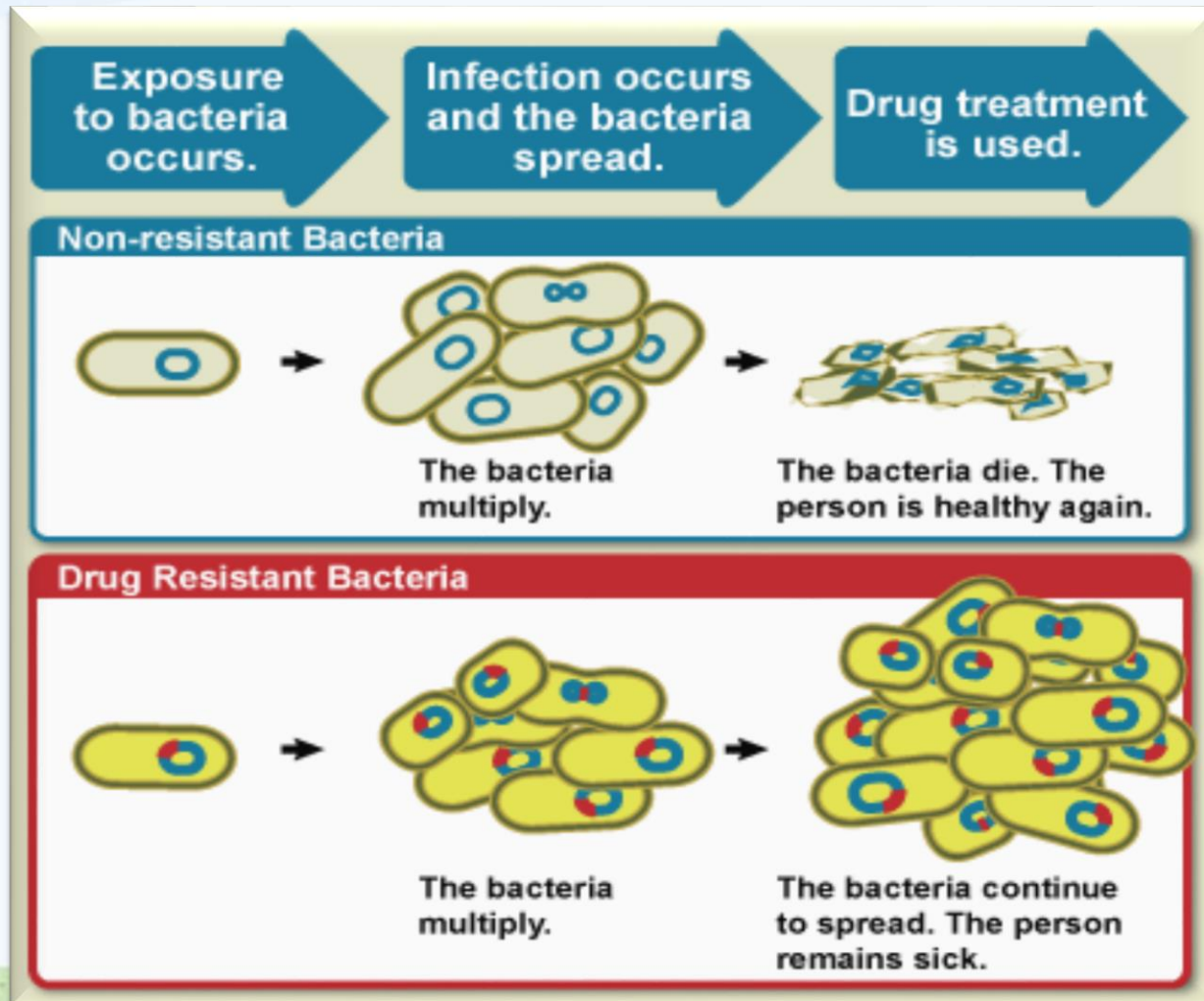
Figure 1) Course of Reverse Tolerance



Drug Resistance

Drug resistance- definition:

It is the “ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject”.



Drug Holiday

A drug holiday is defined as the ***conscious decision*** to stop using a regularly-prescribed medication for a period of time.

Also called
Tolerance Break

Drug holiday is referred to as a “**structured treatment interruption,**” for a period of hours, days, or months, and for a particular reason.

Benefits

- The renewed effectiveness of the medication
- Decreased tolerance for the medication
- Reduced side effects of the medication
- A “vacation” from the side effects of a drug

Drug Holiday

Example

Prolonged use of **nitrates** is (orally/patch/IV inf) associated with Tolerance.

Intermittent use is not associated with tolerance.

MONDAY
DISEASE

Workers of nitroglycerine factory or dynamite factory experience headache, dizziness, flushing, hypotension etc as the workers are sensitized on Monday i.e, after a weekend break but by Friday they become tolerant (desensitized) and don't experience such symptoms.

Drug Holiday

Example

One-day drug holiday in the **lithium** treatment of bipolar disorder, known as "lithium-free days",. **This reduces the toxic effects of lithium.**

Drug holidays from antipsychotic medication such as ***chlorpromazine*** have been used since the early 1980s to alleviate adverse reactions associated with long-term treatment.

Drug holidays from ***L-dopa*** found use in the early 1970s. This was found to be beneficial in terms of restoring the effectiveness of treatment specially when brain starts exhibiting decreased effectiveness

References

<https://www.sciencedirect.com/topics/medicine-and-dentistry/cross-tolerance>

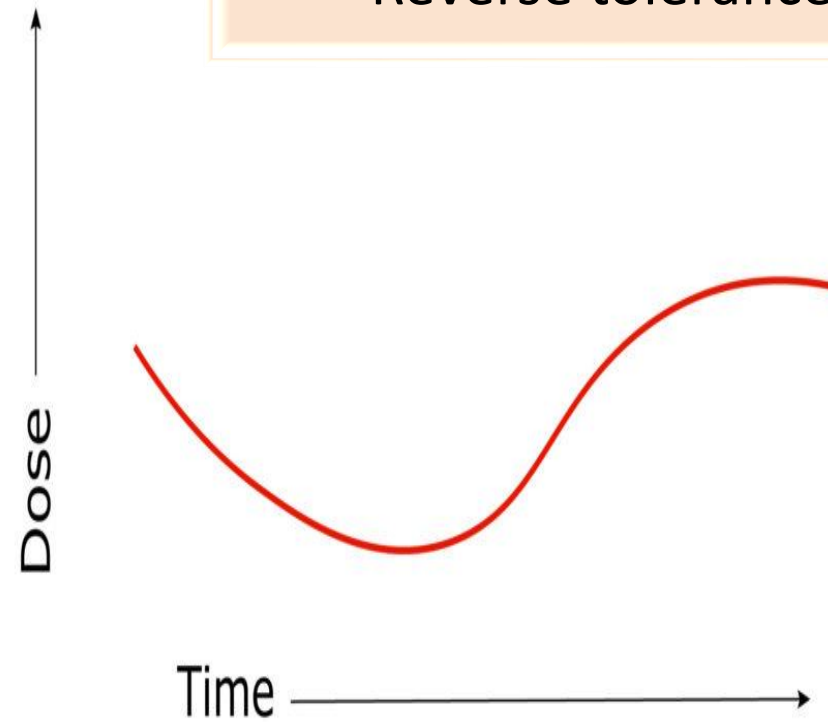
<https://www.verywellhealth.com/drug-holiday-definition-risks-and-benefits-2248870>

RANG AND DALE'S PHARMACOLOGY 6TH EDITION

Tara V Shanbhag/Smita Shenoy Pharmacology 5th edition

Quiz

Reverse tolerance



Thank You

