ADVERSE DRUG REACTIONS & PHARMACOVIGILANCE

Dr. Nashwa Aborayah

Associate professor of clinical and experimental pharmacology

Mu‘tah University- Faculty of Medicine

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Objectives

- What are adverse drug reactions?
- Difference between adverse effects and side effects
- Classification of adverse drug reactions
- Explanation and understanding of drug adverse drug reactions
- Drug abuse
- Pharmacovigilance

Adverse drug reactions

- **<u>Adverse drug reactions are</u>**: Harmful unwanted drug reactions
- **Which is:**

✓ Due to a drug

✓ At normal therapeutic doses

✓ May requires treatment, decrease in dose, stop the drug or caution in the future use of the same drug

Side Effects

•Unwanted (at time of treatment) unavoidable Pharmacological effects of the drug.
•They can be harmful or beneficial depending on time of use
•Occur at therapeutic doses.
•Predictable

Examples.

- H1 Anti-histamines: Sedation
- Aspirin: antithrombotic effect

An effect may be therapeutic in one context but side effect in another context

Adverse drug reactions

•**Incidence of ADR more in**:

• Polypharmacy, Elderly, Children, Patient with multiple diseases, Pregnancy, Malnourished, Immunosuppression, Drug Abusers and addicts

•**Adverse drug reactions develop**:

•Immediately, prolonged drug administration or after drug withdrawal

CLASSIFICATIONS OF ADR

- **A (Augmented)**
- **B (Bizarre)**
- **C (Continuous, chronic)**
- **D (Delayed)**
- **E (Ending Use)**
- **F (Failure of response)**

Type- A (Predictable)- Based on pharmacological properties
Type- B (Non-predictable) – Based on Immunological response and genetic makeup of person

Type A- Augmented

- These are based on the pharmacological actions of the drug so can be predicted.
- They are common and account for 75% of ADRs
- Dose-related and preventable mostly reversible.
- **Examples**:-
- Anticoagulants (e.g., warfarin, heparin) – bleeding
- Anti-hypertensives (e.g.α1-antagonists: prazocin) – hypotension
- Anti-diabetics (e.g. insulin) - hypoglycemia

Predictable

Type B- Bizarre

- Have **no direct relationship** to the dose of the drug or the pharmacological actions of the drug.
- Develop on the basis of:
- Immunological reaction to the drug (**Allergy**)
- Genetic predisposition (**Idiosyncrasy**): abnormal drug reactions to the usual dose of the drug.
- **Examples**????
- More serious clinical outcomes with higher mortality and morbidity.
- Mostly require immediate withdrawal of the drug.
- Uncommon

Un-predictable

TYPE C – CHRONIC (CONTINOUS) USE

- They are mostly associated with **cumulative-long term** exposure
- **Example:-**
- Analgesic (NSAID: aspirin)– interstitial nephritis, papillary sclerosis

Predictable

Type D – Delayed

- They manifest themselves with significant delay
- **Teratogenesis -**Thalidomide – Phocomelia (flipper-like limbs)
- **Mutagenesis**
- **Cancerogenesis**

Predictable

TERATOGENICITY (Teratos- Monster)

• The ability of a drug to cause defects in a developing fetus when it is administered during pregnancy.

•**Drugs can affect the foetus at 3 stages:**

1- Fertilization and implantation: conception to 17 days: failure of pregnancy which often goes unnoticed.

2- Organogenesis: 18 to 55 days of gestation most vulnerable period, deformities are produced.

3- Growth and development: 56 days onwards: developmental and functional abnormalities can occur

Examples: ACE inhibitors(growth retardation) , Thalidomide, Warfarin (eye and hand defects), antiepileptic drugs (cleft lip/palate).

Mutagenicity And Carcinogenicity

•Drugs that can Cause genetic defects and cancer respectively.

•**Mutagenicity**: Reactive intermediate metabolites of the drug can affect genes and may cause structural changes in the chromosomes

•**Carcinogenicity**: Certain chemicals and drugs can promote malignant change in genetically damaged cells, resulting in carcinogenesis.

•**Examples**: anticancer drugs, radioisotopes, oestrogens, tobacco

Type E – End Of Use

- Drug withdrawal syndromes and rebound phenomenons

- **Example:**
- Sudden withdrawal of long term therapy with **β-blockers** can induce rebound tachycardia and hypertension

Predictable

Type F- FAILURE OF RESPONSE (TOLERANCE)

•Failure of responsiveness to the usual dose of a drug

•**Types:** 1- AQUIRED 2- CONGENITAL: atropine can not cause mydriasis in rabbits due to atropinse

•**Acquired tolerance:**

•It occurs on repeated administration of the drug.

•More doses are needed to obtain the original effect.

•It is reversible: it disappears when the drug is stopped for some time.

•**Examples** of drugs causing tolerance: morphine, nitrates.

•**Special types of acquired tolerance**

1.Tachyphylaxis: Tachyphylaxis (Greek word, tachys, "rapid", and phylaxis "protection")

▪Acute, sudden decrease in response to a drug after its administration (a rapid and short-term onset of drug tolerance).

▪It can occur after an initial dose or after a series of small doses.

▪The original effect can not be obtained by increasing the dose.

•**Example: tachyphylaxis to action of salbutamol (**beta 2 agonist bronchodilator) used for treatment of bronchial asthma

•single-use bronchodilator response followed by a significant decline in bronchodilator response

▪**Mechanism**: polymorphism of beta 2 receptors leading to receptor downregulation

Tolerance

- There is not a biochemical, histological marker, or laboratory test that will predict tolerance or degree of tolerance in an individual.

Un-predictable

Drug abuse

- **Tolerance is the basis of drug abuse and addiction**: When a person uses a drug repeatedly, the body may develop tolerance to the drug.
- **Tolerance** may lead to **drug dependence**—the body develops a chemical need for the drug and can't function normally without it.
- Drug abuse occurs when people **intentionally** use any kind of drugs for non-medical purposes.
- A mood-altering drug, also called a **psychoactive drug** , is a chemical that affects brain activity (morphine, cocaine, methamphetamine).
- Most abused drugs are psychoactive.
- Drug abuse (psychoactive drugs) ➡ tolerance ➡ dependence ➡ addiction

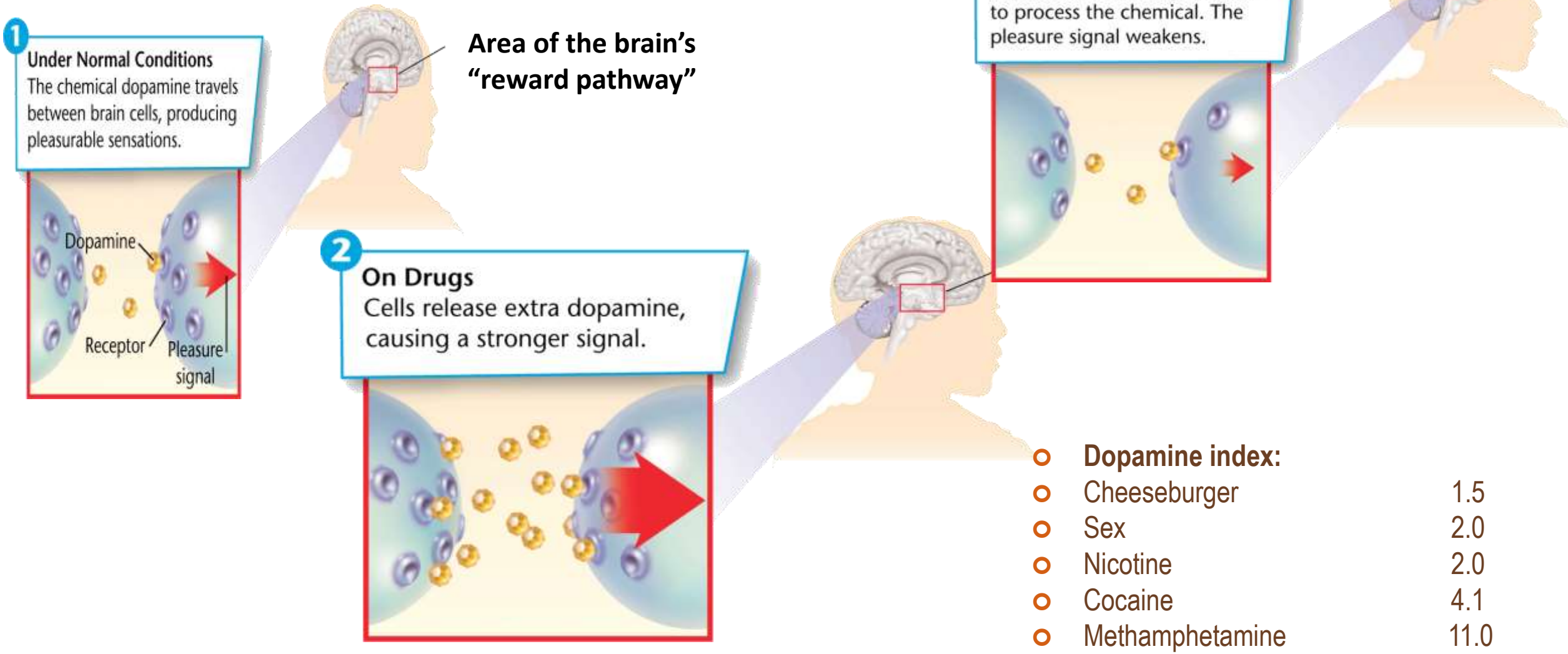
The Reward (system) Pathway

- Many psychoactive drugs trigger activity along a pathway of cells in the brain called the "reward pathway."
- Brain cells along the activated reward pathway release a chemical called dopamine.
- The extra dopamine released during drug use can cause the user to ignore the harmful effects of the drug and want to continue using it.
- Flooding the reward pathway with dopamine may lead to intense cravings for the drug.

How Drugs Affect the Brain?

Tolerance

Area of the brain's "reward pathway"



- **Dopamine index:**
- Cheeseburger 1.5
- Sex 2.0
- Nicotine 2.0
- Cocaine 4.1
- Methamphetamine 11.0

Addiction

•Abuse of psychoactive drugs may result in **addiction**.

•Addiction is the **compulsive use** of a drug, despite any cost to health, family, or social standing.

•Addiction is a disease that changes the structure and chemistry of the brain.

•**Withdrawal symptoms**: If a person who is dependent on a psychoactive drug stops taking the drug, that person will experience withdrawal symptoms including:

•Nausea, vomiting, headache, indigestion, paranoia or panic

•Tremors, seizures or death

DRUG-INDUCED DISEASES

•These are also called **iatrogenic (physician-induced)** diseases, and are disease caused by drugs .

•**Examples:**

•Hepatitis induced by isoniazid and Rifampicin

•Peptic ulcer induced by salicylates and corticosteroids

•Ototoxicity of streptomycin

•Reversible or not?

PREVENTION OF ADVERSE EFFECTS TO DRUGS

- **Avoid inappropriate use** of drugs .
- **Appropriate drug administration (Rational Therapeutics)**
- Dose
- Dosage form
- Duration
- Route
- Frequency
- Technique
- **Ask** for previous history of drug reactions and allergies
- **Always** suspect ADR when new symptom arises after initiation of treatment.
- Ask for laboratory findings like serum creatinine etc.

PHARMACOVIGILANCE (DAUP)

- The **science and activities related to the detection, assessment, understanding and prevention of adverse reactions**

- The information generated is useful in educating doctors and in the official regulation of drug use.
- **Significance:**

1- Rational use of medicines

2- Assessment of safety of medicines.

Various activities involved in pharmacovigilance

- **Post marketing surveillance** and other methods of ADR monitoring such as voluntary reporting by doctors.

- **Dissemination of ADR data** through 'drug alerts', 'medical letters,' sent to doctors by pharmaceuticals and regulatory agencies.

- **Changes in the labelling** of medicines indicating restrictions in use or warnings, precautions, or even withdrawal of the drug.

References

Lippincott's Illustrated Review

Pharmacology, 8th edition

Lippincott Williams & Wilkins

Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters . 16th edition McGraw Hill,*

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 10th edition*

THANK YOU