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ADVERSE DRUG REACTIONS AND DRUGS SAFETY

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Adverse drug reactions – classification, character.

Definition

According to expectations

According to severity

According to frequency

According to the mechanism of origin

A
B
Idiosyncrasy, allergies - type I, II, III, IV
C
D
Mutagenesis, teratogenesis, carcinogenesis
E

1. Adverse drug reactions

- Adverse drug reactions are undesirable responses to therapeutic doses.
- The adverse effect is an unintended or adverse reaction after administration of one or more medicinal products under normal use conditions, even when the drug was not used in accordance with the summary of the product characteristic for which it is suspected that arose in the context of drug administration.
- Adverse reactions represent a very heterogeneous group of reactions.
- They can be classified according to expectations, severity, frequency of occurrence or mechanism of origin.
- ADRs accompany the main pharmacotherapeutic effect of drug:
  - Excessively strong main effect
  - ADR doesn´t dependent on the main effect

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Adverse drug reactions

USA

- 5 - 20% reasons for hospitalization due to ADRs
- cca 100.000 fatal ADRs !

Germany

- 0,3 - 8% reasons for hospitalization due to ADRs
- cca 8.000 fatal ADRs !

5th place in the causes of death

ADRs increase the cost of healthcare!

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Adverse drug reactions

- according to expectations

- **An unexpected adverse reaction** is an adverse reaction whose nature, severity or consequence is not listed in the Summary of Product Characteristics (SPC).

- **An expected adverse reaction** effect is listed in the SPC.

- SPCs of registered products in the Czech Republic are available on the website www.sukl.cz in the Medicines section or on the website of the European Medicines Agency www.emea.europa.eu in the Product information / Human medicines section.

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Adverse drug reactions

- according to severity

- **Serious Adverse Drug Reaction (SADR)** means such adverse drug reaction which results in:
  - death,
  - is life-threatening,
  - requires hospitalisation or prolongation of existing hospitalisation,
  - results in permanent or significant damage to health or
  - limitation of capabilities or is manifested as a birth defect in offspring.

- **Non-serious Adverse Drug Reaction**

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Adverse drug reactions

- according to frequency

Frequency of ADR	Number of cases per patients
Very common	More than 1/10
Common (frequent)	More than 1/100
Uncommon (infrequent)	Between 1/100-1/1000
Rare	Between 1/1000- 1/10 000
Very rare	Less than 1/10 000

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Adverse drug reactions

- According to mechanism of origin

- A – **augmented** – caused by the same mechanism as a pharmacological effect.
- B – **bizzare** - „pacient's reaction" – caused by a genetic mechanism (idiosyncrasy) or by an imunological mechanism (allergies).
- C – **chronic** - caused by a long term taking.
- D – **delayed** - show after a longer period of latency.
- E – **end-of-use** - syndrom caused by discontinuing a drug.

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A - Augmented

- caused by the same mechanism as the pharmacotherapeutic effect.
- Induced by unappropriated dosage or by change in pharmacokinetics as a result of pathological process.
  - predictable
  - directly dependent on the dose
  - frequent, seldom fatal

- Insulin > hypoglycemia
- Anticoagulans > bleeding
- Betalytics > bronchi-constriction > asthmatic attack

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B - Bizzare

- Caused by a genetic mechanism (idiosyncrasy) or by an immunological mechanism (allergies).
  - unpredictable
  - do not depend on the dose
  - less frequent (1:1 000 až 1:10 000)
  - higher mortality
- Idiosyncrasy – reaction on the first dose, without previous sensibilisation (suxamethonium in individuals with atypical cholinesterase), polymorfisms.
- Allergic reaction - reaction after a previous sensibilisation.

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Allergic reaction

- The antigen must have a molecular weight of at least 1000.
- The non-immunogenic molecule of the substance (hapten) covalently binds to endogenous carriers and forms a conjugate> antigen.
- The antigen can cause:
  - production of specific antibodies (humoral response) or
  - T-cell response (cellular response) > inflammatory process.
- Reactions I, II, III - caused by antibodies.
- Reaction IV - caused by cells.

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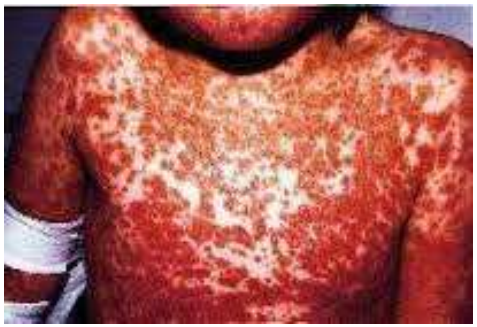
Allergic reaction - Type I

- Immediate anaphylactic reaction mediated by IgE antibodies - life threatening.
- Antigen-antibody reactions on the surface of
  - mast cells > degranulation of mast cells > release of pharmacologically active substances
    (histamine, leukotrienes, prostaglandins, platelet-activating factor, etc.).

    - Insect stings, allergic bronchial asthma, seasonal allergic rhinitis, urticaria,
    - penicillin and erythromycin antibiotics,
    - X-ray contrast agents,
    - salicylates.



http://zdravi.e15.cz/clanek/priloha-lekarske-listy/beta-laktamova-antibiotika-142697

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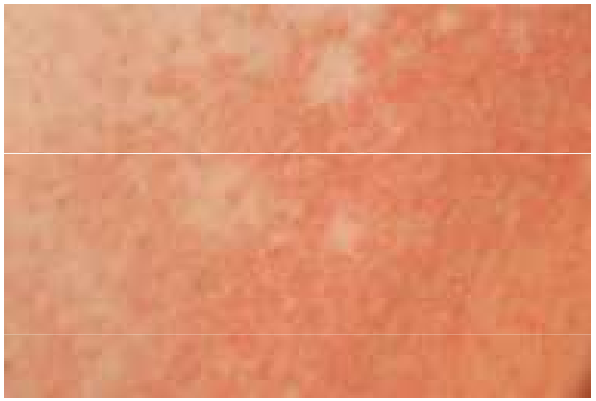
Allergic reaction - Type II

- It depends on IgG and IgM antibodies, which are able to fix complement on the cell surface and induce cell lysis.
- It is clinically manifested as anemia, thrombocytopenia, leukopenia and pernicious anemia.
- This reaction can be provoke by:
  - quinidine,
  - sulfonamides,
  - heparin.



https://escholarship.org/uc/item/5368s5x8

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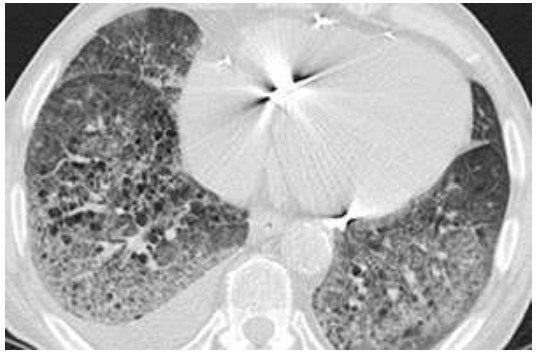
Allergic reaction - Type III

- Antigen-antibody interactions induce the formation of immunocomplexes > serum sickness.
- A similar mechanism probably arises:
  - pulmonary fibrosis during amiodarone therapy,
  - lupus-like syndrome associated with hydralazine treatment or
  - interstitial nephritis caused by non-steroidal anti-inflammatory drugs.

http://www.angisrevue.cz/revue/archiv/cislo/detail/35/



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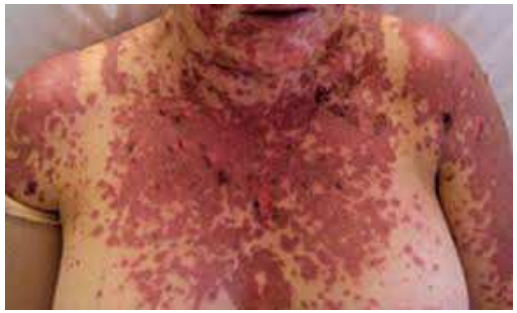
Allergic reaction - Type IV

- Delayed hypersensitivity reaction.
- The substance that enters the skin forms antigenic conjugates with proteins and stimulates the production of sensitized T cells in the regional nodes. If repeated contact with the substance occurs, then a skin reaction (rash) develops.
- This type of reaction can also be induced by systemic administration of the substance.
  - Contact dermatitis after administration of penicillin or after aminoglycoside antibiotics.

http://www.australiandoctor.com.au/clinical/therapy-update/cutaneous-drug-eruptions



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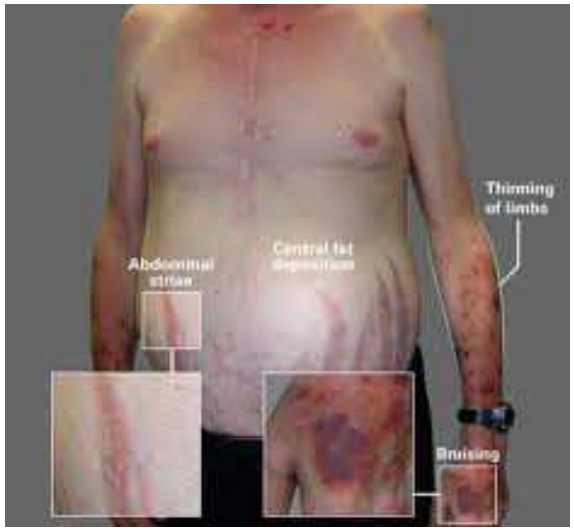
C - Chronic

- caused by a long term taking of drug
  - analgetics > nefropathy
  - prednisolone > iatrogenic Cushing´s syndrome
  - laxative > gastrintestinal dysfunction



http://medlibes.com/entry/cushings-syndrome

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D - Delayed

- manifest after a longer latency period (or in children treated patients)
  - mutagenesis
  - teratogenesis
  - carcinogenesis
- common features:
  - alteration of genetic information by affecting DNA
  - sensitivity of dividing and growing tissue
  - irreversibility of induced changes
  - non-specificity and diversity of external stimuli capable of inducing similar effects

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Mutagenesis

- Sudden, unregulated and permanent change in genotype that is transmitted during cell division.
- Some types of mutations can cause carcinogenic effects because they alter the coding sequence for proteins that are part of growth regulation.
- From the pharmaceuticals, mutagens are, for example, cytostatics from the group of alkylating agents.

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Teratogenesis

- Variations in the development of the individual - from fertilization of the egg to the postnatal period, including death of the embryo or fetus, morphological malformations, mental defects, growth retardation and intellect to various functional organ defects.
- **Thalidomide (Contergan) 1960> Focomelia**
- Decisive factors:
  - Type of substance, physical and chemical properties> placental penetration
  - Dose and duration of exposure
  - New fetal developmental stage - Gametogenesis> Blastogenesis> Organogenesis> Fetal developmental period
  - Maternal organism (age)
  - Individual reactivity

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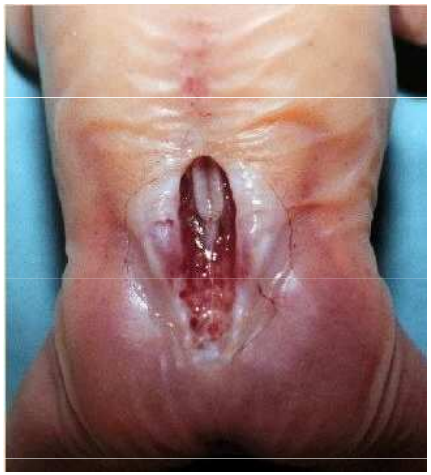
Teratogens



Spina bifida (valproic acid)

http://ec.cotot.com/spina-bifida

Fokomalia (thalidomide)

http://magazin.atlas.sk/spektrum/nezvratny-osud-katastrofy-za-ktore-si-mozeme-sami/727881.html

Gingival hyperplasia (phenytoin)

http://www.otszonline.hu/haziorvoslas/cikk/szisztemas_betegsegek_szajuregi_tunetei

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Cancerogenesis

- Substances which, by exposure, cause tumor growth in predisposed tissues
- carcinogens show a dose-response effect> dose accumulation
- participation of other factors:
  - viral interactions
  - environmental impact
  - age
  - sex
  - immunological factors

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E – End of use

- It manifests itself at the end of the administration of the active substance, eg as a rebound phenomenon (withdrawal syndrome).
- up / down-regulation of receptors

- Examples:
- Tachycardia after discontinuation of beta-drugs.
- Adrenocortical insufficiency after discontinuation of glucocorticoids.
- Seizures after discontinuation of anticonvulsant drugs.

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Pharmacovigilance = monitoring of drug safety

- is the science and activities relating to the:
  - detection,
  - assessment,
  - understanding,
  - prevention of adverse effects or any other medicine-related problem such as misuse or abuse of medicines, drug interactions, effects on foetus, breast-fed babies, etc.
- post-authorisation surveillance over medicinal products aimed at ensuring a maximum safety and as beneficial a risk/benefit ratio of the medicinal product as practicable.

Pharmacovigilance

- a system for collecting and evaluating the reports/signals, especially on how effectively drugs work
- the system for reporting adverse reactions concerns:

  physicians
  pharmacist
  marketing authorization holders
  healthcare providers
  patients
- monitoring the safety of drugs in clinical trials and clinical practice
- identification of safety risks of drugs
- measures to increase the safety of drugs
- OBJECTIVE: to minimize the risk associated with the use of drugs

Terminology in pharmacovigilance

- **Adverse Event (AE)**
  - an adverse change in the health condition affecting the patient or the trial subject who is the recipient of the medicinal product, even if it is not known whether it is in causal relationship with the treatment with this medicinal product. (Section 3(5) of the Act on Pharmaceuticals)
- **Adverse Drug Reaction (ADR)**
  - a reaction to a medicinal product, which is adverse and unintended. (Section 3(4) of the Act on Pharmaceuticals)
  - implies a certain degree of causality. In a clinical trial, it is an adverse event, in the case of which it is possible to state suspicion of a causal relationship with a certain medicinal product or multiple medicinal products, which were used in the study.

Terminology in pharmacovigilance

- **Serious Adverse Event (SAE)**
  - adverse event that results in death, is lifethreatening, requires hospitalisation or prolongation of existing hospitalisation, results in permanent or significant damage to health or limitation of capabilities or is manifested as a congenital anomaly or birth defect in offspring, irrespective of the administered dose of the medicinal product (Section 3(6) of the Act on Pharmaceuticals)
- **Serious Adverse Drug Reaction (SADR)**
  - such adverse drug reaction which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in permanent or significant damage to health or limitation of capabilities or is manifested as a birth defect in offspring. (Section 3(4)(a) of the Act on Pharmaceuticals)

Terminology in pharmacovigilance

- **Unexpected Adverse Drug Reaction**
  - adverse reaction the nature, severity or consequence of which is not consistent with the information available, for example with the investigator's brochure for an investigational medicinal product without marketing authorisation, or with the summary of product characteristics for an authorised medicinal product. (Section 3(4)(b) of the Act on Pharmaceuticals)
- **Unexpected Serious Adverse Reaction**
  - must comply with the definition of a serious adverse reaction and, at the same time, that of an unexpected adverse reaction
- **Suspected Unexpected Serious Adverse Reaction (SUSAR)**
  - occurrence of serious unexpected adverse reaction is in causal relationship with the investigational medicinal product. Evaluation of whether there is reasonable probability of a causal relationship is usually carried out by the investigator. If the investigator presenting the report does not provide information on a causal relationship, the sponsor should contact the investigator and request the investigator to comment on this aspect

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Pharmacovigilance after marketing authorisation

Clinical trials with antidepressants (75 clinical trials)

- Trials with positive result:
  - All 38 trials were published
- Trials with negative result:
  - 3 trials published
  - 23 trials have never been published
  - 11 publlished only in FDA summaries – never in academic litarature

- In fact, we have 38 positive studies and 37 negative ones, but in the academic literature we have 38 positive and only 3 negative ones.

Erick Turner et al., "Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy," *New England Journal of Medicine*, January 17, 2008

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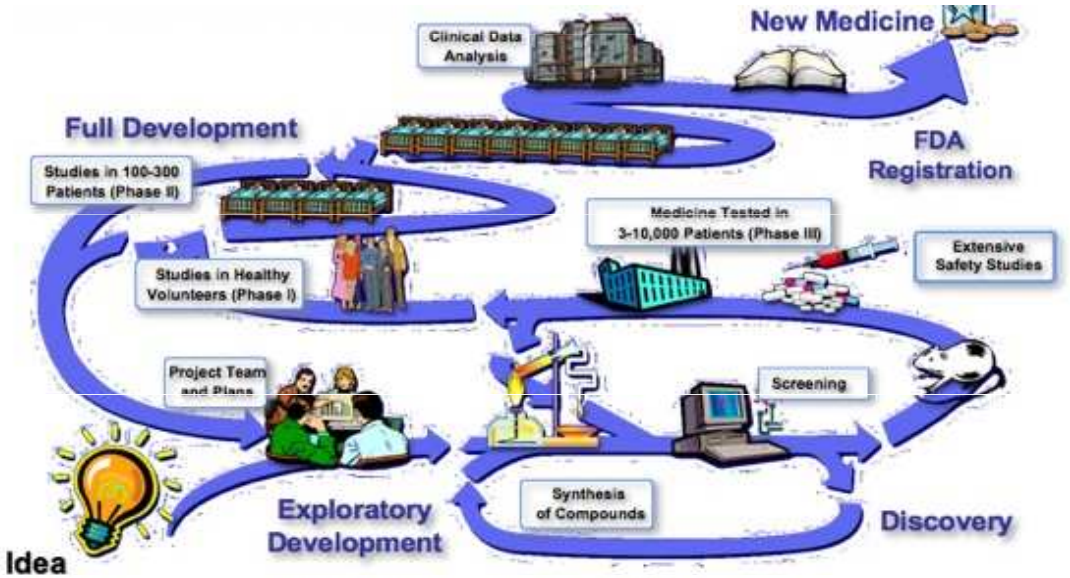
Critical point!

- Data are missing
- The probability that negative results are published is 20 times lower.



- What can we do?
- Re-evaluate in clinical practice!
- Tool: pharmacovigilance

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Drugs withdrawn from the market in connection with safety

- 462 drugs were withdrawn from the market for the period 1953 - 2013 for safety reasons, the most common reason being hepatotoxicity

- The average time from the first notification of an ADRs to withdraw a product from the market is 6 years and the interval does not shorten over time

https://www.ncbi.nlm.nih.gov/pubmed/26843061/

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Withdrawn Drugs (in the US, since 2000)

Drug	Year	Reason
Lumiracoxib	2008	Hepatotoxicity
Aprotinin	2008	Kidney and cardiovascular toxicity
Tegaserod	2007	Cardiovascular ischemic events
Ximelagatran	2006	Hepatotoxicity
Valdecoxib	2005	Dermatology adverse events
Pemoline	2005	Hepatotoxicity
Rofecoxib	2004	Thrombotic cardiovascular events
Levomethadyl	2003	Fatal Arrhytmia
Rapacuronium	2001	Risk of fatal bronchospasm
Cerivastatin	2001	Rhabdomyolosis
Trovafloxacin	2001	Hepatotoxicity
Amineptine	2000	Hepatotoxicity, dermatological side effects, abuse potential
Cisapride	2000	Cardiac arrhythmias
Troglitazone	2000	Hepatotoxicity