Pharmacovigilance:

How to Classify Severity and How to Establish Causality?

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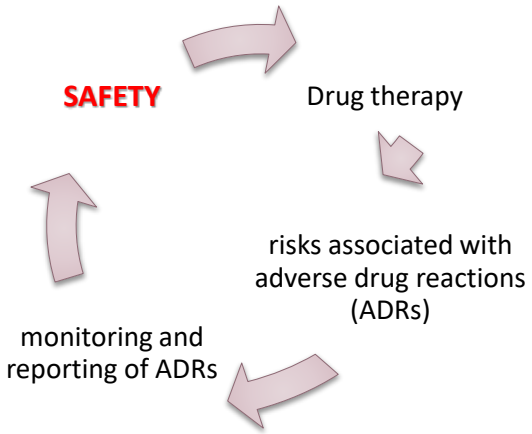


Introduction…

reporting suspected adverse drug reactions is MANDATORY for health professionals in Slovenia * (15 days)

*Medicinal Products Act (Official Gazette of the Republic of Slovenia, No. 17/14)
Rules on pharmacovigilance of medicinal products for use in human medicine (Official Gazette of the Republic of Slovenia [Uradni list RS], No. 57/14 and 27/17)

Pharmacovigilance

- Definition: **pharmacovigilance** is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems".
- Pharmacovigilance is an arm of patient care. It aims at making the best use of medicines for the treatment or prevention of disease.
- A strength of pharmacovigilance is its international nature.
- **spontaneous reports** (reports submitted directly by healthcare professionals and patients) are one of the ways of monitoring the medicinal product during the entire period of its use

Aims of pharmacovigilance

- improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions
- improve public health and safety in relation to the use of medicines
- detect problems related to the use of medicines and communicate the findings in a timely manner
- contribute to the assessment of benefit, harm, effectiveness and risk of medicines, leading to the prevention of harm and maximization of benefit
- encourage the safe, rational and more effective (including cost-effective) use of medicines
- promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public

Partners in pharmacovigilance

- Governments
- Industry
- Hospitals and academia
- Medical and pharmaceutical associations
- Poisons and medicines information centres
- Health professionals
- Patients
- Consumers
- The media

Activities in the field of pharmacovigilance include:

- collecting and assessing **reports** on adverse drug reactions and assessments of the ratio between the benefits and the risks of medicinal products
- assessment of other data related to medicinal products safety (studies, information published in scientific literature, etc.)
- detecting **safety signals**, assessment of identified risks, and adopting and implementing measures for the safe use of medicinal products
- assessment of safety data submitted by marketing authorisation holder in the Periodic Safety Update Reports (PSUR)
- assessment of **Risk management plans**, including risk minimisation measures
- conducting of pharmacovigilance inspections of marketing authorisation holders
- **encouraging healthcare professionals and patients to report adverse drug reactions**
- informing healthcare professionals and the public about pharmacovigilance of medicinal products

Pharmacovigilance – EXAMPLE:

Oncology pharmacists took the initiative for E-reporting of ADRs

Physician enters the ADRs into the application

The pharmacy receives automatically generated e-mail, "a new ADRs arrived "

Pharmacist completes the report, classifies it and consult the physician if necessary

Pharmacist generates the CIOMS and the program displays the form in pdf

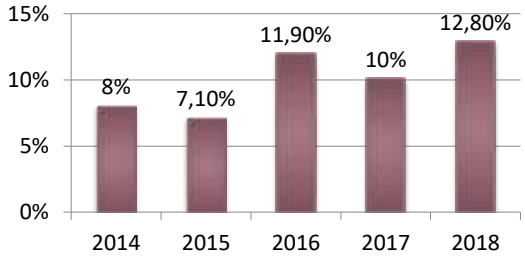
Pharmacist prepares a form for sending and the program automatically generates mail with the relevant addressees

E-mail with an attachment (CIOMS) form is delivered to the Center for pharmacovigilance and Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices

Reporting of ADRs in Slovenia in 2018

- Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP) - responsible
- JAZMP received **2704** reports (47,4% more than in y. 2017)
- Pharmacists contributed **345** reports
  - mostly from hospitals and clinics, but also from public pharmacies

The proportion of reports submitted to the JAZMP by pharmacists



Reporting of ADRs

- The number of reported ADR's has increased by **218%** since y. 2012 on national level
- The LZS - application is in use in several hospitals and community pharmacies in Slovenia
- this year (until October 1, 2019) 225 reports via www.NUZ.si to JAZMP

Frequency of ADRs

- It is based on data obtained in clinical trials and is continually updated
- convention used for the classification of frequency:

Very common	>= 1/10
Common (frequent)	> = 1/100 and < 1/10
Uncommon (infrequent)	>= 1/1000 and < 1/100
Rare	>= 1/10000 and < 1/1000
Very rare	< 1/10000 patients

Severity

Serious adverse event as one when the patient outcome is one of the following:

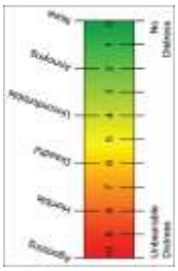
- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.
- Congenital anomaly
- Requires intervention to prevent permanent impairment or damage

Severity (serious ≠ severe)

- **Severity** is a point on an arbitrary scale of **intensity** of the ADR
- The terms **"severe"** and **"serious"** when applied to adverse events are technically very different.
- They are easily confused but can not be used interchangeably, requiring care in usage.

Example:

- *A headache is severe, if it causes intense pain*
- *scales like "visual analog scale" that help clinicians assess the severity.*
- *on the other hand, a headache is not usually serious (but may be in case of subarachnoid haemorrhage, subdural bleed, even a migraine may temporally fit criteria), unless it also satisfies the criteria for seriousness listed on previous slide.*



Assessing the severity of ADRs

Serious ADR

↔

high toxicity of drug

The intensity of adverse events graded by the NCI-CTCAE v 5.0 - Common Terminology Criteria for Adverse Events v5.0

NCI CTCAE

- is a descriptive terminology which can be utilized for Adverse Event (AE) reporting.
- a grading (severity) scale is provided for each AE term
- The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE

Example:

(Organski sistem)	CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Definition
Skin and subcutaneous tissue disorders	Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death	A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.

▼ Medicines under additional monitoring

- medicines that are being monitored particularly closely by regulatory authorities
- *WHY?*
  - new medicine
  - less information available
  - limited data on its long-term use
  - *it does not mean that the medicine is unsafe*
- list of medicines under additional monitoring is available at EMA (October 2019 – 370 medicines)*

EUROPEAN MEDICINES AGENCY *

https://www.ema.europa.eu/human-regulatory/post-authorisation/pharmacovigilance/medicines-under-additional-monitoring/list-medicines-under-additional-monitoring, 3.10.2019

Safety signal

= information obtained from one or more sources, including observation and experiments, indicating a new potential causal link or a new aspect of a known causal relationship between exposure to a medicine and events or a series of related events, for which it is judged that, that it is sufficiently probable to justify the verification

There are three categories of signals:

confirmed signals where the data indicate that there is a causal relationship between the drug and the AE;

refuted (or false) signals where after investigation the data indicate that no causal relationship exists

unconfirmed signals which require further investigation (more data) such as the conducting of a post-marketing trial to study the issue

Causality assessment

- = Determination of whether there is a reasonable possibility that the product is causally related to the adverse event.

- *"Regulatory reporting causality"* (No grey zone)
  - In clinical trial expedited reporting the classification is simple:
    - No: absolutely, positively unrelated
    - Yes: possibly, probably, remotely, unlikely…
- *"Medical causality"* (grey zone?)
  - Attempts to judge & quantify likelihood of causal association for use in signaling & labeling
- *"Legal causality"*

What data are needed?

- All medicines near the time of the event
  - dates
  - doses
  - Indications
- The event description
  - date of onset
  - duration to onset
  - event dictionary term
- Results of dechallenge & rechallenge
- Outcome of the event
- Patient medical history
  - past diseases of importance eg hepatitis
  - 0ther current diseases (co-morbidities) eg

- Dechallenge: the outcome of the event after withdrawal of the medicine

  resolved, resolving, resolved with sequelae, not resolved, worse, death, unknown

- Rechallenge: following dechallenge and recovery from the event, the medicines are tried again, one at a time, under the same conditions as before and the outcome is recorded

  recurrence , no recurrence, unknown, (no rechallenge)

Causality assessment – frequent ADR

Does the drug cause a certain ADR in the whole population?

is **more important** than

Has the medicine caused a certain ADR in a particular patient?

CLINICAL TRIALS

for frequent ones, comparing the incidence of ADRs in the study drug group to that in the placebo or other control group is done

Causality assessment – rare ADR

For rare events, the expected rate in a clinical trial database would be zero. Thus, if even a few cases (sometimes even a single case) of a rare life-threatening event occurred when none was expected, that would represent a serious safety problem for a drug product.

- assessment, whether the drug is capable of causing a particular ADR, is needed

- *Has the patient been exposed to the medicine / or did ADR occur during exposure to the medicine?*
- *Is there another cause for ADR?*

EXAMPLE

An ADR, which does not look related to the drug, but is:

Tendinitis or tendon rupture (eg Achilles tendon) when using quinolones (eg ciprofloxacin)

THEREFORE ... be without prejudice in assessing the causality between drugs and ADRs in the clinical work

„Got Cipro? If You Exercise, Be Careful!“*

* https://thedoctorweighsin.com/got-cipro-if-you-exercise-be-careful/ 9.10.2018

Did the drug do it?

- Some of the answers may be:
- Yes
- Yes, but only in certain circumstances (risk factors)
- Yes, because it interacted with another medicine
- No, it was another drug prescribed with it
- No, it was due to patients disease
- No, that drug could not cause that ADR

Aim of causality assessment

- Aim to answer the following question:
  - Did the drug cause this ADR?
  - Does the drug increase risk of this ADR?
- And therefore:
  - How to decrease the occurrence of this ADR

Drug-related ADRs

additional analysis needed:

- drug dose?
- when did ADR occur?
- adaptation and tolerance to ADR (eg nausea, drowsiness)
- interactions
- concomitant diseases
- demographic data
- analysis of ADR severity

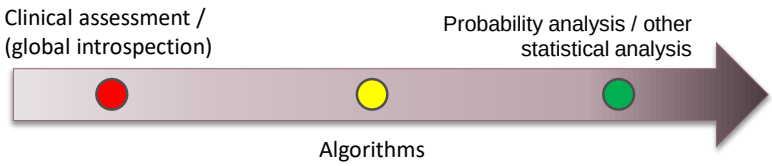
Basic Criteria for Causality

- Pharmacology and previous knowledge of ADRs
- Association (time & place) of AE and drug
- Plausibility (medical/biological)
- Likelihood or exclusion of other causes

Analyze everything in the report
& note what data are NOT in the report

Evaluation methods

3 categories of methods



Methods used to determine causality:

- Global introspection (clinical judgment)
  - Having smart, experienced medical people (usually MDs) make a judgment
- Algorithms - Use of a formal, defined mechanism or decision tree to come to a conclusion
  - Imputability (France), Roussel-Uclaf (France), Venulet (Switzerland), Karsh-Lasagna (US), WHO (Sweden), Naranjo (Canada)
- Probablistic, Baysian analysis & other "statistical methods"
  - Generally require more data than is available or data that is "introspective" – not yet practical.

the Uppsala Monitoring Centre (WHO–UMC)

and

the Naranjo Probability Scale

→are the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a **simple** methodology

→none of the methods is ideal or better because they all contain at least partial global introspection - observation (clinical judgment)

Naranjo algorithm - questionnaire

Naranjo Adverse Drug Reaction Probability Scale				
Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
TOTAL SCORE:				

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharacol Ther 1981; 30: 239-45

Naranjo algorithm - interpretation

- We score the questions according to the answer
- Scoring for Naranjo algorithm:
  - >9 = definite ADR
  - 5–8 = probable ADR
  - 1–4 = possible ADR
- 0 = doubtful ADR.
- One of the most widely used

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, et al. A method for estimating the probability of adverse drug reactions. Clin Pharacol Ther 1981; 30: 239-45

WHO-UMC system

Why causality assessment?

- An inherent problem in pharmacovigilance is that most case reports concern *suspected adverse drug reactions*.
- In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'.
- In an attempt to solve this problem many systems have been developed and causality assessment has become a common routine procedure in pharmacovigilance.

WHO-UMC system

Causality term	*Assessment criteria**
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

* All points should be reasonably complied with

Advances and limitations of standardised case causality assessment

What causality assessment can do	What causality assessment cannot do
Decrease disagreement between assessors	Give accurate quantitative measurement of relationship likelihood
Classify relationship likelihood	Distinguish valid from invalid cases
Mark individual case reports	Prove the connection between drug and event
Improvement of scientific evaluation; educational	Quantify the contribution of a drug to the development of an adverse event
	Change uncertainty into certainty

Evaluation problems

- incomplete information in the report
- polypharmacy - which drug caused the ADR?
- variability of clinical responses
- overdose with a medicine
- a disease is similar to the ADR
- ...

… BUT anyway:

any reporting is better than no-reporting

Key Criteria for Causality

- Product indication; duration of medication use
- Temporal relationship of ADR
  - Appearance of ADR = “challenge”
  - Disappearance of ADR = positive “dechallenge”
  - Reappearance of ADR = positive “rechallenge”
- Previous exposure = “prechallenge” (previous exposure to suspect drug)
  - Positive prechallenge
    - = ADR occurred in past when patient exposed to drug
  - Negative prechallenge
    = ADR did not occur in past when patient exposed to drug

Key Criteria for Causality

- Patient’s drug and medicine history
  - ADR occurred without exposure to suspect drug
  - AE did not occur in past
- Concomitant medications (indication, dosage)
- Preexisting or concomitant conditions, diseases
- Plausible or biologic or pharmacologic explanation

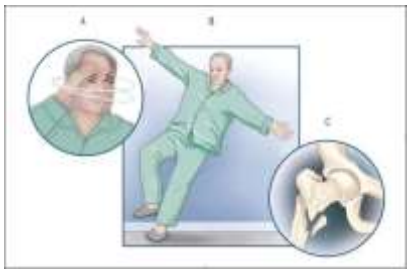
Examples:

- **Definitely Related**
  - Dizziness ¾ hour after ingestion of an oral antihypertensive drug with no concomitant drugs
  - Injection site reaction 30 seconds after a subcutaneous injection
- **Probably Related**
  - Thrombocytopenia after taking an anticancer drug
  - Diarrhea after antibiotics
- **Unlikely Related**
  - Cancer of the colon diagnosed after 3 doses of an antibiotic

Secondary AEs/Causality

Patient takes a drug that produces dizziness causing the patient to fall and break his leg

→ Is leg fracture considered an AE related to/caused by the drug?



Vir: http://www.fspt.guru/news/2015/12/2/dizziness-increases-your-risk-for-falls-and-fractures; Dostop 9.10.2018

Conclusion

the assessment of the causality is difficult and challenging

....

... therefore, complete the report as precisely as possible