Lecture 05: Causality - Methods

1. Basic information

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Content:	This hand-out describes causality assessment of ADRs and provides background information on the lecture 'Causality assessment – Methods' by E. van Puijenbroek, The Netherlands. This lecture is part of the **WHO PV core curriculum for university teaching**. The outline of this core curriculum consists of 5 key aspects on pharmacovigilance. This lecture refers to key aspect 2, 3 and 4 (i.e. preventing, recognizing and managing ADRs).

Current subject

Text to lecture on 'Causality assessment – Methods, by E. van Puijenbroek, The Netherlands.

Learning objectives:	Knowing the difference between extrinsic and intrinsic causality Be able to apply two different causality models: the WHO model ant the Naranjo algorithm
Target audience:	Medical, pharmacy, nursing students; End of Bachelor phase, start of Master phase
Requirements:	Knowledge on pharmacology, pharmacotherapy
Additional methods:	problem solving cases or real patients during internships, collecting information on specific ADRs and apply classification systems, identify risk factors.

Origin

Author:	E. van Puijenbroek, The Netherlands Pharmacovigilance Centre Lareb, University of Groningen
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Aim:	Lecture on Clinical pharmacology of ADRs in a 2-week pharmacovigilance course
Audience:	Pharmacy students, 1st year Master phase

2. Lecture: Causality - methods

Introduction (slide 1)

How sure can one be about the fact that an adverse event (which is an event that is not necessarily related to the use of a drug) is indeed caused by the use of a drug and thus should be called a true adverse drug reaction? By so called "causality assessment" the strength of a causal relationship between a drug and a clinical event that occurs in a patient can be assessed. Causality assessment may be needed for several reasons:

- In individual patient care, since everyone faces uncertainties in diagnosing ADRs. For future advice, it might be useful to know how certain the causal relationship of the ADR was in your patient.
- In addition, causality assessment is needed when analyzing case series that may point to yet unknown ADRs. Examples are clinical research and pharmacovigilance' signal detection.

In the previous lecture on the theory of causality assessment, we discussed the concept of causality in more detail, using the counterfactual theory. We also discussed the Bradford Hill criteria, which all may play a role in the assessment of the causal relationship. However, since circumstances may vary, not all criteria have to be used. Moreover the various aspects may contribute to the causality assessment with different weights. For this reason various methods for causality assessment have been developed over time.

Learning objectives (slide 2) and Outline (slide 3)

In this lecture, we will start by discussing differences between extrinsic and intrinsic factors that play a role in the assessment of causality. Subsequently we will focus on the use of two different causality models; the WHO model and the Naranjo algorithm.

Questions (slide 4 & 5)

To discuss. Of course it is important to annotate the strength of the relationship between drug en adverse event, but it may be more important to mention the reasons underpinning your judgement as well.

It will rarely be possible to exactly determine the strength of the association between drug and event. There will always be subjective elements in the assessment.

Extrinsic factors (slide 6)

We mentioned the difference between extrinsic and intrinsic factors when we discussed the Bradford Hill criteria. Extrinsic factors tell us 'How well known is this ADR'? This information can be found in various sources, for instance

- Product information (Summary of Product Characteristics, Patient Information Leaflet) or in literature.
- Information on the background incidence for developing symptoms similar to the ADR is scarcely present and should be searched for in literature.
- Pharmacovigilance databases with ADRs will not provide data on the prevalence of certain ADRs, due to profound underreporting. However, reporting numbers can be compared to

prescription data to check if an association of a drug-ADR is reported more often than others, which may inform you if a potential signal is present.

Intrinsic factors (slide 7)

Intrinsic factors refer to patient and drug related factors that play a role in developing an ADR. Drug related factors are pharmacologically plausibility in this specific patient, with its chemical, dynamic and kinetic properties. Dechallenge en rechallenge experiment may confirm a suspected ADR. In case of type A (pharmacological) reactions, concomitant medication should be taken into account for possible drug-drug interactions. Patient related factors included indication for drug use, comorbidity and genetic characteristics in drug metabolism or idiosyncratic reactions.

2.3 Causality models

Outline (slide 8)

In this section we will discuss two models that are used most frequently; i.e. the WHO model and the Naranjo model. We will discuss the different types of criteria that are used in these models as well as their advantages and disadvantages. We will end with some practical examples.

When to use causality assessment? (slide 9)

Causality models are relevant for individual patient care, and may be used when you suspect an ADR. Causality assessment is often required when assessing spontaneous reports. In addition, some journals may ask you to assess the strength of the causal relationship when publishing case-reports of ADRs.

Models for causality assessment? (slide 10)

Agbabiaka et al. published an overview of various causality methods and discuss their strengths and weaknesses. They identified 34 different methods. Because of poor reproducibility and validity, no single method is universally accepted. Different causality categories are adopted in each method, and the categories are assessed using different criteria.

Criteria used in causality assessment?(slide 11)

There are various models, that all refer to one or more of the Bradford Hill criteria above. This slide just shows a small section of the table from the article of Agbabiaka. As you can see many of them use similar (though not always the same) elements like

- Temporality
- De- and rechallenge (experiment of the Hill criteria)
- Response pattern (biological gradient of the Hill criteria)
- Epidemiological information (strength of the relationship Hill criteria)

➔ Discuss: which element are extrinsic and which ones intrinsic in nature.

Various types of causality models (slide 12)

It is obvious that a large number or models are in place. They differ from the factors that are taken into account, but also in respect to the extent to which these factors contribute (weigh) to the assessment. Three main categories can be distinguished

- Expert judgement/global introspection: individual assessments based on previous knowledge and experience. There is no standardized tool to arrive at conclusions regarding causality.

- Algorithms, using a set of specific questions (for instance on timing of events or additional risk factors) with associated scores. These scores are used to estimate the strength of the causal relationship.
- Probabilistic methods (Bayesian approaches). These approaches use specific findings in a case to transform the prior estimate of probability into a posterior estimate of probability of drug causation. The prior probability is based on epidemiological information (extrinsic factors) and the posterior probability combines this background information with the evidence in the individual case (both extrinsic and intrinsic factors) to estimate the strength of the causal relationship.

There is no standard in causality models, but a few are used more frequently. These are described below. In this lecture we will focus on two methods. One is the WHO algorithm, an example of an expert judgement or global introspection method, the other one is the Naranjo algorithm, which is an example of an algorithm using a set of specific questions.

We will not focus on probabilistic methods, since these are complex in nature and often designed for a specific situation.

WHO model (slide 13)

This slide just gives you an impression of the criteria used in the WHO method. You don't have to learn this by heart. This method is an example of an expert judgement approach.

Four grades of strength of a causal relationship are defined: unlikely, possible, probable, and certain. It is rather unpractical to compare each case with the wording of each grade.

WHO model (slide 14)

To summarize this WHO model two major factors should be assessed: time relationship and attribution to other factors. Thus, probability of an ADR can be estimated. An ADR (in a certain patient at a certain time) is certain when dechallenge en rechallenge test confirm you suspicion and other factors are absent. In practice, this is rarely feasible. Thus, many suspected ADRs are considered probable or possible, depending on the amount on information and time spent on the diagnosing process.

There is plenty of room for personal interpretation of the data, but it is important that the elements on which you have built your judgement are noted, so you can also explain later on why you reached this conclusion.

Naranjo algorithm (slide 15)

Naranjo algorithm is a widely used tool to assess causality of ADRs, as well as in clinical trials as in clinical practice. However, this tool has only been poorly validated. Three specialists in the field constructed a system of 10 questions that score 1, 2 or 0. The sum score is translated into the same grades of strength as the WHO model: unlikely, possible, probable, and certain.

Naranjo algorithm (slide 16)

An overview of the questions needed to use this algorithm is shown in the slide

Note that Naranjo is supposed to be an objective tool, but is has some subjective questions in it. For instance: what are conclusive reports (question 1)? It is practical to state that the ADR should be listed in SmPC or should be well known in literature. And what is objective evidence (question 10). Hepatic enzymes, electrolyte disturbances can be measured, biopsies can reveal histopathological abnormalities, photos and scans can show tissue damage, but not all reactions can objectively be confirmed. Also note that one should have good quality of information on the situation. With little information, 0 points can be scored. A lack of good quality of documentation is a serious problem with pharmacovigilance activities such as assessing ADR reports.

Naranjo algorithm (slide 17)

Based on the questions in the previous slide, a sum score can be calculated. This sum score translates into an estimation of the strength of the relationship.

- ➔ Question for the students: Do you think it is sufficient to not the outcome of the assessment in your patient file? Can you motivate your answer?
- ➔ Similar to the use of the WHO algorithm, it is wise to motivate your final outcome. Especially the clinical details should be noted, since evaluation of the case later on in the life of the patient can otherwise be bothersome.

Outline (slide 18)

We discussed the characteristics of factors contributing to the strength of the causal relationship and discussed two causality models that are widely used in literature. We will now discuss how these approaches are used in daily practice.

- ➔ The cases used in this presentation are just examples. It is advised to use cases based on drug and corresponding adverse drug reactions that students are likely to encounter later on in daily life. Feel free to use any other example

Case 1 (slide 19)

Flu-like symptoms with bisphosphonates has been a signal in pharmacovigilance, although the mechanism is unknown. More information can be found in literature (https://www.nof.org/patients/treatment/medicationadherence/side-effects-of-bisphosphonates-alendronate-ibandronate-risedronate-and-zoledronic-acid/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3513863/)

Case 1 (slide 20)

This slide shows a more detailed description of the symptoms the patients experienced

Case 1 (slide 21)

Based on the information that is available at this moment how do you rate the possibility and why. It is important that students realize that is it not always needed to rely on the use of a causality model, but they should also be able making up their own mind without using these models.

Case 1 (slide 22)

When she changed the use of risedronate 5 mg once daily into alendronate once weekly, her complaints disappeared.

Case 1 (slide 23)

Based on the information that is available at this moment we can complete only part of the questions form the Naranjo algorithm. Please note the difference between question 4 (did the adverse reaction reappear when the drug was re-administered) and question 9 (Did the patient have a similar reaction to the same or similar drugs in any previous exposure?) The first question is about a ***planned*** rechallenge, second one about a previous exposure in the past. In this case we are dealing with the situation that the patient experienced similar symptoms in the past.

Case 1 (slide 24)

Question 1 refers to the extrinsic factors of causality: What is the previous knowledge about this specific association. You may refer to sources like the Summary of Product Characteristics, Literature (Pubmed) or pharmacovigilance databases like the Uppsala Monitoring Centre, Eudravigilance, FEARS or your own national pharmacovigilance centre.

Case 1 (slide 25)

This is the official product information of the various bisphosphonates. Apparently flu-like symptoms have been reported with risedronate.

Case 1 (slide 26)

Also in the UMC/WHO database a large number of reports were present linking flu-like symptoms to the various bisphosphonates. The association is disproportionally reported in this database, which may point at the existing of ADR instead of an AE. (See the corresponding lecture on signal detection for information on the principles of signal detection)

Case 1 (slide 27)

We can now complete all 10 questions of the algorithm of Naranjo.

Case 1 (slide 28)

The sumscore is 7, which corresponds with “probable”.

Exam question 1 (slide 31)

Answer: D. Description of the ADR is an extrinsic factor, a pharmacological explanation is an intrinsic factor. Dechallenge and rechallenge tests were not performed in this case: the symptoms resolved after 6 hours and occurred after every administration. This reflects dose-response with its pharmacokinetic properties. A true test should stop the drug for at least 5 times elimination half-life and reintroduce the drug when you are sure there was no other cause for the symptoms.

Exam question 2 (slide 32)

Answer b is correct. The severity does not play a role in the causality assessment according to Naranjo. The other factors are present as separate factors that should be assessed.

2.5 Literature used in this lecture:

(slide 33)

1. Taofikat B. Agbabiaka, Jelena Savovi, Edzard Ernst. Methods for Causality Assessment of Adverse Drug Reactions A Systematic Review. Drug Safety 2008; 31 (1): 21-37
2. Anonymous. The use of the WHO-UMC system for standardised case causality assessment. Website Uppsala Monitoring Centre. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf
3. Naranjo et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;239-245