The logic of causality

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Acknowledgments

This presentation is the result of a joint effort by my colleague Dr Ruth Savage and myself

The question

Is there a reasonable possibility that the drug caused the suspected adverse drug reaction (ADR) observed?

Probability

We can rarely say without any doubt that a specific drug caused a specific reaction

Causality assessment deals with probability

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 the patient's disease**
- **No, that drug could not cause that reaction**

Rationale for causality assessment in PV

To define relationship drug-ADR

As an aid in signal detection

To base risk minimizing action on evidence

Causality Assessment Methods

Structured approach to determining relationship between reported event and suspected drug

Many methods

Fall into 3 categories:

- 'Global introspection' qualitative (e.g. WHO-UMC) or quantitative (e.g.French imputability system)
- Algorithms e.g. Naranjo, RUCAM
- Probabilistic methods e.g. Bayesian

Generally poor agreement between methods

Agbabiaka, T., J. Savović, et al. (2008). "Methods for Causality Assessment of Adverse Drug Reactions." Drug Safety 31(1): 21-37

The WHO-UMC standardised system for causality assessment

Categories

Certain

Probable

Possible

Unlikely

Unclassifiable/Conditional/Unclassified

http://www.who-umc.org/Graphics/26649.pdf

Naranjo algorithm

- **Uses a series of 10 questions**
- **Questions can be answered as**
  Yes, *No* or *Do not know*
- **Answers are weighted with scores (-1 to +2)**
- **Total score is ranked on a probability scale**

> 9	certain
5-8	probable
1-4	possible
0	unlikely

Naranjo algorithm

Naranjo, C. A., U. Busto, et al. (1981). "A method for estimating the probability of adverse drug reactions." Clin. Pharm. Ther. 30(2): 239-245.

	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
Did the adverse reaction appear when the drug was readministered	+2	-1	0	
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
Did the reaction appear when a placebo was given?	-1	+1	0	
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0	
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

certain > 9; probable 5-8; possible 1-4; unlikely 0.

Naranjo Algorithm

The Naranjo algorithm appears more straightforward to use.

Still requires clinical judgement

Gives a score for previous evidence of the suspected ADR, WHO-UMC method looks at each report independently.

Designed for clinical trials so includes questions that usually can't be answered from the information in spontaneous reports.

No conditional/unclassified category. Can achieve a ¨possible¨ ranking without a reasonable time to onset.

So tendency for large ¨possible¨ category. New suggestion is to split this group into those that are more or less likely to be ADRs.

Supra-therapeutic blood levels do not always imply the drug is causal. Applicable in clinical trials where looking for dose-related effects.

Bayesian probability method

Probability of an event occuring in the presence of a drug relative to probability of the event occuring in absence of the drug

$$\frac{\text{Probability of Event (Drug)}}{\text{Probability of Event (No Drug)}}$$

Based on Case Information

Based on Clinical Trial and Epidemiological Data

Requires:

- specific information about the event (history, timing, dechallenge, rechallenge)
- detailed knowledge of clinical event and its epidemiology

The logistic (probabilistic) method

Theophile et al 2013

Seven causality criteria, similar to Naranjo's, given statistical weighting

- **Time to onset**
- **Dechallenge**
- **Rechallenge**
- **Search for alternative causes**
- **Risk factors (eg drug/disease or drug/drug interactions)**
- **Reaction at site of application, toxic plasma concentration or validated laboratory test**
- **Previous information on the drug and symptomatology (suspected ADR)**

The WHO-UMC standardised system for causality assessment

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Criteria for WHO-UMC Causality Categories

Certain

Event or laboratory test abnormality, with a pharmacologically and pathologically plausible time relationship to drug intake

Cannot be explained by disease or other drugs

Response to withdrawal (dechallenge) is pharmacologically, pathologically plausible

Event definitive pharmacologically or pathologically (ie an objective and specific medical disorder or a recognised pharmacological phenomenon)

Rechallenge satisfactory

Positive dechallenge

Improvement/resolution of the ADR after therapy stop

- Not applicable when irreversible tissue damage has occurred
- Changes in tissue function might mimick natural disease→time to improvement follows natural evolution

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Positive rechallenge

The same event reappears after restarting treatment -> a strong indicator of a causal relationship between drug and ADR

Intentional rechallenge is often not feasible for ethical reasons

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Rechallenge

A true rechallenge occurs after the patient has fully recovered after the first exposure to the drug is ended and the drug is re-administered in the same formulation, at the same dose and by the same route.

However, a positive skin test result for allergy would be acceptable for a ¨certain¨ report

In a few instances rechallenge is not necessary for a ¨certain¨ report, eg a patient with renal stones almost entirely composed of the suspect drug (eg an anti-retroviral agent).

Criteria for WHO-UMC Causality Categories

Probable

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

Criteria for WHO-UMC Causality Categories

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

Criteria for WHO-UMC Causality Categories

Unlikely

Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable

Disease or other drugs provide more plausible explanations

Criteria for WHO-UMC Causality Categories

Conditional/Unclassified

Event or laboratory test abnormality

More data for proper assessment needed, or

Additional data under examination

Criteria for WHO-UMC Causality Categories

Unassessable/Unclassifiable

Report suggesting an adverse reaction

Cannot be judged because information is insufficient or contradictory

Data cannot be supplemented or verified

The «French Method»

Developed in 1978

- J. Dangoumou, J.C. Evreux et J.Jouglard …?

Updated in 1985

- B. Bégaud, J.C. Evreux; J. Jouglard et Lagier, Thérapie 1985;40:111-8

Applied to each Drug-ADR pair in a single report

Mandatory for reporting to French Authorities

Intrinsic and extrinsic imputability

Intrinsic imputability established on the basis of the information the single report provides and performed for every single drug in the report

Extrinsic imputability established on the basis of previous knowledge of the ADR-drug pair(s)

Intrinsic imputability

3 chronologic criteria

- Time to onset
- Evolution after dechallenge
- Evolution after rechallenge

4 semiologic criteria

- Mechanism of action
- Differential diagnosis
- Investigations
- Risk factors

Scoring

Chronology		Semiology	
C3	suggestive	S3	suggestive
C2	plausible	S2	plausible
C1	doubtful	S1	doubtful
C0	incompatible	S0	incompatible

Intrinsic imputabilty

The values in the C table are combined with those of the S table resulting in an intrinsic imputability score I between

I4 (very suggestive) and I0 (incompatible)

Extrinsic imputability - Scoring

B3

- Drug/ADR pair described in standard literature (Meyler's, Martindale, SmPC etc)

B2

- isolated publications related to similar drug or similar ADR

B1

- available documentation does not cpver either B3 or B2

B0

- no information available despite extensive literature search

Final score

Combination of I0 – I4 and B0 – B3

Sometimes it's difficult…

For all methods, if report causality is clearly *probable* or *certain* this is a key report.

If it is difficult to know whether to assess report causality as *probable* or *possible* the decision is not very important.

What causality assessment can do

Classify the relationship

Mark individual case reports - key reports

Improve scientific evaluation by systematic use of available data

Decrease disagreement between assessors

What causality assessment cannot do

Prove the connection between drug and event

Factors to consider

Temporal association between drug exposure and event

- Plausible (exposure and effect)

Extrinsic imputability

- Pharmacological plausibility, possible mechanism
- Existing information on the drug and ist safety profile

Intrinsic imputability

- Patient's characteristics and medical history
- Clinical characteristics of the event
- Comedication
- Dechallenge/rechallenge/outcome

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Single case causality assessment

Demographic data
Medical history
Chronology – Time to onset
Risk factors
Differential diagnosis
De-/Rechallenge
Concomitant medication
Other confounders/bias

Summary

Use of a causality assessment method provides structured approach to assessing the relationship between drug and adverse event

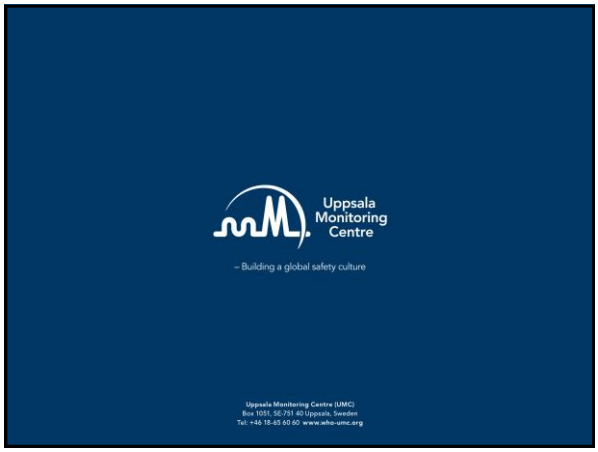
Causality assessment deals with probability

There is no gold standard for causality assessment

Depends on good information (high quality reports)

Different assessors may draw different conclusions based on the same information

A causality assessment is always provisional as knowledge about a drug increases with time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