Causality assessment

20 April 2015
Meyler course 2015
Eugene van Puijenbroek, MD PhD, clinical pharmacologist
Learning objectives

• Understand the concept of counterfactuals

• Know how to apply the Bradford Hill criteria in drug safety

• To be able to use two different causality model for the assessment of adverse drug reactions.
  - Causality scheme of Naranjo
  - knowing the difference between extrinsic and intrinsic causality
Outline

• Counterfactual theory

• Bradford Hill Criteria

• Causality algorithms
Counterfactual theory
"Do you think all these film crews brought on global warming or did global warming bring on all these film crews?"
Question..

It is important to annotate the strength of the causal relationship between drug and adverse drug reaction

1) Agree
2) Do not agree
Drug X  →  ADR B

[Diagram showing the process from Drug X to ADR B with crossed-out elements indicating actions to avoid]
Counterfactual theory

- When B occurs after X and B does not occur without X, than X is considered to be the cause of B

  - Someone entered his house (B) because the door was open (X)
  - Because he uses this drug (X), he go and ADR (B)

- X causes B because the counterfactual “when X is not used, that B does not occur” is true.
Drug X → ADR B
Counterfactual theory

• Theory, answering the question “how do I know if something is a cause of a certain event”?

• Is a theoretical approach but provides no practical solution for causality issue

• As a proxy for counterfactuals we use control groups in epidemiology
The epidemiological approach..

- **Exchangeability of groups**
  - Patients (using X) → occurrence of B, given use of X
  - Patients (no X) → occurrence of B, given no use of X

- When both groups are “exchangeable”, and B differs between both groups, we state the B has a causal relationship with X

- Size of both groups can be very large
Conclusive epidemiological evidence?

- Conclusive proof of cause-effect relationship is often not possible

- Statements about chances are often desired

- Guidelines on how the likelihood of causality can be determined are needed
Bradford Hill criteria
Bradford Hill Criteria

1. Strength of the evidence
2. Order in time
3. Consistency
4. Plausibility
5. Specificity
6. Biological gradient
7. Coherence
8. Experiment
9. Analogy
<table>
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<th>Second</th>
<th>Third</th>
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<td>1.3 (1.0 to 1.8)</td>
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Data are relative risk (95% confidence interval) of venous thrombosis.
Bradford Hill Criteria

1. Strength of the evidence
2. order in time
3. consistency
4. plausibility
5. specificity
6. Biological gradient
7. coherence
8. Experiment
9. analogy
Time to onset analysis

Diarrhoea

Diarrhoea haemorrhagic

Gastroenteritis

Haematochezia

Van Holle et al. PEDS 2012;21:603-10
Bradford Hill Criteria

1. Strength of the evidence
2. Order in time
3. Consistency
4. Plausibility
5. Specificity
6. Biological gradient
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8. Experiment
9. Analogy
THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (‘Distaval’) during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales.

W. G. McBride.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide (‘Distaval’) with harmful effects on the fetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—Ed.L.
<table>
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<tr>
<th>Subgroup</th>
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<th>Controls</th>
<th>Study Weighting (%)</th>
<th>Odds Ratio (95% CI)</th>
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<td>12.41 (1.27–121.03)</td>
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<tr>
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<tr>
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Bradford Hill Criteria

1. Strength of the evidence
2. Order in time
3. Consistency
4. Plausibility
5. Specificity
6. Biological gradient
7. Coherence
8. Experiment
9. Analogy
Risk management plan
Bradford Hill Criteria

1. Strength of the evidence
2. Order in time
3. Consistency
4. Plausibility
5. **Specificity**
6. Biological gradient
7. Coherence
8. Experiment
9. Analogy
Maculopathie door chloroquine
Nicolau syndrome
### Specificiteit van het verband

**Examples of definitive anecdotal adverse drug reactions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example events</th>
<th>Drug examples</th>
<th>Crime scene analogy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a: Extracellular deposition of drug or metabolite</td>
<td>Urinary calculi</td>
<td>Aciclovir, amoxicillin, ephedrine/guaifenesin, indinavir, methotrexate, primidone, sulfasalazine, triamterene</td>
<td>Culprit caught at scene of the crime</td>
</tr>
<tr>
<td>1b: Intracellular deposition of drug or metabolite</td>
<td>Crystal storing histiocytosis</td>
<td>Aluminium containing vaccines</td>
<td>Culprit caught at scene of the crime</td>
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<tr>
<td>2: Specific location or pattern of injury</td>
<td>Extravasation reactions</td>
<td>Cancer chemotherapy drugs</td>
<td>Culprit seen committing the crime</td>
</tr>
<tr>
<td>3: Physicochemical dysfunction or tissue damage</td>
<td>Photosensitivity</td>
<td>Carbamazepine, dapsone, fenofibrate, flutamide, non-steroidal anti-inflammatory drugs</td>
<td>Culprit incriminated by recreating the crime scene</td>
</tr>
<tr>
<td>4: Infection related</td>
<td>Sepsis</td>
<td>BCG and mumps vaccine</td>
<td>Culprit’s DNA found at scene of crime</td>
</tr>
</tbody>
</table>

Aronson & Hauben. BMJ 2006;333:1267-69
Bradford Hill Criteria

1. Strength of the evidence
2. Order in time
3. Consistency
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5. Specificity
6. Biological gradient
7. Coherence
8. Experiment
9. Analogy
Dose-response curve for allergic reaction in susceptible patients

- Dose-response curve for the analgesic effect of morphine
- Margin of safety
- Dose-response curve for the depressive effect of morphine on respiration

low  |  Dose of drug  |  high
Bradford Hill Criteria

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2. Order in time
3. Consistency
4. Plausibility
5. Specificity
6. Biological gradient
7. Coherence
8. Experiment
9. Analogy
Coherence
Bradford Hill Criteria

1. Strength of the evidence
2. Order in time
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4. Plausibility
5. Specificity
6. Biological gradient
7. Coherence
8. Experiment
9. Analogy
Bradford Hill Criteria

1. Strength of the evidence
2. order in time
3. consistency
4. plausibility
5. specificity
6. Biological gradient
7. coherence
8. Experiment
9. analogy
Mercaptopurine and photosensitivity

Introduction
Mercaptopurine (Puri-Nethol®) has been registered since August 1967. It is indicated for the treatment of acute lymphatic leukaemia (ALL) and for lymphoid blast crisis in patients with chronic myeloid leukaemia (CML) [1]. The mechanism of action of mercaptopurine is based on its cytotoxic antimetabolite activity. The drug is an inactive pro-drug which acts as a purine antagonist but requires cellular uptake and intracellular anabolism to tioguanine nucleotides for cytotoxicity. The mercaptopurine metabolites inhibit de novo purine synthesis and purine nucleotide interconversions.

In the first quarter of 2008, Lareb wrote a quarterly report on photosensitivity reactions in patients using azathioprine [2]. The conclusion of that report was that photosensitivity reactions could be related to the use of this drug. Since mercaptopurine is the active metabolite of azathioprine, it is plausible to assume that similar reactions may occur in patients using mercaptopurine.

The current observation describes the possible association between mercaptopurine and photosensitivity reactions.
Table 1. Reports of photosensitivity reactions associated with mercaptopurine and azathioprine in the databases of the Netherlands Pharmacovigilance Centre Lareb, WHO and EMA.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number of reports</th>
<th>ROR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercaptopurine</td>
<td>Lareb: 2</td>
<td>N.A.*</td>
</tr>
<tr>
<td></td>
<td>WHO: 9</td>
<td>1.1 (0.6 – 2.1)</td>
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<td></td>
<td>EMA: 3</td>
<td>1.8 (0.6 – 5.6)</td>
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<tr>
<td></td>
<td>Lareb: 13</td>
<td>7.2 (4.1 – 12.6)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>WHO: 75</td>
<td>2.2 (1.7 – 2.7)</td>
</tr>
<tr>
<td></td>
<td>EMA: 22</td>
<td>2.0 (1.3 – 3.0)</td>
</tr>
</tbody>
</table>

* Not applicable since the number of cases is lower than 3
“None of these nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis .... What they can do, with greater or less strength, is to help answer the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”
Causality schemes
Methods for Causality Assessment of Adverse Drug Reactions
A Systematic Review

Taofikat B. Agbabiaka,¹ Jelena Savović² and Edzard Ernst¹

1 Complementary Medicine, Peninsula Medical School, Universities of Exeter and Plymouth, Exeter, UK
2 Department of Social Medicine, University of Bristol, Bristol, UK
<table>
<thead>
<tr>
<th>Author</th>
<th>TTC/ temp seq</th>
<th>Prev exp/ drug info</th>
<th>All antiol cand</th>
<th>Drug level / evidence of OD</th>
<th>Challenge</th>
<th>De-chall</th>
<th>Re-chall</th>
<th>Response pattern to drug</th>
<th>Confirmed by lab evidence</th>
<th>Concomitant drugs</th>
<th>Background epidemiol / clin info</th>
<th>ADR char mech</th>
<th>Other</th>
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<td><strong>Expert Judgement or Global Introspection</strong></td>
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</tr>
<tr>
<td>Stricker et al.[30]</td>
<td>x</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benichou and Danari[25]</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
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<tr>
<td>Hoskins and Marmino[22]</td>
<td>✓</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
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</tbody>
</table>

Continued next page
Approaches causality assessment

- WHO model
- Naranjo
WHO causality definitions

CERTAIN
A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

PROBABLE/LIKELY
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

POSSIBLE
A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

UNLIKELY
A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Question

Naranjo's algorithm is widely used in determining the causal link between drug and clinical event. How has this model been validated?

1) At less than 100 cases with various adverse reactions from the literature

2) In about 250 cases with adverse effects on the cardiovascular system (reports)

3) In 1985, at about 1000 cases from the Spanish PV system

4) For 16 different classes of side effects with a minimum of 250 cases
Naranjo-algoritm

Systematic causality assessment

- 10 questions
- Sumscore
- 63 cases from the literature
- only 3 authors!

Naranjo score

- ≥ 9  certain
- 5-8  probable
- 1-4  possible
- ≤ 0  unlikely
<table>
<thead>
<tr>
<th></th>
<th>Question</th>
<th>1</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Are there previous <em>conclusive</em> reports on this reaction?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Did the event appear after the suspected drug was administered?</td>
<td>2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Did the adverse reaction improve when the drug was discontinued or a <em>specific</em> antagonist was administered?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Did the adverse reaction reappear when the drug was readministered?</td>
<td>2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Did the patient have a similar reaction to the same or similar drugs in <em>any</em> previous exposure?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Was the adverse event confirmed by any objective evidence?</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</table>
# WHO classification

<table>
<thead>
<tr>
<th></th>
<th>time relationship</th>
<th>attribution to other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>certain</td>
<td>dechallenge and rechallenge</td>
<td>absent</td>
</tr>
<tr>
<td>probable</td>
<td>dechallenge</td>
<td>possible</td>
</tr>
<tr>
<td>possible</td>
<td>not improbable</td>
<td>possible</td>
</tr>
<tr>
<td>unlikely</td>
<td>improbable</td>
<td>plausible</td>
</tr>
</tbody>
</table>
Extrinsic factors

- Literature and product information
  - MEB / EMA
  - Medline

- background Incidence
  - Literature

- Prescription data

- Databases
  - Lareb
  - EMA
Intrinsic factors

• pharmacological plausibility
  - kinetic, dynamic, chemical structure
  - latency, dechallenge
  - co-medication

• patient-related
  - indication, comorbidity
  - Drug metabolism
Summary

- Causation is difficult in practice to prove

- There are various models of causality in use

- Validation leaves much to be desired, situations in which they are applied are often too specific

- Create your own judgment on the basis of individual criteria
Learning objectives

• Understand the concept of counterfactuals

• Know how to apply the Bradford Hill criteria in drug safety

• To be able to use two different causality model for the assessment of adverse drug reactions.
  - Causality scheme of Naranjo
  - knowing the difference between extrinsic and intrinsic causality
Thank you for your attention!