Causality assessment in individual case reports

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Outline

• Causality review
• Why do causality assessment on ADR reports?
• General features of assessment methods
• Selected methods
  – WHO (probabilistic)
  – Naranjo (algorithmic)
Causality

• Most outcomes have multiple interacting causes
• Our aim is to define the contribution due to drug(s)
## Genetics or environment?

### Lightning-Associated Deaths
**United States, 1980-1995 (MMWR)**

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1125 (85%)</td>
<td>193 (15%)</td>
</tr>
</tbody>
</table>
Causality assessment

• What causality assessment can do:
  - highlight individual case reports
  - identify areas of uncertainty
  - reduce disagreement between assessors
  - ... help regulatory decision making
Uses of causality assessment

• Initial report review
• Signal detection
• Scientific publications
Causality assessment methods

- Published methods
  - Venulet J, Ciucci AG, Bernecker GC. IntJ ClinPharmacol 1986; 24: 559-68
  - Kramer MS, Leventhal JM, Hutchinson TA et al. JAMA 1979; 242: 623-31

- National Centres Methods
- WHO-UMC Method
Causality assessment methods

• General design, usually two alternatives:
  - algorithmic
    • series of questions
    • answers are weighted
    • overall score defines causality category
    • example: Naranjo method
  - probabilistic
    • set of explicitly defined causality categories
    • example: WHO-UMC method
Four basic criteria

- Pharmacology (+ previous knowledge of ADRs)
- Association (time / place) between drug and event
- Medical plausibility (eg, characteristic events)
- Likelihood or exclusion of other causes

- [drug, relationship, reaction, other]
- Pharmacoepidemiol Drug Saf 1992; 1: 87-97
Individual report assessment

• Make use of everything on the report
  – patient (age, sex, medical history)
  – drugs
  – adverse events

• And what is not on the report?
  – knowledge of drug
  – knowledge of disease
Importance of criteria

- Importance of basic criteria may vary for different types of reactions:
  - application site reactions
  - pharmacological effects (‘Type A’)
  - immunological reactions (‘Type B’)
  - congenital malformations
  - cancer
Previous knowledge

• “Is this drug known to cause this ADR?”
• Previous knowledge is asked for:
  – Karch & Lasagna
  – Kramer & Hutchinson
  – Naranjo
  – Several national centres
• Previous knowledge is not *explicitly* asked for:
  – WHO-UMC classification
  – French system
  – Australian system
Previous knowledge

- ADR unknown – signal detection
  - previous knowledge of ADR is always: No
- Established ADR – frequency estimation
  - previous knowledge of ADR is always: Yes

- These types may need different approaches for causality assessment
Time relationship

• Many ADRs have a characteristic timing:
  - anaphylaxis
  - alopecia
  - cancer

• Implies knowledge of pharmacology and mechanism of ADR

• What is time relationship?
  - time to onset
  - dechallenge, rechallenge
  - when given (pregnancy)
Plausibility

• Implies a knowledge of other possible causes
• Events with a higher probability of drug causality:
  - erythema multiforme
  - rhabdomyolysis
  - agranulocytosis
  - renal failure
  - anaphylaxis

  • Pharmacoepidemiol Drug Saf 2009; 18: 1176-1184
Other causes

• Other causes may be:
  - other drugs
  - disease being treated
  - other medical condition
  - other patient factors (smoking, family history)
  - coincidental

• Very dependent on:
  - prior knowledge
  - information provided on report
Ideal System?

- None of the available systems has been validated, i.e. that it consistently and reproducibly gives a reasonable approximation of the truth
- No gold standard
- Handling missing data and 'don’t know' answers
- Causality category definitions
WHO method

- Typical probabilistic method
  - defined causality categories
  - mutually exclusive
  - information on report defines causality category
WHO-UMC causality categories

- Certain
- Probable
- Possible
- Unlikely
- Conditional/unclassified
- Unassessable/undiscernible
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
- Event definitive “pharmacologically or phenomenologically”
- Rechallenge positive (if done)
Definitive event

- Time relationship
  - anaphylaxis to IV injection

- Spatial relationship
  - injection site or contact reactions

- Specific laboratory tests
  - anti-drug antibodies
  - drug in renal stones
Probable

- Event or laboratory test abnormality with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drug
- Response to withdrawal clinically reasonable
- Rechallenge not necessary
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

- Time relationship makes a connection improbable (but not impossible)
- Diseases or other drugs provide more likely explanations
Conditional / Unclassified

- More data needed
- Data under examination
Unassessable / Unclassifiable

- Suggesting an adverse reaction
- Insufficient or contradictory information
- Cannot be supplemented or verified
Summary of WHO method

- **Certain**
  - good timing, no other cause, withdrawal, “definitive”
- **Probable**
  - good timing, other cause unlikely, withdrawal
- **Possible**
  - good timing, other causes possible
- **Unlikely**
  - poor timing, other causes more likely
- **Unassessable**
  - insufficient or contradictory information
Problems with WHO method?
Naranjo method

• Typical algorithmic method
  - series of specific questions
  - assign a score to each answer
  - total score results in a causality category
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports of this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspect drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse reaction reappear when the drug was readministered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternate causes that on their own could have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction appear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. 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>
<td></td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Naranjo interpretation

• Total scores of 9 or more mean that an ADR is highly probable.
• Scores from 5 to 8 mean that an ADR is probable.
• Scores from 1 to 4 that an ADR is possible.
• Scores of zero or less mean that an ADR is doubtful.
Problems with Naranjo?
Causality Category Definitions

• No complete agreement
  - certain (definite)
  - very probable (very likely)
  - probable (likely)
  - possible
  - unlikely
  - unrelated
  - ...

• What do these mean?
When to do assessment?

- When receiving reports?
  - enables rapid identification of key reports
  - identify key missing data

- When identifying signals?
  - focus on more important reports
Thank you!