Why is it important to assess causality?

Did / Does a combination of agents really produce a specific clinical outcome?

Double-speak on issues of causality, particularly in the arena of interactions

Differences in goals and needs

Clinical / Public Health / Scientific / Legal

Objectives for Today’s Presentation

Consider the nature of scientific data.

Consider the nature of a cause & means of assessing a cause.

Compare means of assessing data on herbal-herbal & herbal-drug interactions.

Argue our position.

Scientific Data ↑ Clinical Scales ↓

Fundamental Tenets of Science

1. The identity of the measurements are demonstrable and amenable to estimation of error
2. The elimination of extraneous factors that can affect the measurements is certain
3. The result is repeatable in independent hands

Causality: 1800’s - 1900’s

Henle-Koch, 1882

[In Schachter & Pliobam, 1996]  

1) Cause always present in disease  
2) Cause NOT in other diseases  
3) Cause is isolable from diseased individual  
4) Isolated cause produces same disease in other individuals (animals)

Hill, 1965

1) Strength  
2) Consistency  
3) Specificity  
4) Temporality  
5) Biological Gradient  
6) Plausibility  
7) Coherence  
8) Experiment  
9) Analogy

Causal Chains

Linear Causalism

Attena, 1999

1) Strength  
2) Consistency  
3) Specificity  
4) Temporality  
5) Biological Gradient  
6) Plausibility  
7) Coherence  
8) Experiment  
9) Analogy
Causal Constellations / Mosaics

Causal Propositions vs Causal Assessment

“Hill, Susser, and others recognize that these criteria do not define cause per se, but merely provide guidelines for assessing it. Nonetheless, the criteria are occasionally used by epidemiologists and clinical researchers as though they provide an operational definition of causality:

Kramer & Lane, 1992

Definitions of “Cause”

: that which produces an effect.

: that which brings about any condition or produces any effect.
Dorland’s Medical Dictionary, 27th Edition

: that which makes a difference.

: ‘...an object followed by another ... where, if the first object had not been, the second never had existed.’
David Hume, 1748 [In Maldonado & Greenland 2002]

Hume’s Definition of “Cause”

“A key innovation of this definition was that it pivoted on a clause of the form if C had not occurred, D would not have either,’ where C and D are actually what occurred.”

Maldonado & Greenland, 2002

Constructing the Counterfactual

• An alternative to the world observed;
• An alternative world that cannot be observed epidemiologically;
• The truth of a retrospective causal proposition depends on the choice of the alternative world;
• “This principle applies to all three types of causal proposition; when a causal proposition interests us because we face a decision to which it is related, the choice of alternative world will be determined by the actions available to us.”
  Kramer & Lane, 1992
• Clinical trials [experiment] creates the counterfactual.

Ranges of Rigor

<table>
<thead>
<tr>
<th>Stringent Causal Criteria</th>
<th>Relaxed Causal Criteria</th>
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<tbody>
<tr>
<td>Based on linear causalism</td>
<td>Based on causal mosaic</td>
</tr>
<tr>
<td>Implies chain of connected events</td>
<td>Implies web of related events</td>
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<td>Implies necessity of each event</td>
<td>No single event necessary or sufficient</td>
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<tr>
<td>Can be refuted by disproving a link in the chain</td>
<td>Refutation requires disproving all events</td>
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<td>Causal propositions insecure</td>
<td>Causal propositions tenured</td>
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<td>May reject real causes</td>
<td>May accept unfounded causes</td>
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Clinical Diagnostic Scales

**Modified Drug Interaction Probability Scale**

- Previous conclusive reports in humans
- Observed interaction consistent with known interactive properties of drug and supplement
- Temporal consistency
- Challenge / De-challenge . . . Dose-response
- Alternative causes


Drug–Dietary Supplement Interaction Literature Sources

- Case Reports
- Clinical Studies
- Laboratory Studies


Problems Inherent in Published Literature on Interactions


- Literature over-populated.
- Case-Reports: relevant but anecdotal.
- Lab/Clinical Study: controlled, but questionable relevance & general applicability.
- Terminology used ambiguously; Incorrectly.
  - "interaction," "synergism," "potentiation"
  - "No-Interaction" concept sorely lacking
- Data quality poorly evaluated.

Criteria for Evaluating Interaction Studies

1. Dose-response curves for the mixture components should be adequately characterized.
2. An appropriate "no-interaction" hypothesis should be explicitly stated and used as the basis for assessing synergy and antagonism.
3. Combinations of mixture components should be assessed across a sufficient range to support the goals of the study.
4. Formal statistical tests should be used to distinguish interaction from non-interaction.
5. Interactions should be assessed at relevant levels of biological organization.


Isobologram

- T + R (EC_{50})
- High variance
- Low variance
- Synergy
- Antagonism
- Activity: no interaction
Algorithm for Applying Criteria

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- Does not weight individual criteria.
- Does not evaluate clinical relevance.
- Apply cautiously to mechanistic & p’kinetic studies.
- Challenging for whole animal or clinical studies.

Applying the Criteria

**Ginkgo**

Steinke et al., 1993:
Ginkolides A + B synergistically inhibit platelet aggregation.

- Full dose-response characterization of ginkolides A and B.
- Dose-addition defined as no-interaction hypothesis.
- Tested 7 combinations at 90% inhibitory effect.
- Applied formal statistical procedure to test differences between observed and expected (dose-additive) effects (Concave isobole).
- Assessed interaction at interpretable level of biol. organization.

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Applying the Criteria

**Kangen Karyu (KGK)**

Makino et al., 2002 (lab study in rats)

- KGK increases warfarin AUC at 2 g/kg, but not at 0.5 g/kg in rats.
- KGK has no effect on PT at any dose tested in rats.
- 0.2 g/kg and 0.5 g/kg + fmg/kg warfarin increased bleeding time above warfarin alone by 20% and 25%, respectively.
- “Since KGK and warfarin synergistically exhibit anti-thrombotic effects, their combination would be therapeutically valuable.”

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- KGK alone inhibits platelets; increases bleeding time in mice.

Applying the Criteria

**American Ginseng**

Duda et al., 1999: American ginseng and breast cancer therapeutic agents synergistically inhibit MCF-7 cancer cell growth.

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<tr>
<th>RX</th>
<th>Cell Survival</th>
<th>Expected Effect (?)</th>
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<tr>
<td>TAM (1E-6M)</td>
<td>87%</td>
<td>(87) x (.80)</td>
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<tr>
<td>TAM (1E-5M)</td>
<td>10%</td>
<td>(.13) + (.20)</td>
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<tr>
<td>AG (60mg)</td>
<td>90%</td>
<td>.696 survival</td>
</tr>
<tr>
<td>AG (100mg)</td>
<td>80%</td>
<td>.33 cell death</td>
</tr>
<tr>
<td>TAM + AG (100mg)</td>
<td>75%</td>
<td>.67 survival</td>
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- Deterministic, Objective
- Requires measurement validity and error estimation
- Requires counter-factual (i.e., controlled conditions)
- Allows independent replication
- Necessary for hypothesis-testing approach (Science)
- Capable of establishing causality
- Consistent with Evidence-Based Medicine

**Fundamental Tenets of Science**

1. The identity of the measurements are demonstrable and amenable to estimation of error
2. The elimination of extraneous factors that can affect the measurements is certain
3. The result is repeatable in independent hands
   - Satisfied by Henle-Koch
   - May be satisfied by Hill, but requires criterion 8!
   - Satisfied by Evaluative Criteria
   - Not Satisfied by current formulations of CDS

**Conclusion 1**

- Evaluative Criteria
  - Deterministic, Objective
  - Requires measurement validity and error estimation
  - Requires counter-factual (i.e., controlled conditions)
  - Allows independent replication
  - Necessary for hypothesis-testing approach (Science)
  - Capable of establishing causality
  - Consistent with Evidence-Based Medicine
Conclusion 2

- Clinical Scales ("Diagnostic" or "Probability")
  - Probabilistic, Subjective
  - Requires no measurement validity or controlled condition
  - Impossible to estimate error rate
  - Difficult to replicate
  - Cannot establish causality
  - May be useful for clinical judgments when data are absent
  - Inconsistent with Evidence-Based Medicine
  - Useful for hypothesis-generation about causes

Price et al. 2002. HERA 8(2): 305-326