

Causality Assessment of Herb-Drug Interactions: Scientific Data vs. Diagnostic Scales

International Conference
Quality and Safety Issues Related to Botanicals
August 15-18, 2005. University, MS

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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

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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 ↓

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Fundamental Tenets of Science

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

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Causality: 1800's - 1900's

Henle-Koch, 1882
[In Scheutz & Poulsen, 1999]

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

Hill, 1965

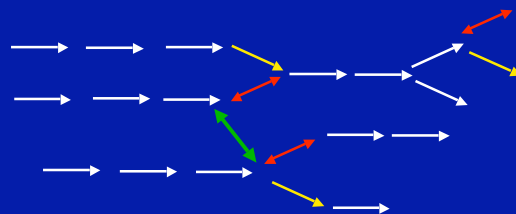
- Strength
- Consistency
- Specificity
- Temporality
- Biological Gradient
- Plausibility
- Coherence
- Experiment
- Analogy

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Causal Chains Linear Causalism



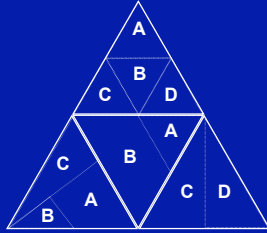
Attena, 1999

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Causal Constellations / Mosaics



Scheutz & Poulsen, 1999

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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

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Definitions of “Cause”

: that which produces an effect.

Oxford Dictionary [In Podrebarac et al. 1996]

: 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]

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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

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Constructing the Counterfactual

- An alternative to the world observed;
- An alternative world that cannot be observed epidemiologically;
- The truth of a retrodictive 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.

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Ranges of Rigor

Stringent Causal Criteria

- Based on linear causalism
- Implies chain of connected events
- Implies necessity of each event
- Can be refuted by disproving a link in the chain
- Causal propositions insecure
- May reject real causes

Relaxed Causal Criteria

- Based on causal mosaic
- Implies web of related events
- No single event necessary or sufficient
- Refutation requires disproving all events
- Causal propositions tenured
- May accept unfounded causes

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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

Wittkowsky A. 2005. *Thrombosis Research* (in press, June, 2005; online at <http://www.sciencedirect.com/science/journal/00493848>.)

Drug–Dietary Supplement Interaction Literature Sources

- Case Reports
- Clinical Studies
- Laboratory Studies

Borgert CJ, Borgert SA, Findley KC. Synergism, antagonism or additivity of dietary supplements: application of theory to case studies. *Thrombosis Research* (in press, June, 2005; online at <http://www.sciencedirect.com/science/journal/00493848>)

Problems Inherent in Published Literature on Interactions

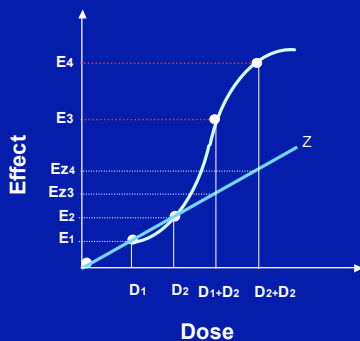
McInnes & Brodie 1988. Drug interactions that matter. *Drugs* 36: 83-110.

- 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.

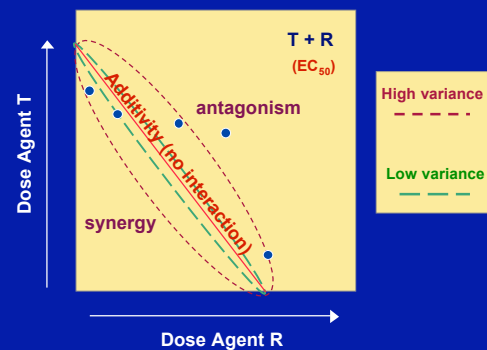
Criteria for Evaluating Interaction Studies

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.

Borgert et al., 2001. *Human & Ecological Risk Assessment*, 7(2): 259-306.



Isobologram



Algorithm for Applying Criteria

Fails Criterion						T	C
Partially Satisfies Criterion	0						
Satisfies Criterion	0.5						
	1.0						
Criterion	1	2	3	4	5	T	C
Score	X	X	X	X	X	Sum	0-1

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

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Applying the Criteria Ginkgo

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

1. Full dose-response characterization of ginkgolides A and B.
2. Dose-addition defined as no-interaction hypothesis.
3. Tested 7 combinations at 50% inhibitory effect.
4. Applied formal statistical procedure to test differences between observed and expected (dose-additive) effects (Concave Isobole).
5. Assessed interaction at interpretable level of biol. organization.

Criterion	1	2	3	4	5	T	C
Score	1	1	1	1	1	5	1

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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 0.5g/kg in rats.
- KGK has no effect on PT at any dose tested in rats.
- 0.2g/kg and 0.5 g/kg + 1mg/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."

Criterion	1	2	3	4	5	T	C
Score	0	0	0.5	0	1	1.5	0.3

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

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Applying the Criteria American Ginseng

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

R _x	Cell Survival	Expected Effect (?)	
TAM (1E-6M)	87%	(.87) x (.80)	(.13) + (.20)
TAM (1E-5M)	10%		
AG (60mg)	90%	.696 survival	.33 cell death
AG (80mg)	85%		
AG (100mg)	80%	.67 survival	
TAM + AG (100mg)	75%		

Criterion	1	2	3	4	5	T	C
Score	.5	0	0	0	0	0	0.1

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Fundamental Tenets of Science

1. The identity of the measurements are demonstrable and amenable to estimation of error
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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

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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

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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

