Synergism, Antagonism or Additivity of Dietary Supplements

Christopher J. Borgert, Ph.D. [1,2]
Kathleen Cullen Findley, MST, PharmD. [1,3]

[1]Applied Pharmacology & Toxicology, Inc.
Gainesville, FL

[2]Department of Physiological Sciences, College of Vet. Med.
University of Florida, Gainesville, FL

[3]Veterans Administration Medical Center, Gainesville, FL

Drug–Dietary Supplement Interaction Literature Sources

- Case Reports
- Clinical Studies
- Laboratory Studies

Problems Inherent in Published Literature

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.

Data Evaluation

- Clinical & Laboratory Studies

Data Quality Assessment Depends on Objectives

Prediction & Clinical Management

-Validate interaction.
  »Generalize & define patient conditions.
-Direction & type of interaction.
-Magnitude of interaction.
-Variance / confidence intervals.
-Mechanism of interaction.
-Incidence (post-marketing surveillance).

Interactions

Synergism

More response / less drug *than expected.*

Antagonism

Less response / more drug *than expected.*

- Extrinsic, *NOT* Intrinsic
  - Dependent Upon the "Expected" Effect.
  - Highly Dependent Upon Dose *AND* Ratios.
- Quantitative, *not* Qualitative.
- Dose-Response, *not* Mechanism
- Mathematical, *not* Biological

What is "Expected" ?

2 Classical Models for Non-Interaction

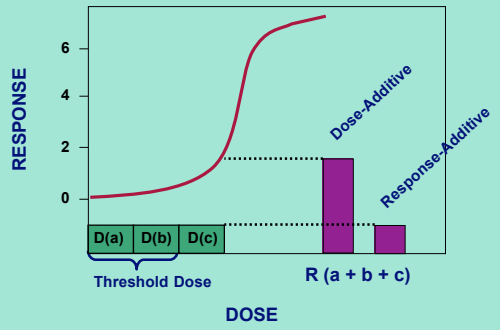
Loewe Additivity
[Dose Additivity]

- No self-interaction
- Agents act as simple dilutions (potency)
- Sum doses & potencies of each agent
- $D_a/D_A + D_b/D_B = 1$

Bliss Independence
[Response Additivity]

- Statistical independence
- Relative effect of A not influenced by B
- Sum effects of each agent
- $E_{A+B} = E_A + E_B - (E_A \times E_B)$

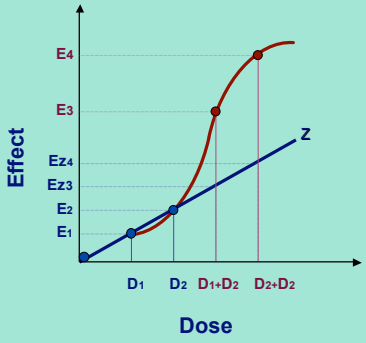
Impact of the No-Interaction Model



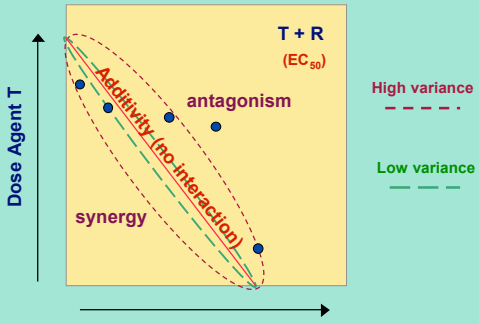
Criteria for Evaluating Interaction Studies

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	0
Partially Satisfies Criterion	0.5
Satisfies Criterion	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.

Applying the Criteria
Ginkgo

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

1. Full dose-response characterization of ginkolides 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

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.

Applying the Criteria
American Ginseng

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

Rx	Cell Survival
TAM (1E-6M)	87%
TAM (1E-5M)	10%
AG (60mg)	90%
AG (80mg)	85%
AG (100mg)	80%
TAM + AG (100mg)	75%

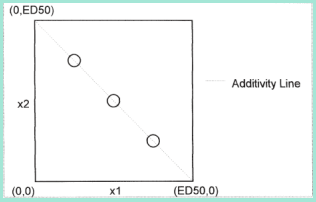
Expected Effect (?)	
(.87) x (.80)	(.13) + (.20)
.696 survival	.33 cell death .67 survival

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

Observations / Recommendations / Challenges

- Synergism / antagonism useful information for specific drug combination therapies.
  - Apply sound methodologies - difficult but still important for clinical study designs.
  - Magnitude, direction and variability of interaction may be important for appropriate clinical management.
- Focus on clinical significance of interactions
  - Intra-individual variations in drug levels with fluctuations in diet, sleep, stress, activity level, etc.
- Efficient Study Designs Needed for Clinical Studies.

  Price, Borgert, Simon & Wells. 2002. HERA *8*(2): 305-326



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