

## Synergism, Antagonism or Additivity of Dietary Supplements

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## 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.*

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

### Antagonism

Less response /  
more drug *than*  
*expected.*

## What is “Expected” ?

### 2 Classical Models for Non-Interaction

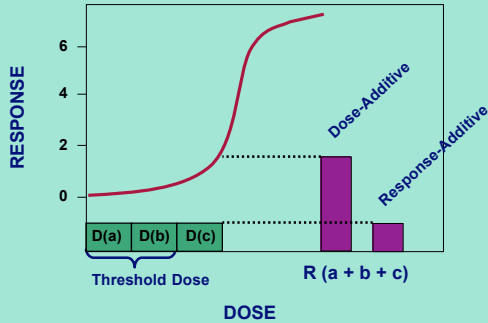
#### Loewe Additivity [Dose Additivity]

- 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
- $E_{A+B} = E_A + E_B - (E_A \times E_B)$

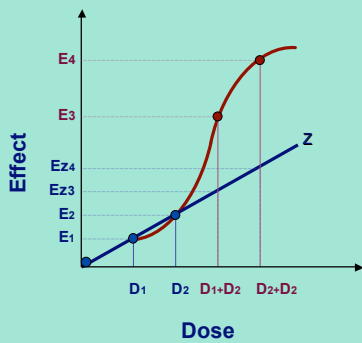
### Impact of the No-Interaction Model



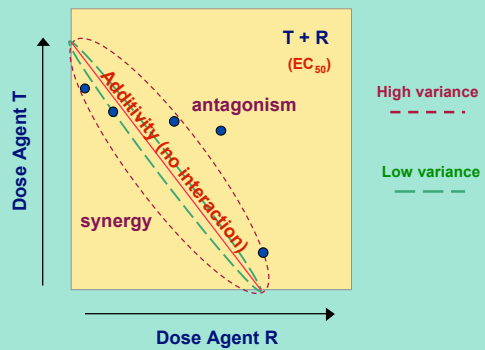
### Criteria for Evaluating Interaction Studies

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: 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

## 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.

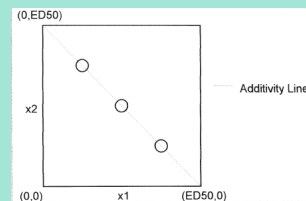
Rx	Cell Survival	Expected Effect (?)	
TAM (1E-6M)	87%	(.87) x (.80)	(.13) + (.20)
TAM (1E-5M)	10%		
AG (60mg)	90%	.696 survival	.33 cell death
AG (80mg)	85%		
AG (100mg)	80%	.67 survival	
TAM + AG (100mg)	75%		

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

## 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.  
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