ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

Current Approaches to Pharmaceutical Benefit-Risk Assessment

Bennett Levitan, M.D.-Ph.D.
Director, Quantitative Safety Research
J&J Pharmaceutical Research & Development, L.L.C.

ISCTM 6th Annual Scientific Meeting
February 22, 2010

Agenda

- Background
- Selected unweighted methods for benefit-risk
- Selected weighted methods for benefit-risk

Why Pay Attention to Benefit-Risk Assessment?

FDA Urged To End Sales Of Forest Labs' Fibromyalgia Drug

Dow Jones Newswire, 1/20/10

A nonprofit
fibromyalgi
immediatel
benefits.

FDA panel backs Zavesca to treat patients with Niemann-Pick disease

Dow Jones Newswire (1/13/10) reports that a FDA advisory pan
approving … Zave
…Niemann-Pick D
question, "… does
Zavesca support i
voted 10-to-3 in fa

Most women do not think benefits of tamoxifen outweigh risks.

The New York Times 12/14/09

In a study appearing in Breast Cancer Research and Treatment, researchers investigated why
patients choose n
drugs. … The res
participants "did
tamoxifen outwe

Panel Urges Mammograms at 50, Not 40

The New York Times 11/6/09

… Over all, the report says, the modest **benefit** of mammograms — reducing the breast cancer death rate by 15 percent — **must be weighed against the harms**. …

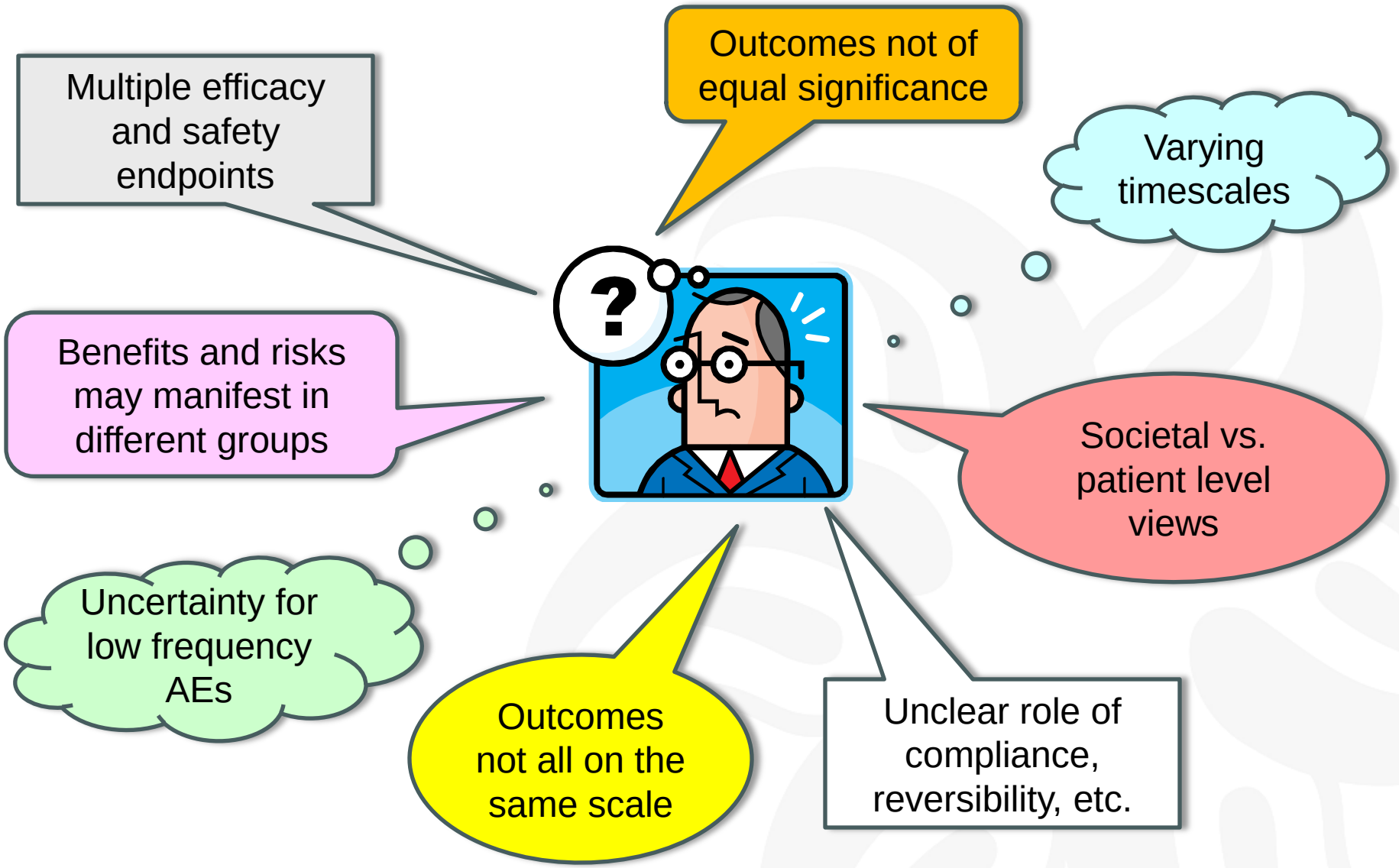
Current State of Benefit-Risk Assessment

- Increasing pressure to demonstrate benefit exceeds risk compared to alternative treatments
- Current approaches rely primarily on expert judgement
- Limited regulatory guidance
- B-R considerations often delayed until late in development

End result:

  - Sponsors are handicapped
  - Discussions are often at a conceptual level
  - Benefit/risk information useful for treatment decisions is not readily available to healthcare professionals or patients

Technical Challenges



Industry and Regulatory Efforts to Improve Benefit-Risk Assessment

- Increased frequency of workshops/meetings on B-R
- EU series of benefit-risk initiatives
  - Five work packages (current practice, applicability of current tools/processes, field tests, development of B-R tools/process, training package)
- Framework approaches
  - FDA qualitative framework
  - PhRMA Benefit risk framework team (BRAT)
  - CMR International's Institute for Regulatory Science framework

Agenda

- Background
- Selected unweighted methods for benefit-risk
- Selected weighted methods for benefit-risk

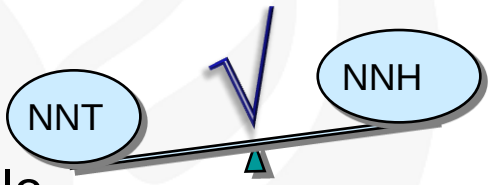
Number Needed to Treat/Harm (NNT/NNH)

- Benefit and risk measures are inherently on different scales
  - Ex: Can not directly trade off reduced risk of death with increased risk of stroke

- Number need to Treat/Harm (NNT/NNH)
  - Puts different types of events on the same scale

    NNT = # patients who need to be treated to provide one additional favorable event

    NNH = # patients who need to be treated to cause one additional AE



If NNT < NNH, benefit outweighs risk of AE

Calculating Number Needed to Treat:

From Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study

Outcome	Drug A	Drug B	Risk Difference
D/C due to lack of efficacy	0.25	0.15	-0.107
Any moderate or severe AE	0.30	0.36	0.060

$$NNT = \frac{1}{\text{Event Rate A} - \text{Event Rate B}} = \frac{1}{0.25 - 0.14} \approx 9$$

$$NNH = \frac{1}{\text{Event Rate B} - \text{Event Rate A}} = \frac{1}{0.36 - 0.30} \approx 17$$

NNT < NNH ➔ benefit outweighs risk for drug B compared to drug A

Lieberman, et. al., NEJM. 353(12), 2005
Citrome & Stroup, Int. J. Clin. Pract, 60(8), 2006

Number Needed to Treat/Harm with CIs

Outcome	Drug A	Drug B	Risk Diff + 95% CI
D/C due to lack of efficacy	0.25	0.15	-0.11 (-0.17, -0.04)
Any moderate or severe AE	0.30	0.36	0.06 (-0.02, 0.14)

$$NNT \approx 9\ (5, 29)$$

$$NNH \approx 17\ (7, -59)$$

- Safety outcome not statistically significant → NNH CI?
- Intervals overlap → does benefit really exceed risk?
- Better question: Are these the right endpoints to compare? Will discuss …

Benefits of NNT/NNH

- Easy to calculate
- Easy to interpret – aligns with perspective of physician
- Simple algorithms exist to modify for baseline risks of individual patients
- Very helpful for comparing one drug against many

Antipsychotics	NNT (discontinuation)	NNH (hospitalization)
Drug B vs. Drug A	9.0	22.7
Drug B vs. Drug C	5.5	11.3
Drug B vs. Drug D	10.1	27.4

Citrome & Stroup, Int. J. Clin. Pract, 60(8), 2006

Limitations with NNT/NHH

- Confidence intervals can be confusing when results are not statistically significant
  - ➔ NNH = 17 with CI 7 to -59 ???
  - – Interpretable*, but adds a layer of complexity
- Hard to assess B-R when CIs being compared overlap
- Blows up with tiny risk differences
  - – Rate Difference ≈ 0 ➔ NNT ≈ ∞
  - – Values become difficult to interpret
- Does not lend itself easily to comparing > 2 endpoints
- Consider an alternative: “excess number of events”

* Altman, BMJ 317(7168), 1998

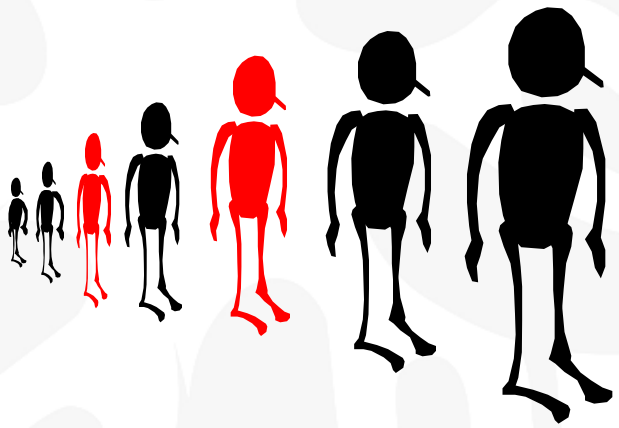
Excess Number of Events

- Excess number of events
  - The additional number of patients, out of a hypothetical population, who would experience a particular event when using one treatment compared to another treatment
- Excess number of events calculation

  = population size x risk difference

  = population size / NNT

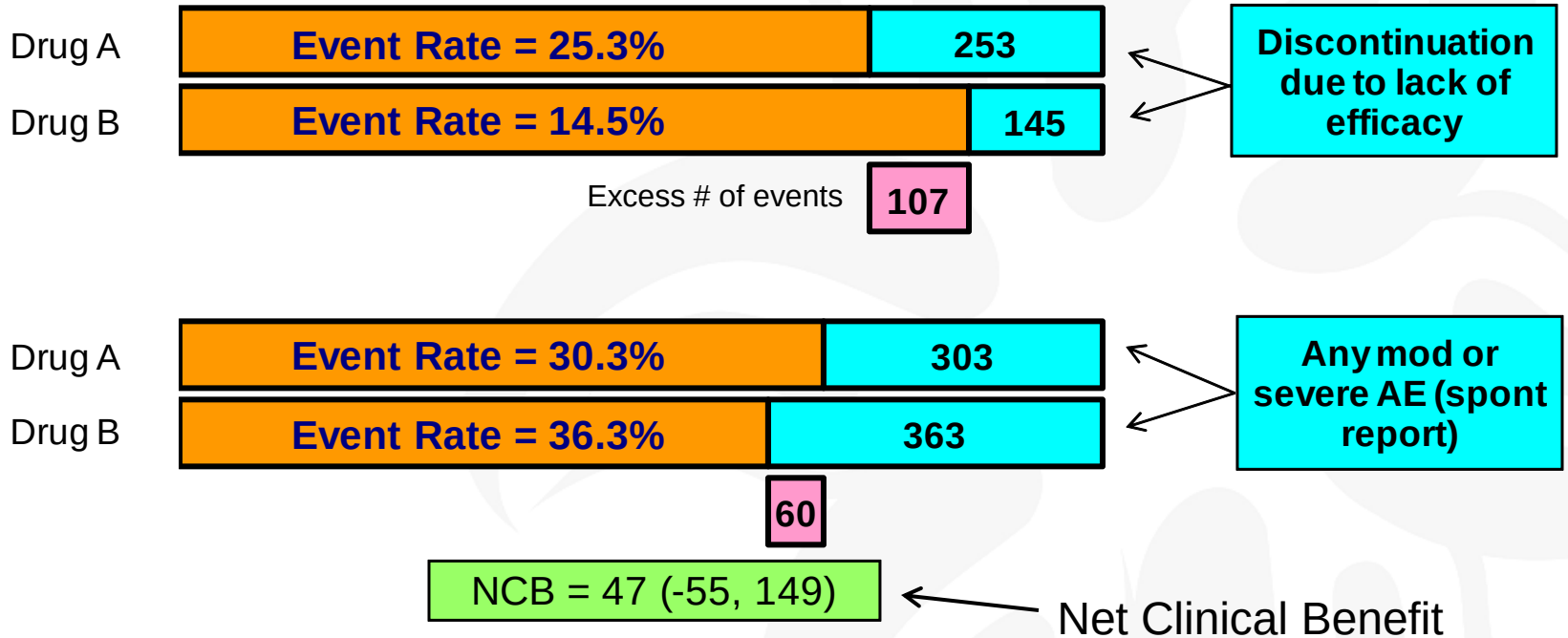
- Why worth using?



Excess # of Events:
Example from CATIE Study

Outcome	Drug A	Drug B	Risk Difference
D/C due to lack of efficacy	0.253	0.145	-0.107 (-0.174, -0.041)
Any moderate or severe AE	0.303	0.363	0.060 (-0.017, 0.138)

➔Treating 1,000 patients in each group:



Real questions

- What about all the other AEs and health states?
- How to account for the differential impact of these events on the patient?

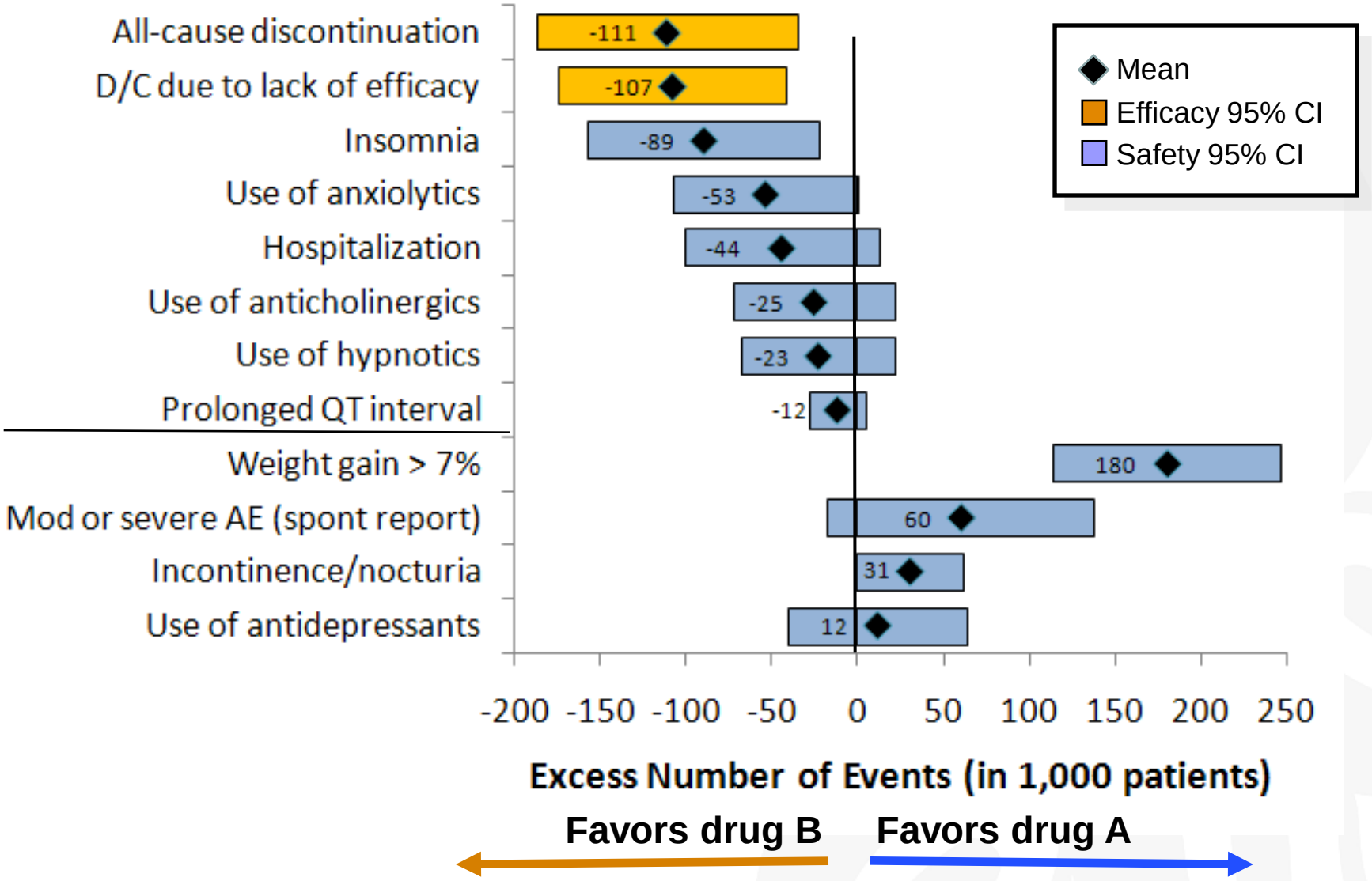
Excess # of Events for Many Endpoints: Full Table + Intuition

Outcome	Drug A (/1000 patients)		Drug B (/1000 patients)		Excess # Events (/1000 patients)		NNT	NNH
All-cause discontinuation	747	(693, 801)	636	(583, 689)	-111	(-187, -35)	9.0	
D/C due to lack of efficacy	253	(199, 307)	145	(107, 184)	-107	(-174, -41)	9.3	
Insomnia	253	(199, 307)	164	(123, 204)	-89	(-156, -22)	11	
Use of anxiolytics	146	(102, 189)	92	(61, 124)	-53	(-107, 1)	19	
Hospitalization	157	(112, 202)	113	(79, 148)	-44	(-101, 13)	23	
Use of anticholinergics	100	(63, 137)	74	(46, 103)	-25	(-72, 22)	40	
Use of hypnotics	88	(53, 123)	65	(38, 92)	-23	(-67, 22)	44	
Prolonged QT interval	12	(-5, 28)	0	(0, 0)	-12	(-28, 5)	86	
Weight gain > 7%	119	(78, 161)	300	(247, 352)	180	(114, 247)		6
Mod or severe AE (spont report)	303	(246, 360)	363	(311, 416)	60	(-17, 138)		17
incontinence/nocturia	23	(4, 42)	54	(29, 78)	31	(0, 61)		33
Use of antidepressants	107	(69, 146)	119	(84, 154)	12	(-40, 64)		85

But can be difficult to interpret quickly. Visualization often assists …

Visualization of Excess # of Events

Confidence intervals give the complete picture



Agenda

- Background
- Selected unweighted methods for benefit-risk
- Selected weighted methods for benefit-risk

Weighting Outcomes for Benefit-Risk

- Putting benefit and risk outcomes in the same units only solves part of the problem
- Patients and physicians put different weight on different outcomes
  - 1 weight gain ≠ 1 discontinuation ≠ 1 hospitalization
  - 1 death ≠ 1 MI ≠ 1 stroke ≠ 1 DVT ≠ 1 headache
- All approaches shown so far make the implicit assumption that all events are of equal weight

Variety of Weighted Approaches

- Methods
  - Utility weighting
  - Preference weighting
  - Multicriteria decision analysis (MCDA)
  - Quality-adjusted life years (QALYs)

- No standardized approach
- All four methods are in the literature
- QALYs are the basis for reimbursement decisions in the UK's National Institute for Health and Clinical Excellence (NICE)

- Will demonstrate preference weighting

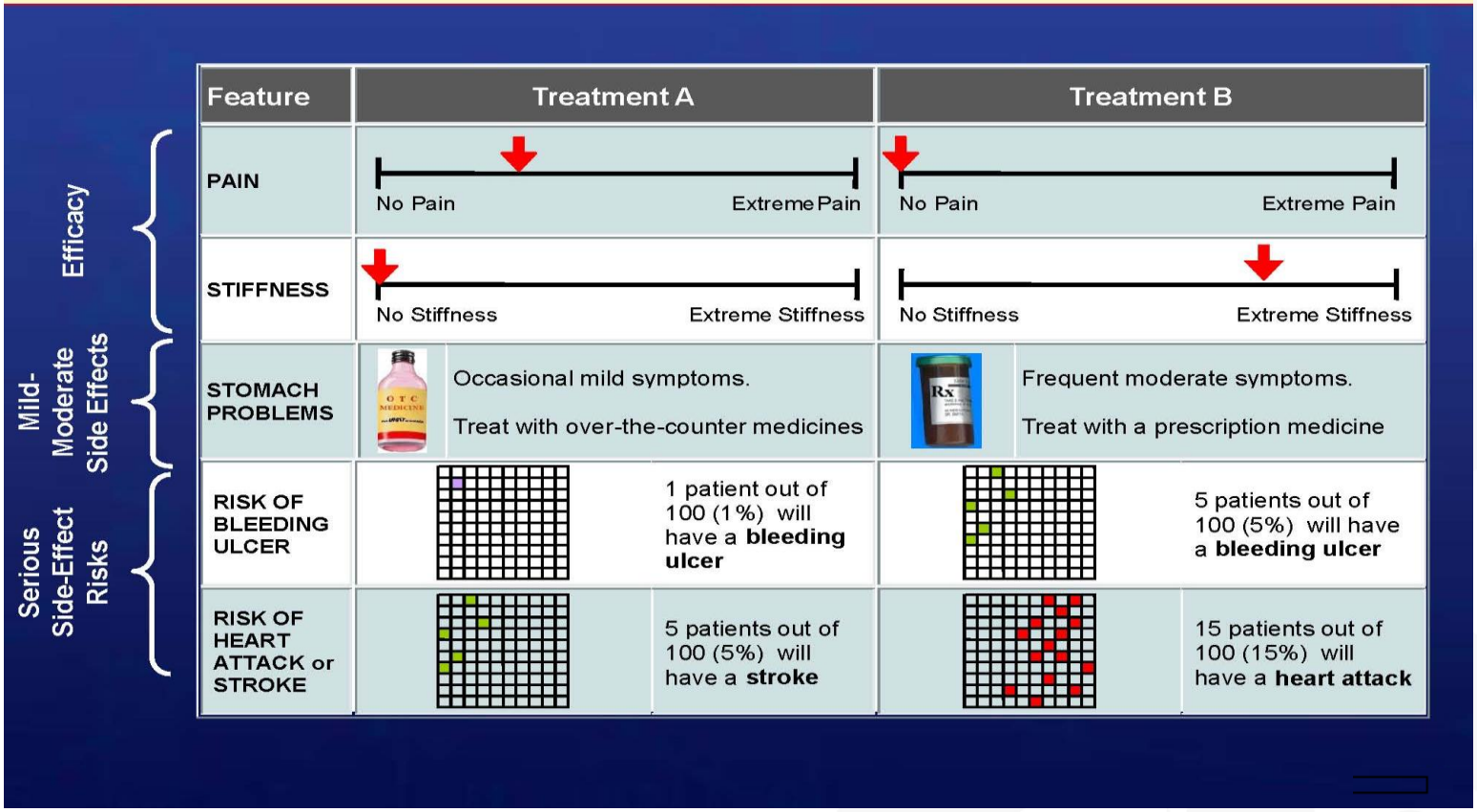
Preference Weights
Stated Choice / Conjoint Analysis

- Weights are obtained by asking subjects to make a series of choices between hypothetical treatments
- Treatments are based on different combinations of properties, e.g.,
  - X% chance for a condition being cured
  - Y% chance for experiencing an event, e.g., fatigue
  - etc.
- Preferences are elicited by varying the combination of properties and analyzing the different decisions made
- Preferences are then converted to weights that reflect the relative importance of the properties

Conjoint Preference Weights

(Example Stated Choice Question)

Choice-Format Stated-Preference or Conjoint Question



Courtesy Reed Johnson, RTI-HS

Stated choice Survey for Acceptance of Risks When Using Hormone Therapy for Vasomotor Symptom Relief

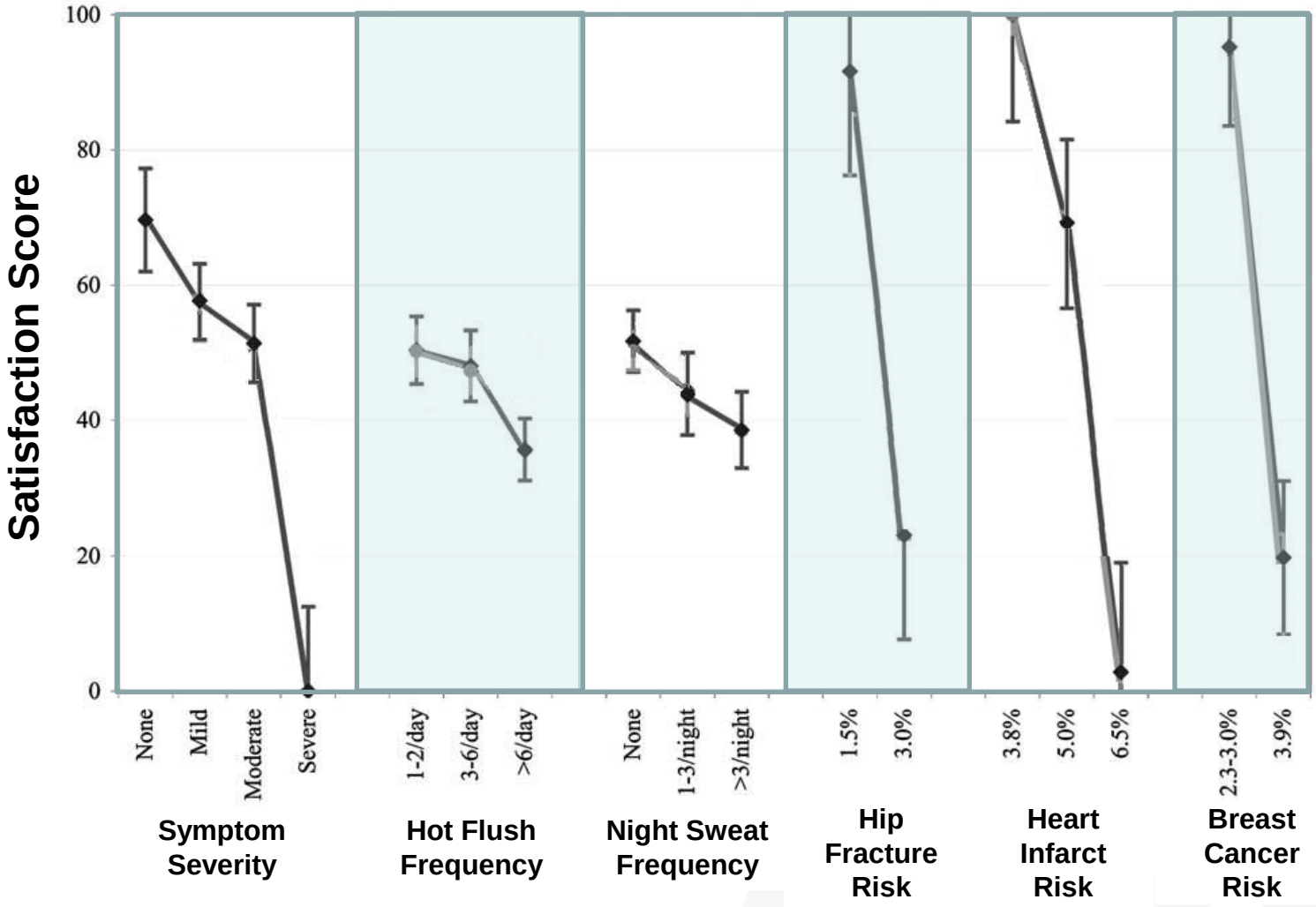
Considering the different results and risks associated with Treatments A and B, which would you prefer if these were the only options available?

	Results of Treatment A	Results of Treatment B
Severity of Daytime Hot Flushes	Mild	Severe
Frequency of Dayime Hot Flushes	1 - 2 times a day	More than 6 times a day
Frequency of Night Sweats	None	1 - 3 times a night
Duration of Hot Flashes and Night Sweats	7 years	1 year
Risk of Hip or Back Fracture (within 10 years)	15 / 1,000 (1.5%)	15 / 1,000 (1.5%)
Risk of Heart Infarct (within 10 years)	38 / 1,000 (3.8%)	65 / 1,000 (6.5%)
Risk of Breast Cancer (within 10 yeasr)	30 / 1,000 (3%)	23 / 1,000 (2.3%)

Check the box that best describes your opinion	☐	☐	☐	☐	☐
	A is much better	**A is somewhat better**	**A and B are the same**	**B is somewhat better**	**B is much better**

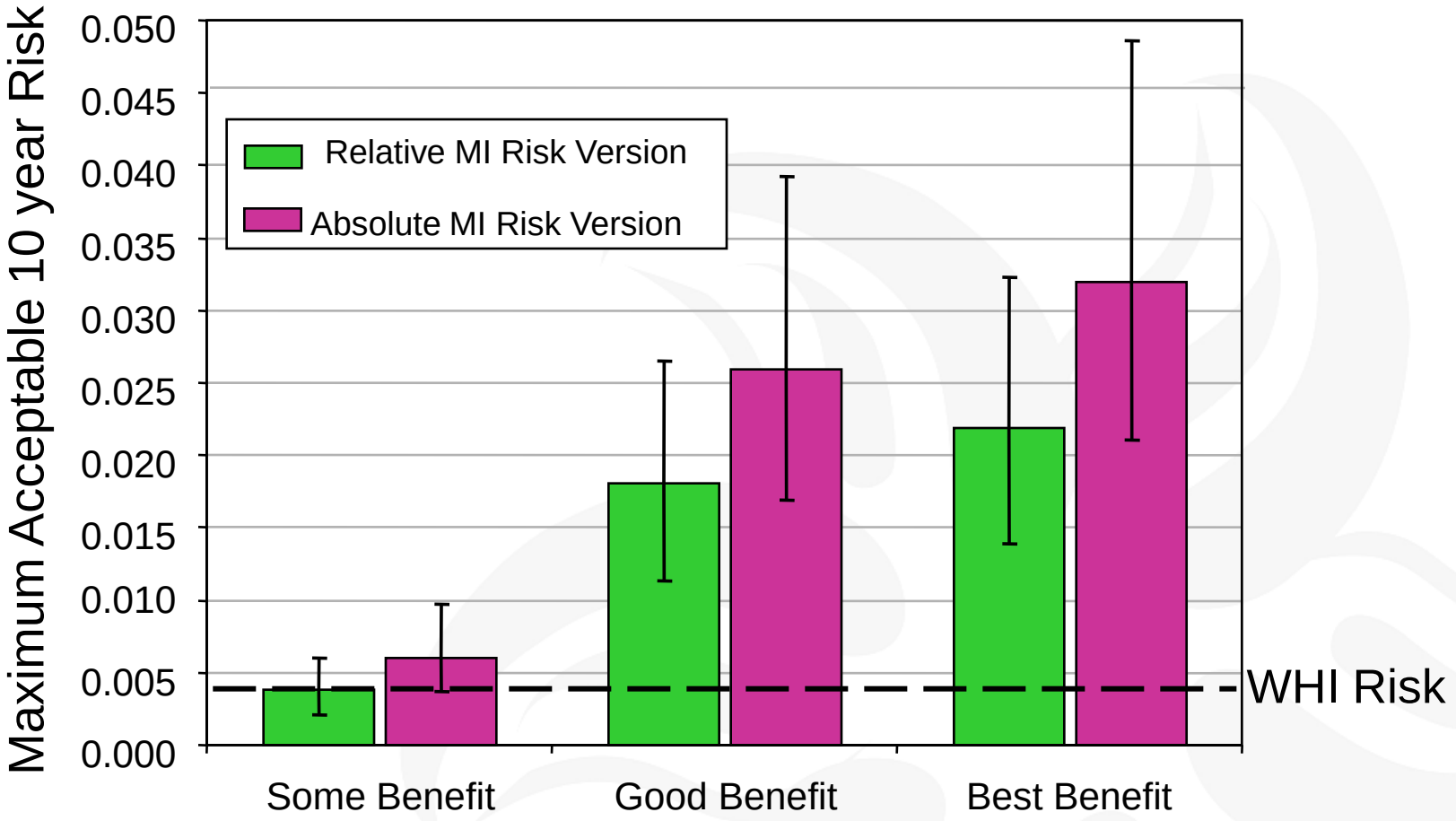
Johnson et. al., J. Women's Health, 16(7), 2007

Preference Scores for Using Hormone Therapy for Vasomotor Symptom Relief



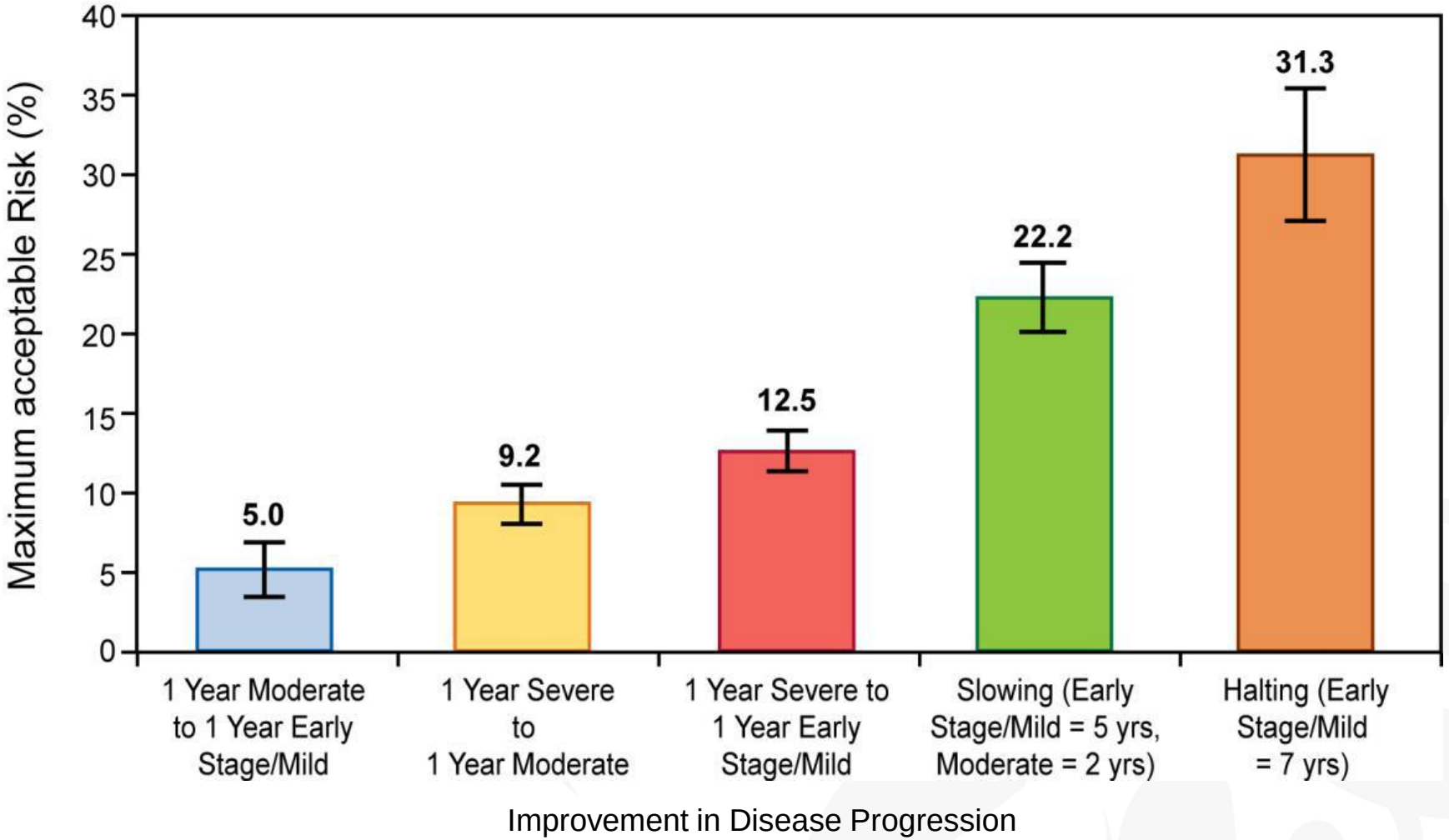
Maximum Acceptable Risk:

Postmenopausal Women's Preferences for HRT Benefits vs. MI Risk



Degree of benefit defined using composite measure: Ex: Best benefit defined as (> 6 daytime hot flushes, > 3 night sweats / night, 3% hip fracture risk) → no symptoms

Maximum Acceptable Risk for Stroke or Permanent Severe Disability in Alzheimer's Patients



Hauber, et. al., Alh Dz Assoc Disord, 23(1), 2009

Some Parting Words

- Benefit-risk assessment is challenging both technically and organizationally
- Several industry and regulatory organizations have sponsored initiatives on B-R
- Plan B-R approach early
- Role play trial results
- Plan for several approaches to B-R – both unweighted and weighted