Symptoms and their Measurement

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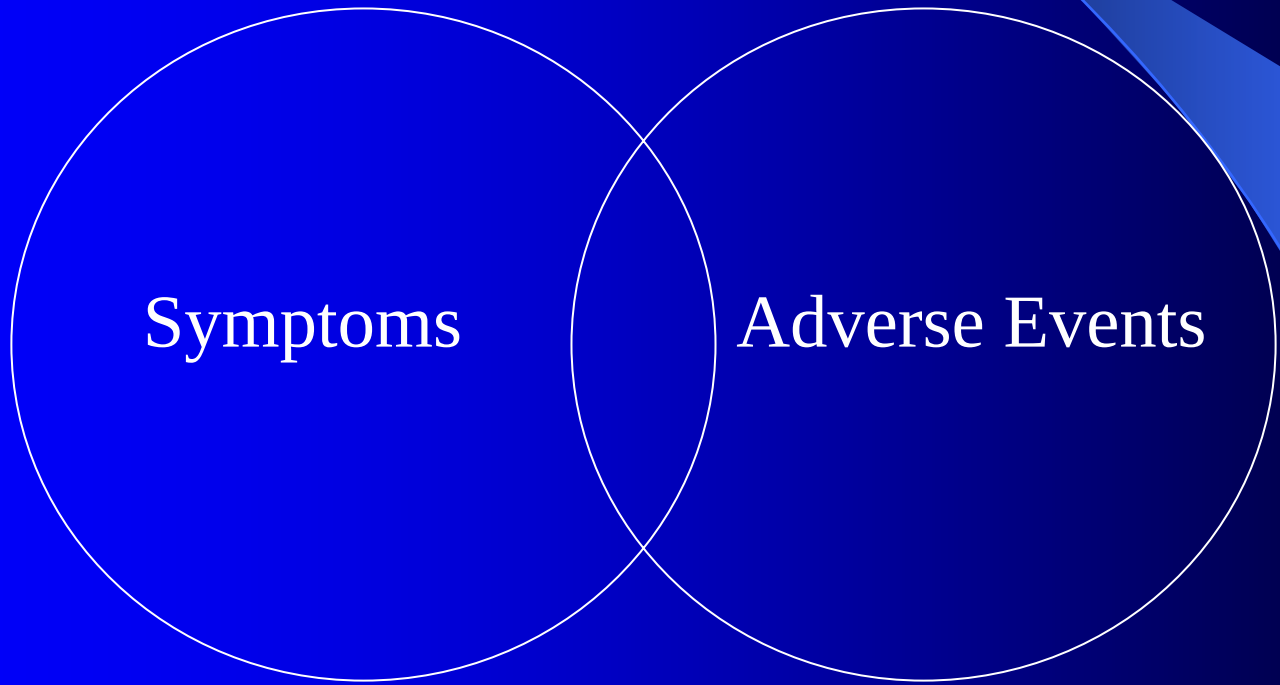
Drug Safety



Overall Treatment Result

Questions

- How to assess symptoms and their impact
- How to assess the overall balance of benefit (e.g. pain reduction) and side effects (symptoms) of a treatment

Symptom Assessment

- Passive capture of adverse events
- Open-ended questions
- Specific AEs of interest
- Comprehensive symptom checklists
  - Frequency
  - Duration
  - Intensity
  - Distress
  - Impact on daily function
- Symptom Importance

Passive Capture of AEs

- Advantage
  - Level playing field
  - May capture unanticipated side effects
- Disadvantages
  - Patient perspective filtered through nurse, investigator
  - Less sensitive to meaningful symptoms than prospective assessment
  - May reveal differences that are in fact unimportant

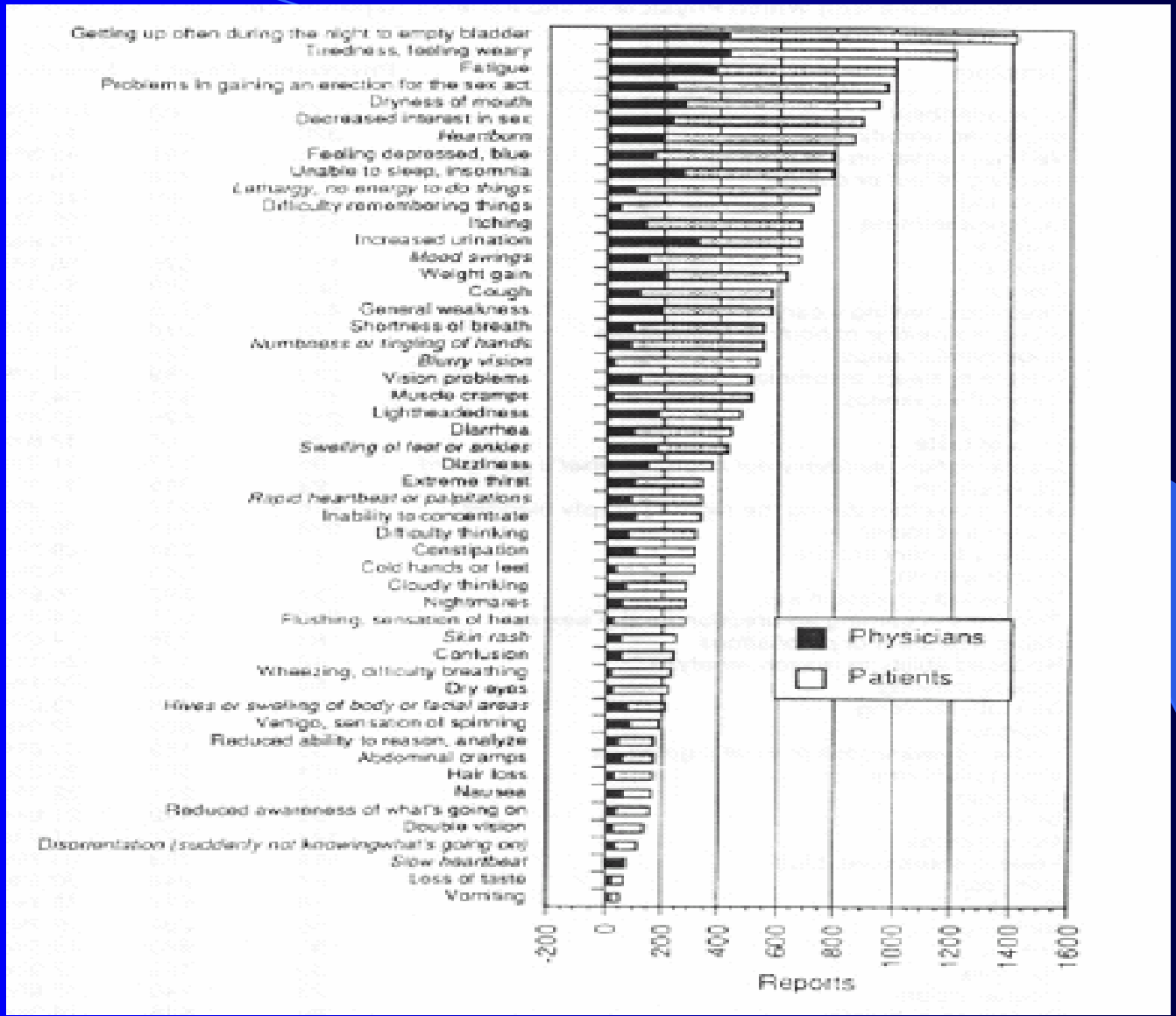
Table 3. Frequency of Symptoms From Physical Symptom Distress (PSD) Index and Corresponding Spontaneously Reported Adverse Events*

	Percentage of Subjects Reporting									
	Edema		Palpitations		Increased Urination		Muscle Cramps		Constipation	
	COER-Verapamil	Nifedipine GITS	COER-Verapamil	Nifedipine GITS	COER-Verapamil	Nifedipine GITS	COER-Verapamil	Nifedipine GITS	COER-Verapamil	Nifedipine GITS
Adverse events	1.4	12.8	1.4	2.8	0.4	1.1	0.7	3.2	14.9	8.2
PSD Index†										
Total	26.6	47.2	17.0	27.5	35.5	39.0	23.9	36.4	38.2	31.0
Distressed	12.4	33.8	7.3	13.4	17.4	23.0	12.0	22.7	25.1	18.2
Extremely distressed	2.4	12.3	0.4	1.9	1.9	7.0	1.2	2.2	6.1	5.5

*COER indicates controlled onset, extended release; GITS, gastrointestinal therapeutic system.

†Total indicates all subjects who had the symptom; distressed, all subjects who had any distress from symptom; and extremely distressed, all subjects who were extremely or very much distressed.

Anderson, Arch Int Med, 1999



Anderson, Drug Inf J, 1994

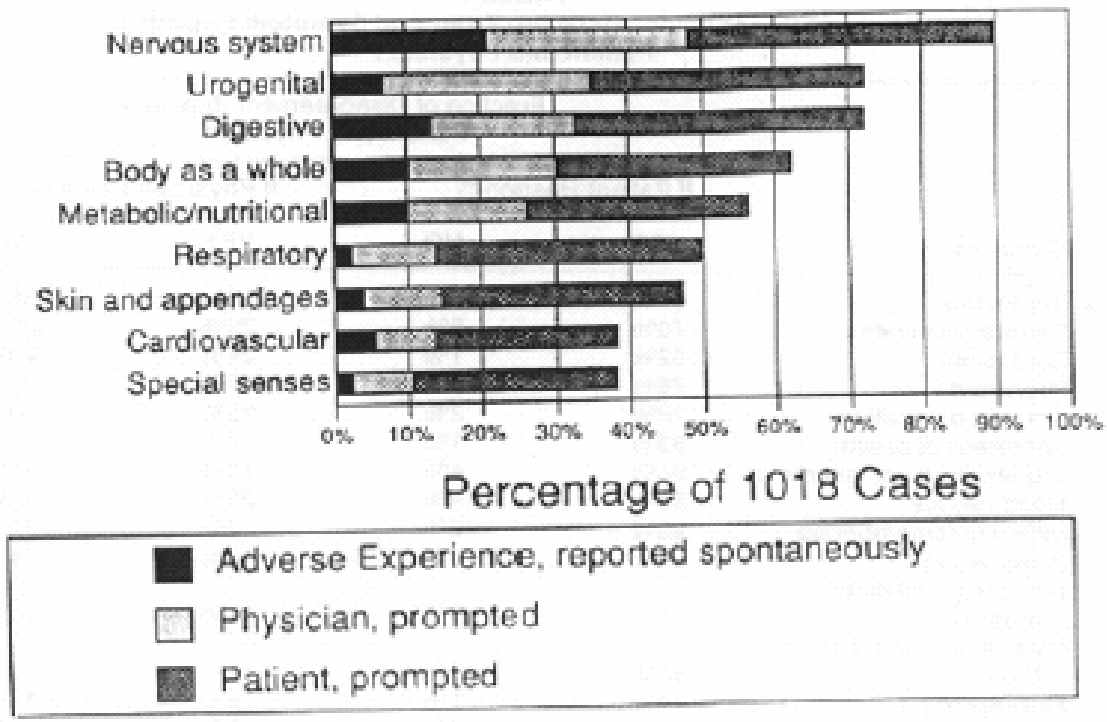


FIGURE 4. Fractions of patients with COSTART Symptom Category Reports from three sources.

Anderson, Drug Inf J, 1994

How AEs are Reported

AE*	Group 1 (n=150)	Group 2 (n=140)
Headache	25 (17%)	14 (10%)
Infection	6 (4%)	9 (6%)
Diarrhea	13 (9%)	19 (14%)
Pain	31 (21%)	22 (16%)
Depression	9 (6%)	11 (8%)

*Adverse events seen in $\geq$5% of the ITT population

Minimum Reporting Criteria for Adverse Events

- Proportion of subjects in each group reporting ≥1 AE
- Proportion reporting ≥1 drug-related AE
- Proportion with ≥1 severe AE or “Serious Adverse Event”
- Proportion who drop out due to an AE
- Proportion of subjects in each group who have each AE, and AE category

Prospective Assessment of Specific Side Effects of Interest

- Rofecoxib 25 mg, 50 mg, placebo in the treatment of chronic low back pain
- Customary AE capture showed no difference in renovascular AEs
- Prospective capture of renovascular AEs revealed greater pedal edema, HTN in high-dose group, with no difference in efficacy
- 25 mg considered optimal dose

Katz NP et al, Spine, in press

Prospective Comprehensive Symptom Checklists

Percent Reporting Symptoms

Adverse Effect	Value (%) for Indicated Group			
	Total (N = 36)	No Opioid (N = 12)	Set Dose (N = 13)	Titrated Dose (N = 11)
Dry mouth	26.1	19.3	26.0	34.7
Drowsiness	24.1	14.6	22.1	36.9
Headache	22.1	15.1	20.2	31.8
Constipation	19.1	10.4	17.8	30.1
Nausea	16.2	4.7	13.9	31.3
Itching	12.9	8.9	14.9	14.8
Dizziness	11.6	9.4	18.8	5.7
Sweating	6.8	6.8	9.6	3.4
Weakness	6.3	5.7	7.7	5.1
Sneezing	2.0	1.0	1.0	4.0
Muddled thinking	1.6	3.1	1.4	.0
Nightmares	1.2	1.0	1.0	1.7
Heart palpitation	.7	.5	.0	1.7
Visual distortions	.7	.0	1.9	.0
Memory lapse	.5	1.6	.0	.0

Note: Wilcoxon matched-pairs signed-ranks test: No opioid vs. set dose, $z = -15.7$; $P < 0.001$. Set dose vs. titrated dose, $z = -16.8$; $P < 0.001$. No opioid vs. titrated dose, $z = -18.0$; $P < 0.001$.

Jamison RN et al, Spine, 1998

Side Effect Intensities

	Total (N = 36)		Intensity Ratio for Indicated Group		
Adverse Effect	Frequency	Intensity Ratio*	No Opioid (N = 12)	Set Dose (N = 13)	Titrated Dose (N = 11)
Dry mouth	152	0.48	0.54	0.63	0.32
Drowsiness	139	0.40	0.46	0.44	0.35
Headache	127	0.45	0.60	0.53	0.32
Constipation	110	0.57	0.66	0.61	0.50
Nausea	93	0.33	0.40	0.36	0.30
Itching	74	0.45	0.74	0.43	0.29
Dizziness	67	0.41	0.43	0.41	0.34
Sweating	39	0.54	0.58	0.50	0.33
Weakness	36	0.49	0.60	0.52	0.29
Sneezing	11	0.34	0.50	0.23	0.33
Muddled thinking	9	0.43	0.46	0.37	—
Nightmares	7	0.29	0.28	0.35	0.25
Heart palpitation	4	0.24	0.35	—	0.20
Visual distortions	4	0.36	—	0.36	—
Memory lapse	3	0.38	0.38	—	—

* Ratios from 1.0 to 0.0; sum of intensities/(no. of responses × 100).

Jamison RN et al, Spine, 1998

Are Symptoms Important?

Symptom Distress Predicts Survival

- Several studies in cancer patients (ambulatory and palliative care) demonstrate that symptom distress is an independent predictor of survival

Symptom Distress Associated with Clinically Important Outcomes in Clinical Trials

- Captopril vs. enalapril for HTN: SD associated with psychosocial QOL (Testa, NEJM, 1993)
- Nifedipine vs. verapimil for HTN: SD only predictor of dropout (Anderson, 1999)
- Verapimil, amlodipine, amlodipine-atenolol for angina: SD predicted change in QOL (Hollenberg, Arch Int Med, 2000)

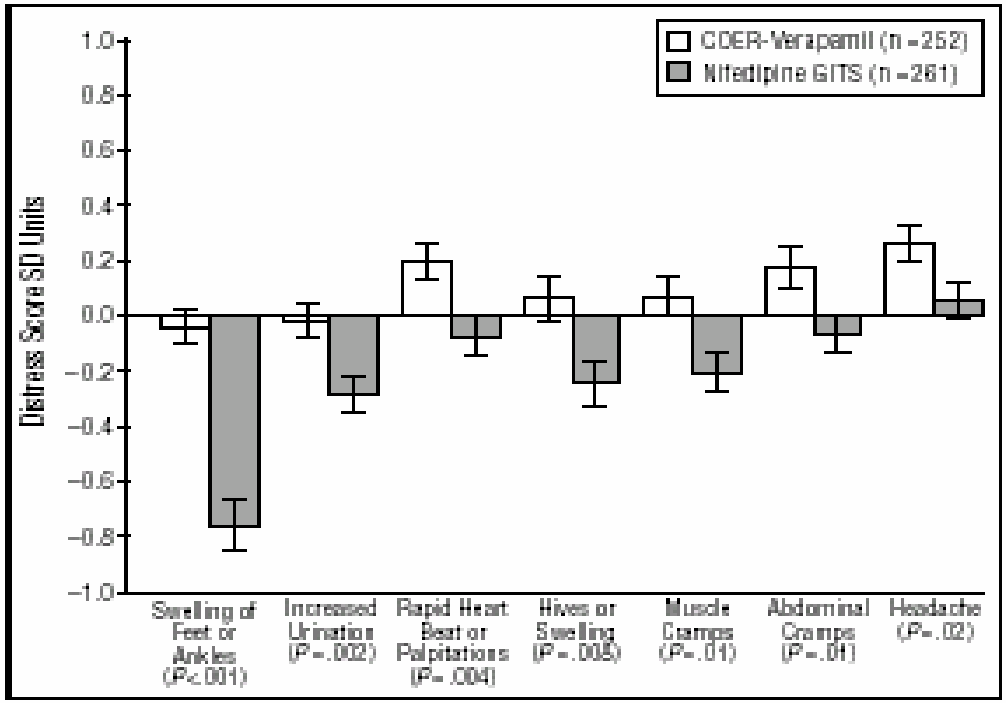
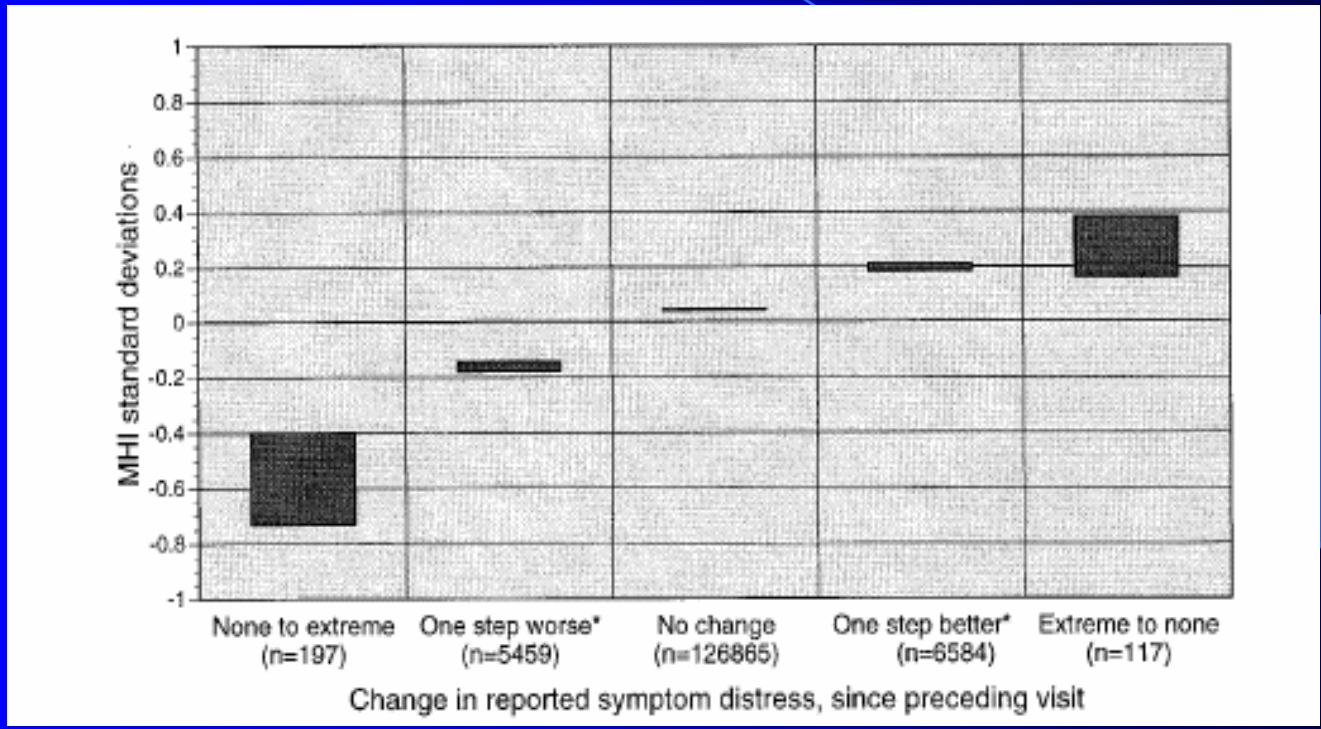


Figure 2. *Physical Symptom Distress Index scores. Change from baseline in SD units for individual symptoms demonstrating a significant univariate treatment effect by treatment group (positive change reflects reduced distress; P = .002 for multivariate analyses of variance). CDER indicates controlled onset, extended release; GITS, gastrointestinal therapeutic system.*

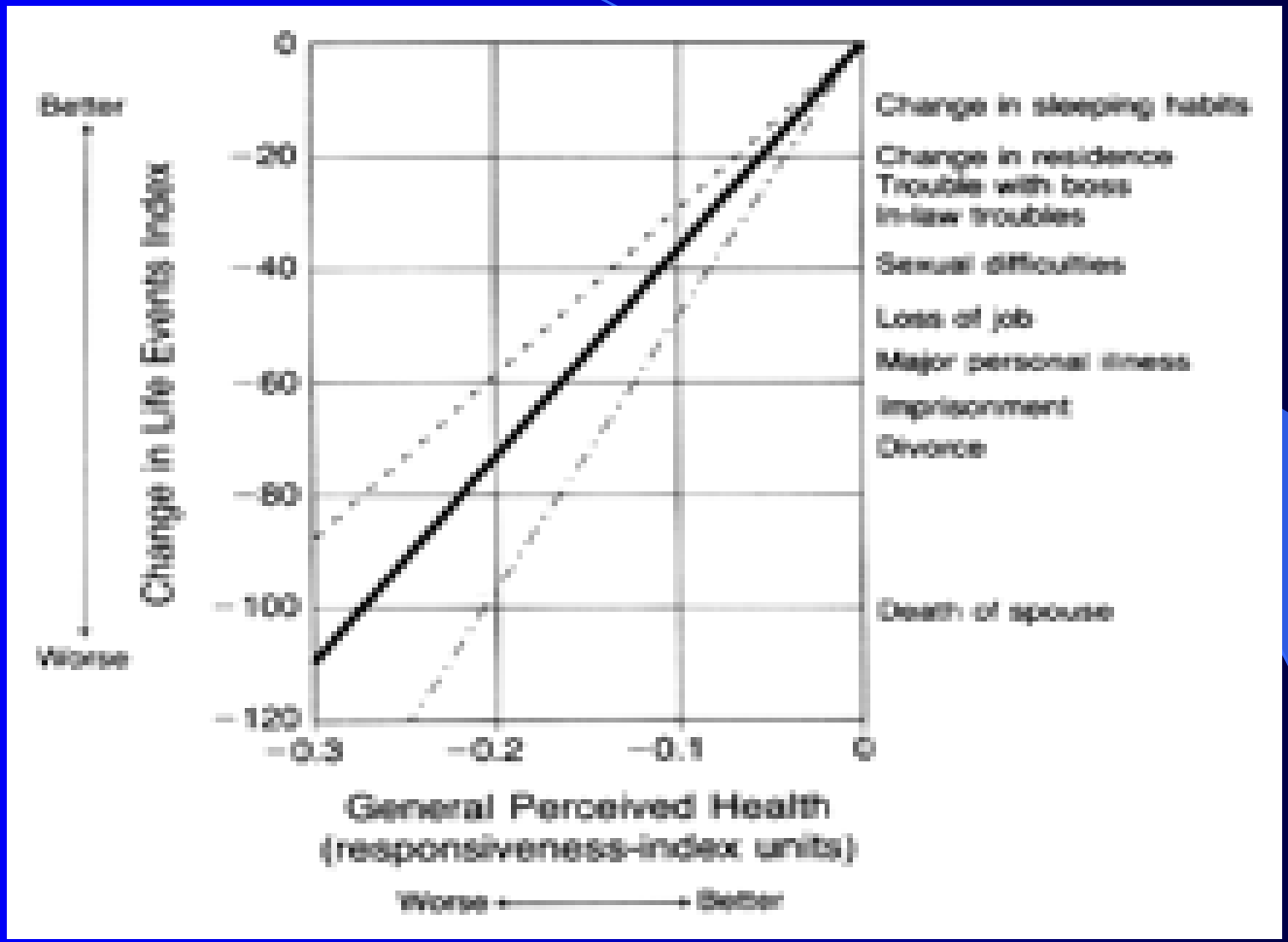
Anderson, Arch Int Med, 1999



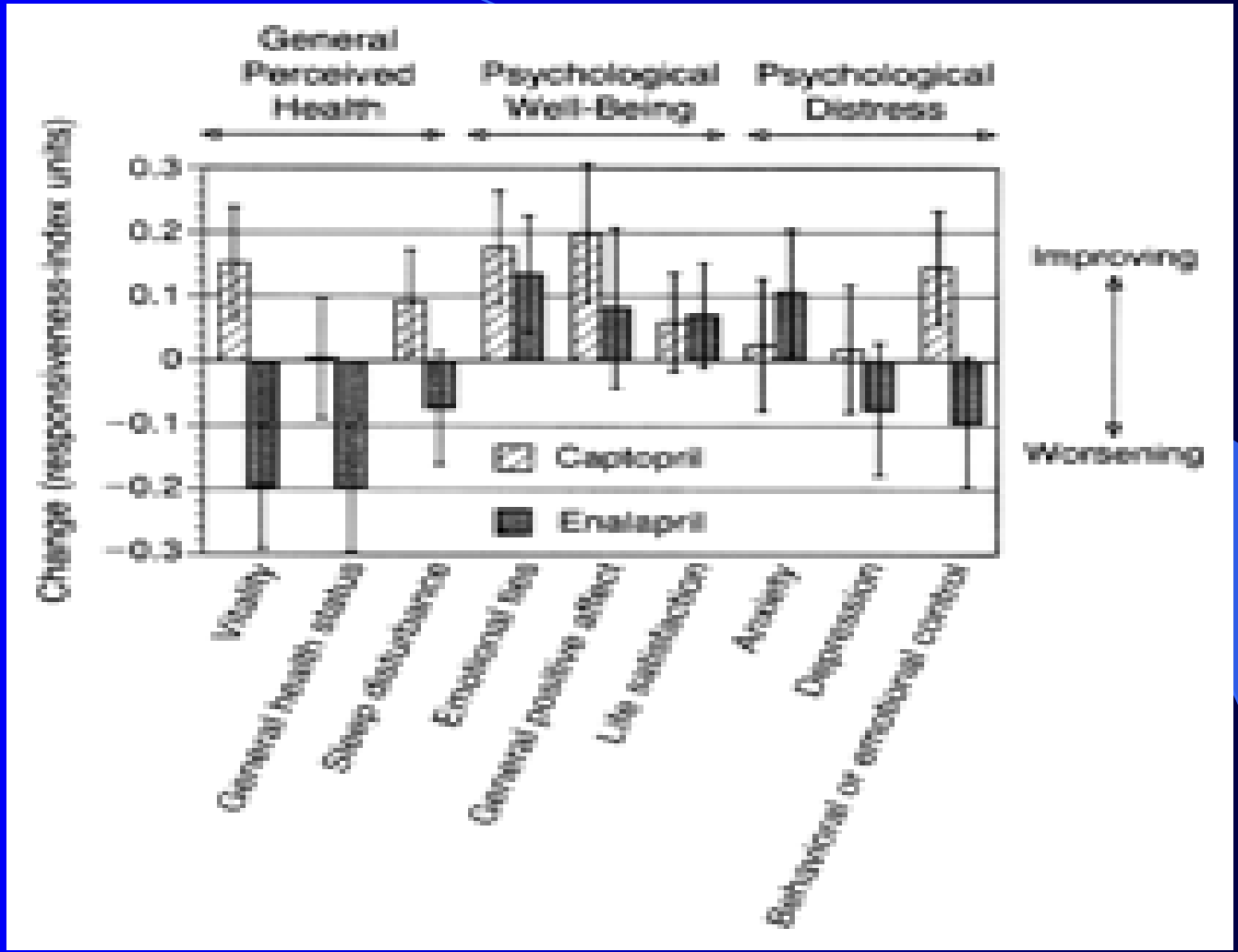
Anderson, Drug Inf J, 1999

Symptom Distress Important by Calibration Analysis

- Captopril vs. enalapril in HTN, n=379
- 6-month study
- Comprehensive QOL battery
- Life Events Index
  - Very stressful: death of spouse
  - Moderately stressful: retirement, change in health of family member
  - Less stressful: trouble with in-laws
- Symptom distress best predictor of QOL change
- Differences in QOL by treatment corresponded to moderately stressful life events



Testa, NEJM, 1993


General Perceived Health
Psychological Well-Being
Psychological Distress
Change (responsiveness-index units)
0.3
0.2
0.1
0
−0.1
−0.2
−0.3
Captopril
Enalapril
Improving
Worsening
Vitality
General health status
Sleep disturbance
Emotional self
General positive affect
Life satisfaction
Anxiety
Depression
Behavioral or emotional control

Side Effects Predicts Treatment Preference for Analgesics Despite Similar Efficacy

Logistic Regression Modeling of Patient Treatment Preference in a Study Comparing Two Opioid Analgesics (n=264)

Variable	**Estimated OR**	**95% CI**	**p-value**
Index Adverse Events	5.211	1.900, 14.294	0.0013
Pain difference	2.744	1.029, 7.320	0.0438

Symptom Distress is a Sensitive Discriminant of Treatments

Symptom Distress is a Sensitive Discriminant of Treatments

- Verapimil vs. nifedipine for HTN, n=259
- No difference in efficacy
- AEs: more edema in nifedipine; more DC/AE in nifedipine: 24 vs. 18
- QOL same between groups
- Significant differences in symptom distress between groups
- Increased symptom distress predicted decreseased QOL

The Importance of Symptom Importance

Thurstone Scale Order	Intensity (Mean) Order
Outlook	Fatigue
Breathing	Outlook
Pain	Insomnia
Insomnia	Breathing
Cough	Appearance
Bowel	Appetite
Appetite	Pain
Fatigue	Cough
Appearance	Bowel

Symptom Distress Inventories

- Symptom Distress Scale (McCorkle, 1978)
- Memorial Symptom Assessment Scale (Portenoy, 1994)
- Edmonton Symptom Assessment System (Bruera, 1991)
- Symptom Experience Scale (Rhodes, 2000)
- Adapted Symptom Distress Scale-1,2 (Rhodes, 1984, 1987)
- Gastrointestinal Symptom Rating Scale (Dimenas, 1995)
- GERD Symptom Assessment Scale (Rothman, 2001)
- MD Anderson Symptom Inventory (Cleeland, 2000)
- Rotterdam Symptom Checklist (de Haes, 1990)
- Physical Symptoms Distress Index (Anderson, 1999)

"Do you feel that the benefits of this treatment outweighed the side effects?"

- Yes, definitely
- Yes, probably
- Not sure
- No, probably not
- No, definitely not

Possible Recommendations from IMMPACT

- Minimum reporting standards for passively captured AEs?
- Prospective capture of specific AEs of interest?
- Prospective symptom distress inventories?
  - Frequency, duration, intensity, importance
  - Which scale(s)?
  - Include side effects of disease?
- Calibration, other utility analysis?
- Direct side effect-benefit assessment by patient?

Recommendations

Minimum reporting standards for passively captured AEs?	Yes
Prospective capture of specific AEs of interest?	Yes*
Prospective symptom distress inventories?	Yes
- Frequency, duration, intensity, importance	As appropriate**
- Which scale(s)?	Any
- Include side effects of disease?	Yes
Calibration, other utility analysis?	No
Direct side effect-benefit assessment by patient?	Explore

*If appropriate

**Minimum frequency, intensity