

THE UNIVERSITY OF TEXAS
MD ANDERSON
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Endometriosis Pain: How Best to Assess It?

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- ▶ **The investigator who would study pain is at the mercy of the patient, upon whose ability and willingness to communicate he is dependent.**

– *Lasagna, 1960*

Objectives

- ▶ **Context of pain measurement**
- ▶ **Introduction to the Brief Pain Inventory**
- ▶ **How is assessment used in clinical practice?**
- ▶ **How to measure pain in clinical trials?**
- ▶ **What is a clinically significant reduction in pain?**
- ▶ **A program for developing pain assessment in endometriosis**

What do we need to know about pain to treat it?

- ▶ **Severity**
- ▶ **Location**
- ▶ **Temporal pattern**
- ▶ **Interference with activities**
- ▶ **Pain quality (how it is described)**
- ▶ **Response to prior treatment, adverse effects of prior treatment**
- ▶ **Determine etiology (somatic, visceral, neuropathic)**

Can We Trust Patient Ratings?

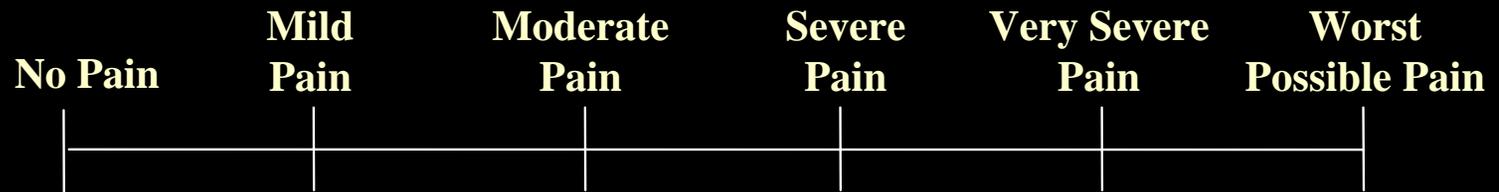
- ▶ **Medical management depends on systems of measurement – blood pressure, temperature, cultures**
- ▶ ***But* pain is a “subjective state” – multiple determinants**
- ▶ **Can we believe the ratings patients give us?**
- ▶ **Can we base treatment on what patients tell us?**

Patient Barriers to Pain Reporting

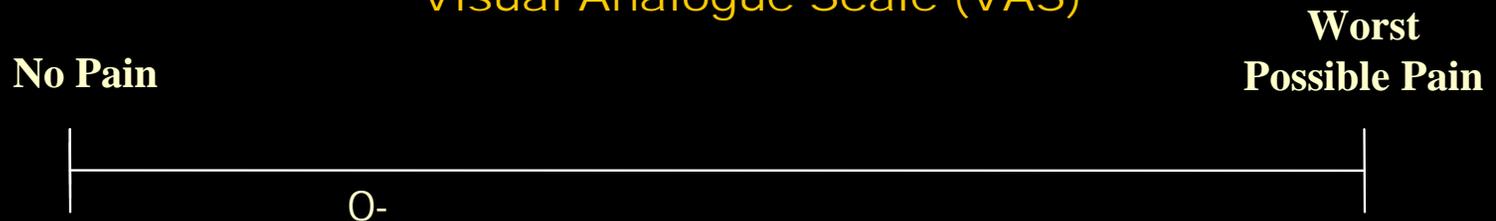
- ▶ **Want to be a “good” patient**
- ▶ **Don’t want to use the doctor’s time**
- ▶ **Are afraid of new medicines and addiction**
- ▶ **Don’t want to complicate the treatment**
- ▶ **Want to “save” the effectiveness of analgesics - “I’ll need more later”**
- ▶ **Are afraid of the meaning of worsening pain**

Pain Intensity Scales

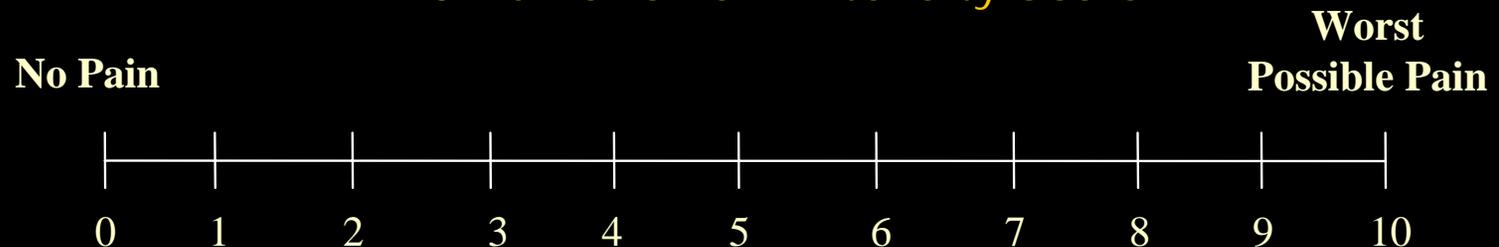
Verbal Rating Scale



Visual Analogue Scale (VAS)



10 Numeric Pain Intensity Scale



Verbal Rating Scales

▶ Strengths

- Easy to administer
- Easy to score
- Correlates with other intensity measures
- Sensitive to treatment effects

▶ Weaknesses

- Limited response categories
- Assumes equal intervals between adjectives
- Not appropriate for low literacy patients

Visual Analogue Scales

▶ Strengths

- High number of response categories
- Ratio data
- Correlates with other measures of intensity
- Sensitive to change
- Widely used

▶ Weaknesses

- Scoring issues
- Patient comprehension

Numerical Rating Scales

- ▶ **Patients rate pain intensity from 0–10 (11-point scale) or 0–100 (101-point scale)**
- ▶ **Number chosen represents pain intensity score**
- ▶ **Zero represents “no pain” and 10 or 100 represents “pain as bad as it could be” or “pain as bad as you can imagine”**

The Brief Pain Inventory

- ▶ **Quick (11 items plus pain drawing)**
- ▶ **Uses 0–10 scales, easy for patients and easy to interpret**
- ▶ **Measures both pain severity and the interference caused by pain**
- ▶ **Many translations available**
- ▶ **Very responsive (sensitive) to effective treatment**

Development of the Brief Pain Inventory

- ▶ **Items based on 50 in-depth interviews with patients who had cancer-related pain**
- ▶ **First version: Wisconsin Brief Pain Questionnaire (Daut and Cleeland 1982, Daut et al 1983)**
- ▶ **Current version: Brief Pain Inventory (Cleeland 1989, Cleeland et al 1994)**
- ▶ **Cross-cultural examination of interference items (Serlin et al 1995, Cleeland et al 1996)**

Critical Components of Pain

- ▶ **Sensory**
 - Intensity
 - Quality
- ▶ **Reactive**
 - Affective
 - Motivational
 - Interference with activities

Brief Pain Inventory (Interference)

7. Circle the number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Brief Pain Inventory Interference Items

- ▶ **General activity**
- ▶ **Work (including housework)**
- ▶ **Ability to walk**
- ▶ **Mood**
- ▶ **Ability to relate to others**
- ▶ **Enjoyment of life**
- ▶ **Sleep**

Activities Impaired by Increasing Pain

N = 186 Multi-institutional study

					relate
				walk	walk
		sleep	sleep	sleep	sleep
		active	active	active	active
		mood	mood	mood	mood
	work	work	work	work	work
enjoy	enjoy	enjoy	enjoy	enjoy	enjoy
3	4	5	6	7	8

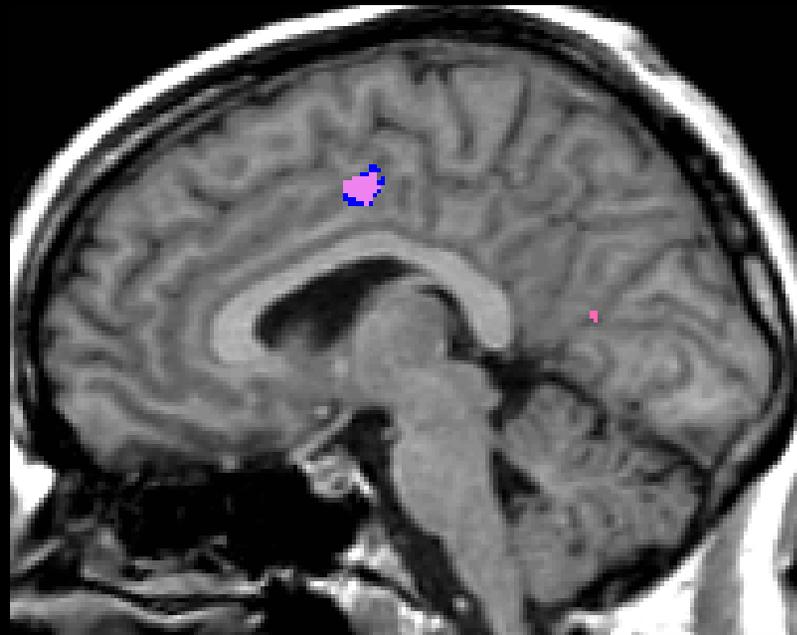
> > > > **worst pain rating** > > > >

Mild, Moderate, and Severe Pain in a Four-Country Sample

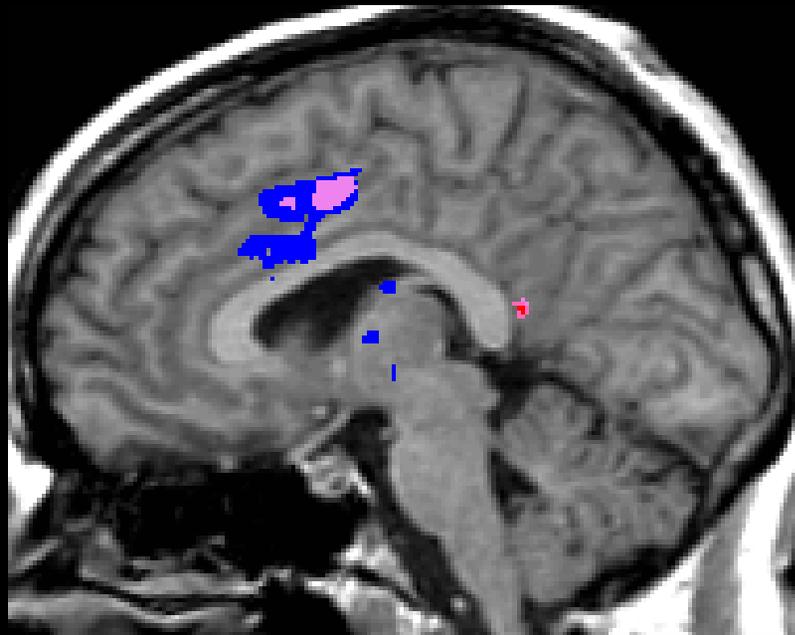
Serlin, Mendoza, Nakamura, Cleeland, 1995

- ▶ **MILD** 1 - 4
- ▶ **MODERATE** 5 - 6
- ▶ **SEVERE** 7 - 10

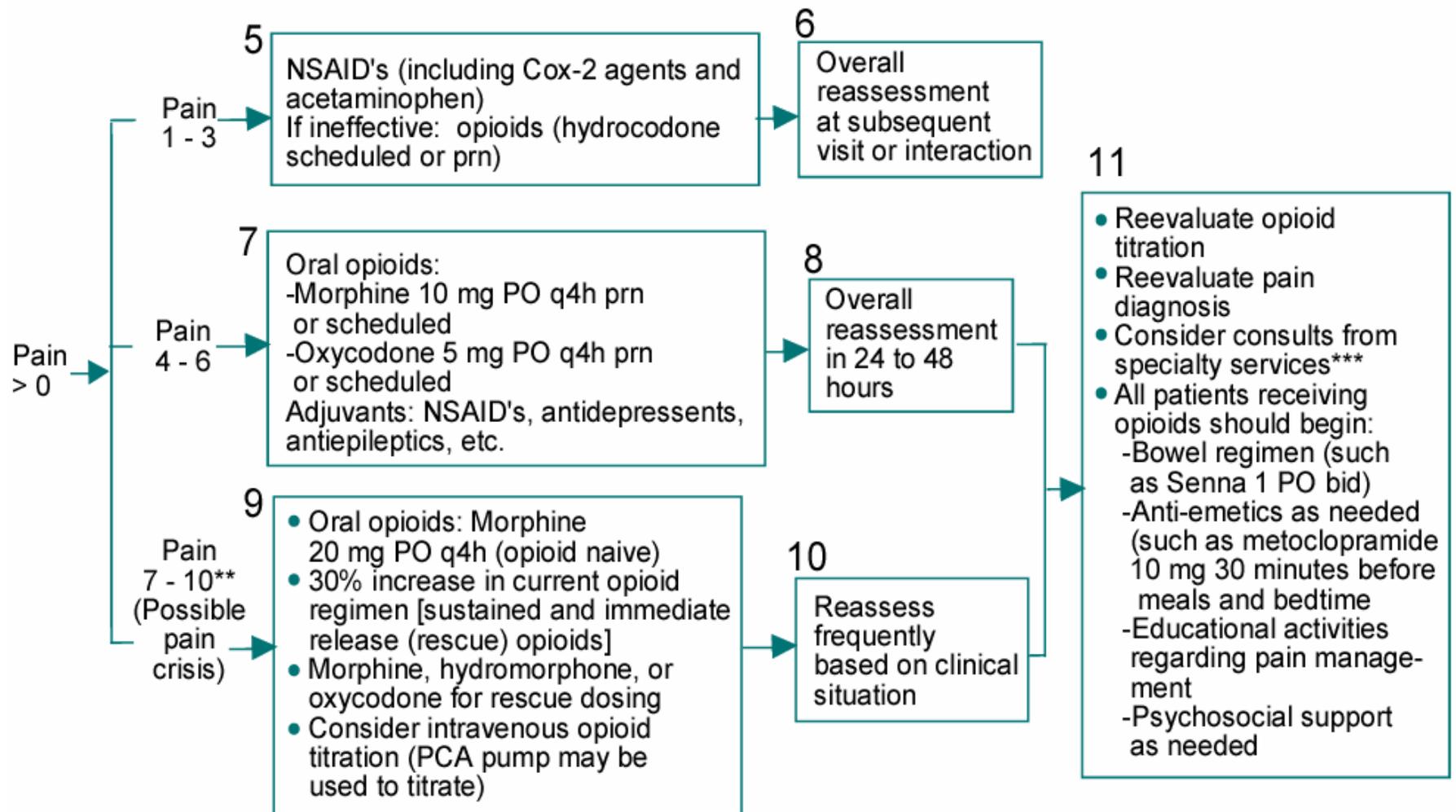
Focus Away from Pain – Rating 3.3



Focus on Pain – Rating 6.4



Cancer Pain

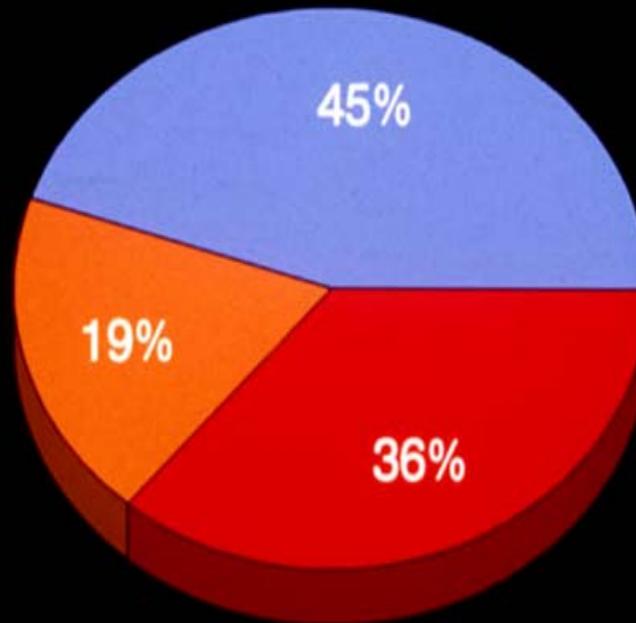


Pain Prevalence and Severity in Patients with Recurrent or Metastatic Cancer – ECOG 0390 (Cleeland, et al, NEJM, 1994)

- ▶ **Patients sampled from ECOG main, CCOP and CGOP sites**
- ▶ **Patients completed the BPI administered by research nurses**
- ▶ **Sample size 1309**
- ▶ **Physicians attributed cause of pain, recorded pain treatment, and estimated severity of patients' pain**

Percent of Patients with Pain

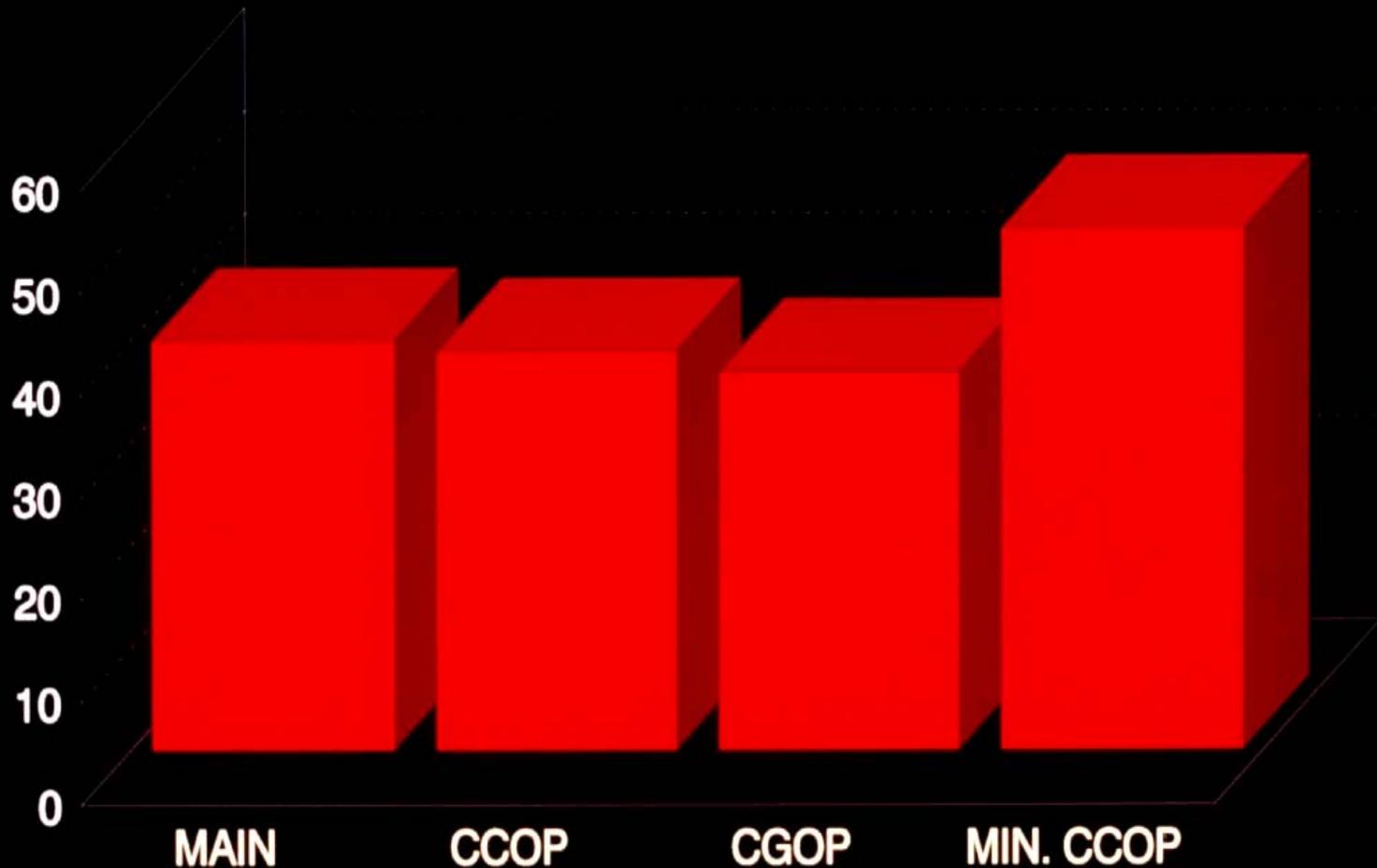
EST C-0390



■ NO PAIN ■ PAIN, 1 TO 4 SEVERITY ■ PAIN, 5 OR GREATER SEVERITY

UNDERMEDICATION BY INSTITUTION TYPE

PERCENT OF PAIN PATIENTS WITH NEGATIVE PMI



ECOG PATIENT NEEDS STUDY

Variability of Analgesic Treatment (Pain Management Index, N=310, 25 study sites)

Data from ECOG protocol E4Z93 database

- ▶ **The Pain Management Index represents the prescription of analgesia (none, NSAID, weak opioid, strong opioid) for the level of pain (mild, moderate, severe)**
 - Underprescribed **33%**
 - Appropriate **67%**
- ▶ **Adequate PMI ranged from 17% - 69% across 25 study sites**

Pain Measures Used – Endometriosis Pain Trials

- ▶ **Patient report (not specified)**
- ▶ **Visual analogue scales**
- ▶ **Ordinal scales with 0–3, 0–4, 0–5 categories**
- ▶ **Multiple pain measurement tools**
- ▶ **Physician estimate of pain response**
- ▶ **Patient satisfaction with treatment**

***Need* – common trial measurement strategy so comparison can be made across treatments**

The *ideal* treatment for pain from due to endometriosis would:

- ▶ **Eliminate pain**
- ▶ **Eliminate pain-related interference with activities**
- ▶ **Reduce other pain-related symptoms**
- ▶ **Reduce analgesic requirement**
- ▶ **Act quickly**
- ▶ **Have a persistent effect**
- ▶ **Have an “acceptable” cost**

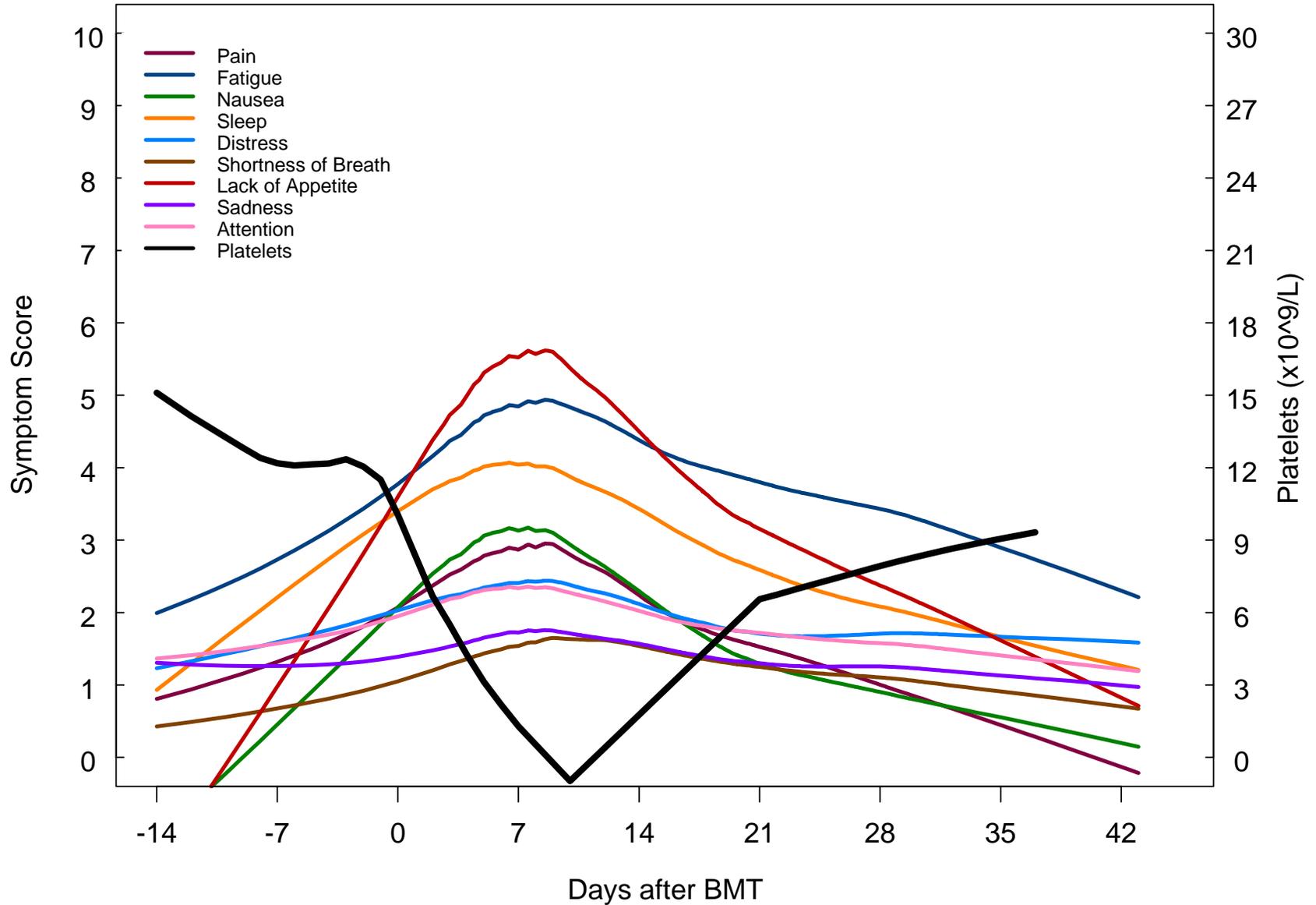
Clinical Outcome Measures for Pain Trials

Turk DC et al. *Pain* 106:337-345, 2003

Recommendations:

- ▶ **Pain (0–10 scales)**
- ▶ **Physical functioning (BPI interference)**
- ▶ **Emotional functioning (POMS, Beck)**
- ▶ **Participant ratings of improvement and satisfaction (7- or 9-point scale)**
- ▶ **Symptoms and adverse events**
- ▶ **Patient disposition (who drops out and why)**
- ▶ **Responder analysis (i.e., those with mild pain or 30% reduction)**

MDASI Symptoms and Platelets Relative to BMT



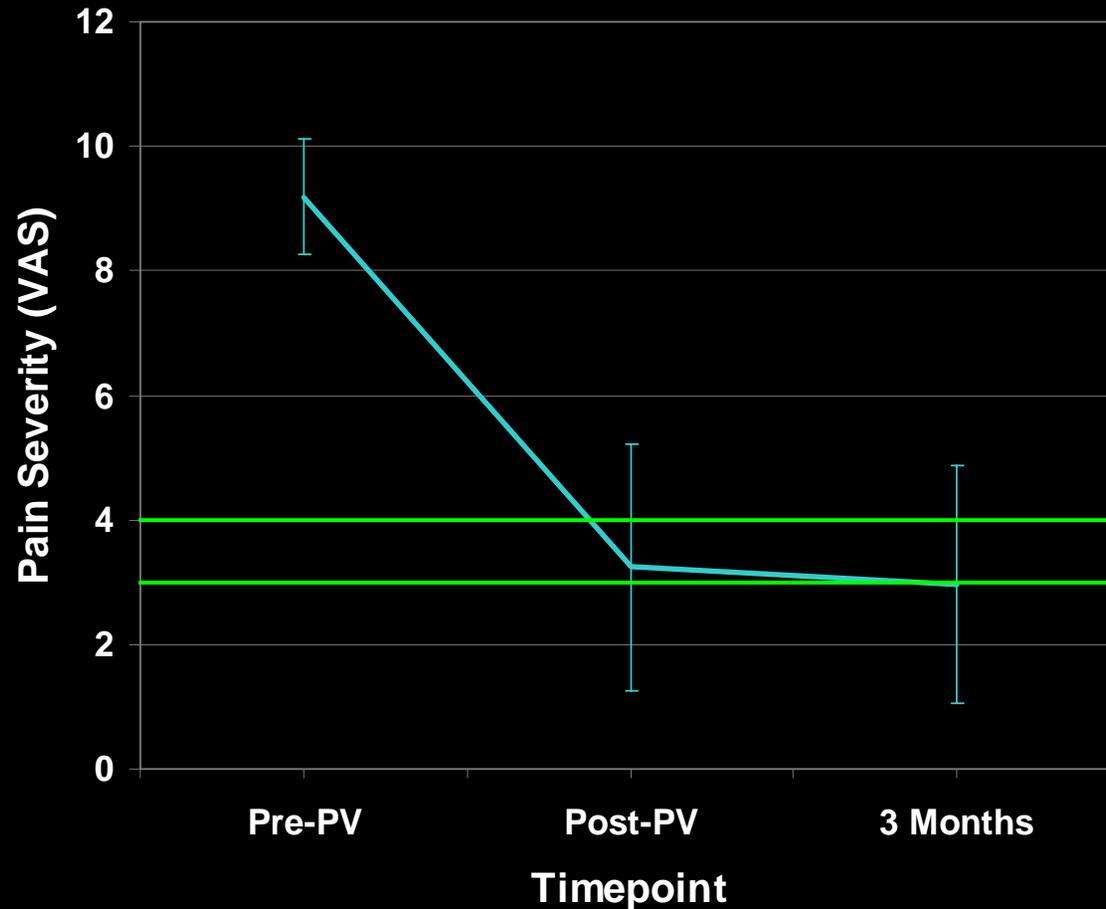
Definition of Pain Response – Bone pain trials

Wong and Wiffen. *Cochrane Database Syst Rev* 2005

- ▶ **Proportion with no pain**
- ▶ **Major pain reduction, not otherwise specified**
- ▶ **More than or equal to two “category” reductions**
- ▶ **More than 10mm decrease in pain**

Different responder definitions to vertebroplasty for metastatic bone pain

Alvarez et al. *Eur Spine J* 2003; 12: 366-368



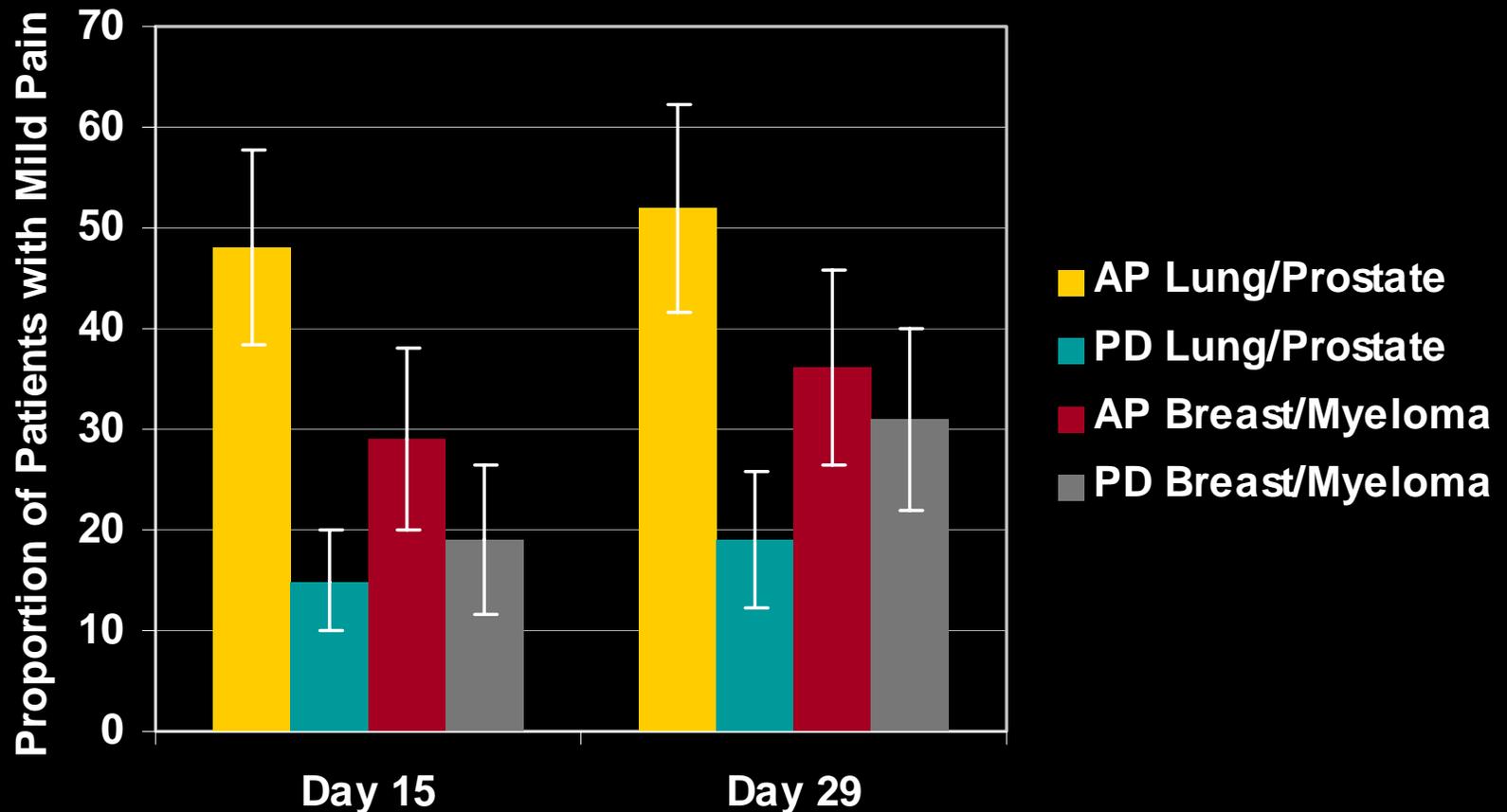
After vertebroplasty:

- 20% reduction in pain: 100%
- 30% reduction in pain: 95%
- Pain 4 or less: 76%
- Pain 3 or less: 67%
- Pain 0: 5%

PV – Percutaneous vertebroplasty

Proportion of Patients Whose Pain Went From Moderate or Severe to None or Mild – Use of Analgesic Protocol

Cleeland CS et al. *Ann Oncol*, in press



PD – Patients treated as usual, physician’s discretion

AP – Patients treated per analgesic protocol

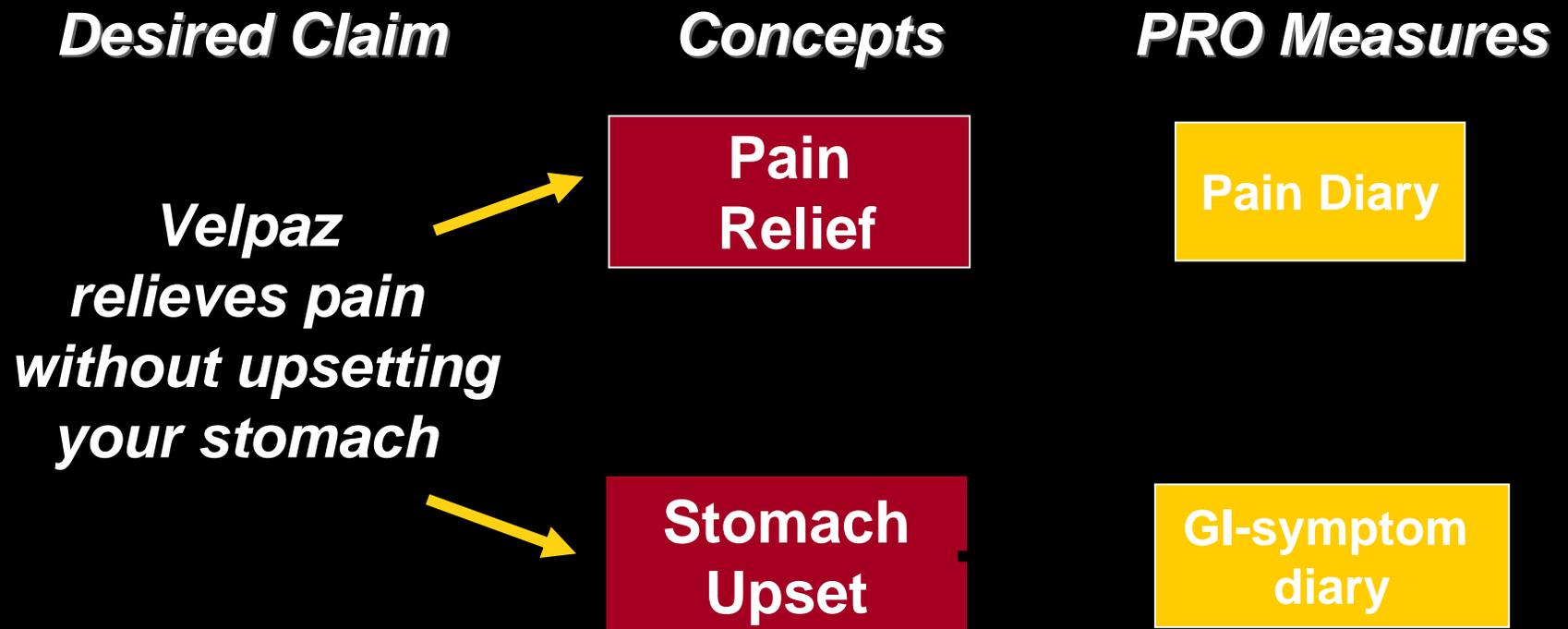
Suggestions for Pain Clinical Trials

- ▶ **Carefully define responders**
 - Use a definition that makes sense to consumers of trial data and is within expectations
 - Defining responders allows meta-analysis
- ▶ **Use 0–10 numeric scales for pain, other subjective reports**
- ▶ **Pick common time points relevant to the condition under study**
- ▶ **Consider latency of pain relief as an important secondary outcome**
- ▶ **Use pain as an eligibility criterion**

Guidance on Use of PROs as Endpoint Measures in Drug Development Trials (FDA, 2006)

- ▶ **Purpose: Provide guidance on FDA's current thinking about application of federal regulations to the use of PRO measures to support statements in labeling or advertising of regulated products**
- ▶ **Result: Standardization of ways of thinking about PROs as outcomes**
- ▶ **Product: Developing process of standardization of expectations for PROs, including patient input, validation, demonstration of clinical benefit**
- ▶ **Should provide a basis for measurement schema for trials in pain reduction in endometriosis**

FDA -Linking Claims to PRO Endpoints



What Does FDA Mean by “Clinical Benefit”

- ▶ **How long the patient lives**
 - As opposed to a surrogate endpoint
 - ▶ E.g., tumor shrinkage → survival
- ▶ **How the patient feels or functions**
 - Patient’s experience of treatment effect
 - ▶ Feelings: pain, nausea, tiredness, worry
 - ▶ Functions: physical limitations, self-care

A Programmatic Approach to Pain Assessment in Endometriosis: Suggestions

- ▶ **Focus groups: What other symptoms go with pain that cause similar distress (bloating, fatigue)? What would a “successful” treatment provide? What current scales are most user friendly?**
- ▶ **Pain epidemiology: Severity, interference, and duration of endometriosis pain. What treatments are currently used and work/don't work? Who is at greatest risk for high pain or treatment resistance?**
- ▶ **Expert agreement on assessment strategy**

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