

# **Innovation in Clinical Research: From Molecules to Medicare**

**November 26, 2007**

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# **Opportunities in design of small clinical trials**

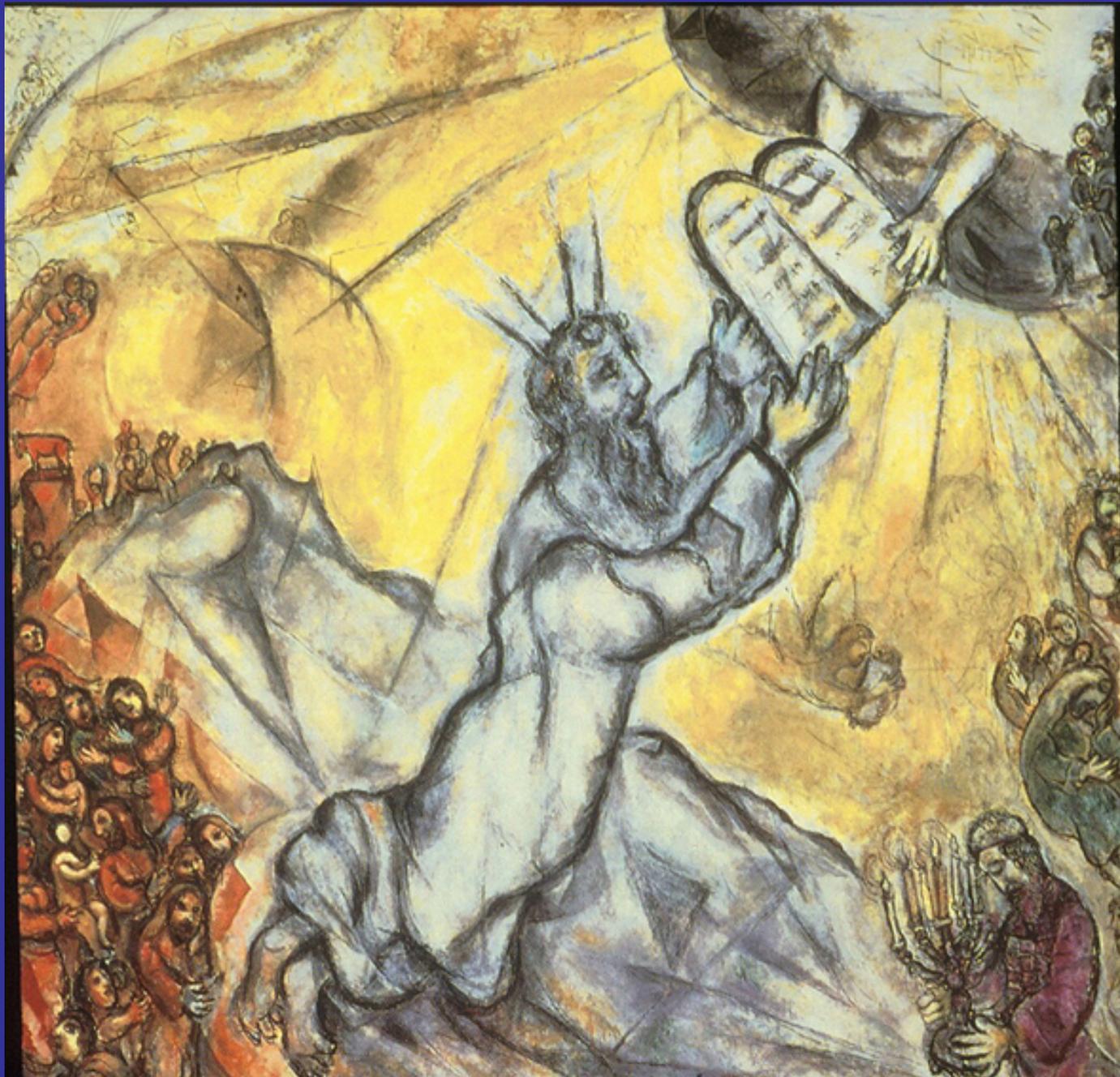
**Historical perspective: Clinical trials  
are new research tool**

**Explanatory vs. pragmatic trials**

**Challenges posed by heterogeneous  
disease mechanisms, small N's**

**Placebo response**

**Interpreting results of studies of  
symptom treatments**



## **History of clinical trials**

**Apart from widely cited exceptions (scurvy, bleeding, puerperal fever, pellagra) virtually no controlled therapeutic trials until 1948 (MRC TB).**

**Kefauver amendment, 1962 required FDA to develop standards of evidence.**

**These guidelines predated current insights into disease mechanisms.**

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# **Main question of clinical trial**

## **Explanatory:**

**What neurotransmitter mediates tricyclic antidepressants' analgesia?**

## **Pragmatic:**

**How should clinician treat painful neuropathy in practice?**

# Choice of patients

**Explanatory:**

**Selective**

**A beta fiber mediated pain**

**Definite neuropathy**

**Pragmatic:**

**Inclusive**

**Probable neuropathy**

# **Treatments**

## **Explanatory:**

**Pharmacologically specific**  
**Single agent preferable**

## **Pragmatic:**

**Clinical favorites, even if "dirty"**  
**Combinations are fine**

# Controls

## Explanatory:

Placebo  $\pm$  other selective  
treatments

## Pragmatic:

Other common treatments

# Treatment Dose

## Explanatory:

Usually try to maximize dose that  
safety data will permit

## Pragmatic:

Use standard, conservative dose

# Treatment Monitoring

Explanatory:

Intense supervision and support

Pragmatic:

Monitoring similar to busy clinical practice

# **Analysis: study population**

**Explanatory:**

**Those who complete regimen**

**Pragmatic:**

**Intent-to-treat**

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**A small N is the mother of  
invention**

$$t = \frac{\text{treatment effect}}{\text{sqrt}(\text{variance}/N)}$$

# Explain Variance Any Way You Can

$$N = \frac{\sigma^2 \cdot f(\alpha, \beta)}{(\text{treatment effect})^2}$$

*If you explain 20% more variance, you  
save 20% of the cost of all future  
studies!*

# Challenges of explanatory clinical trials

## Improving power of study

Maximize treatment effect

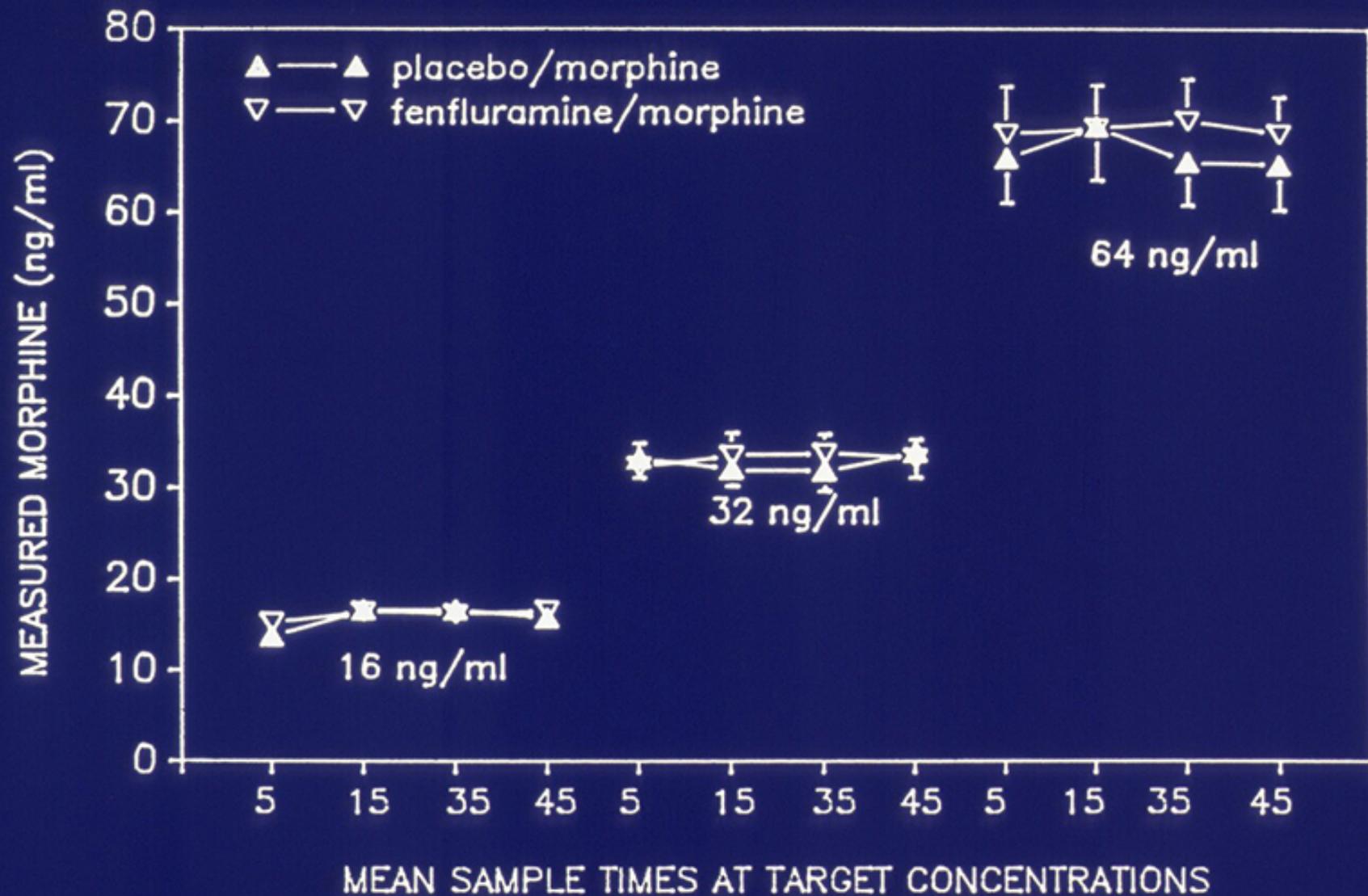
Minimize variance

pharmacokinetic adjustments

improve assessment methods

crossover designs





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Maximize treatment effect

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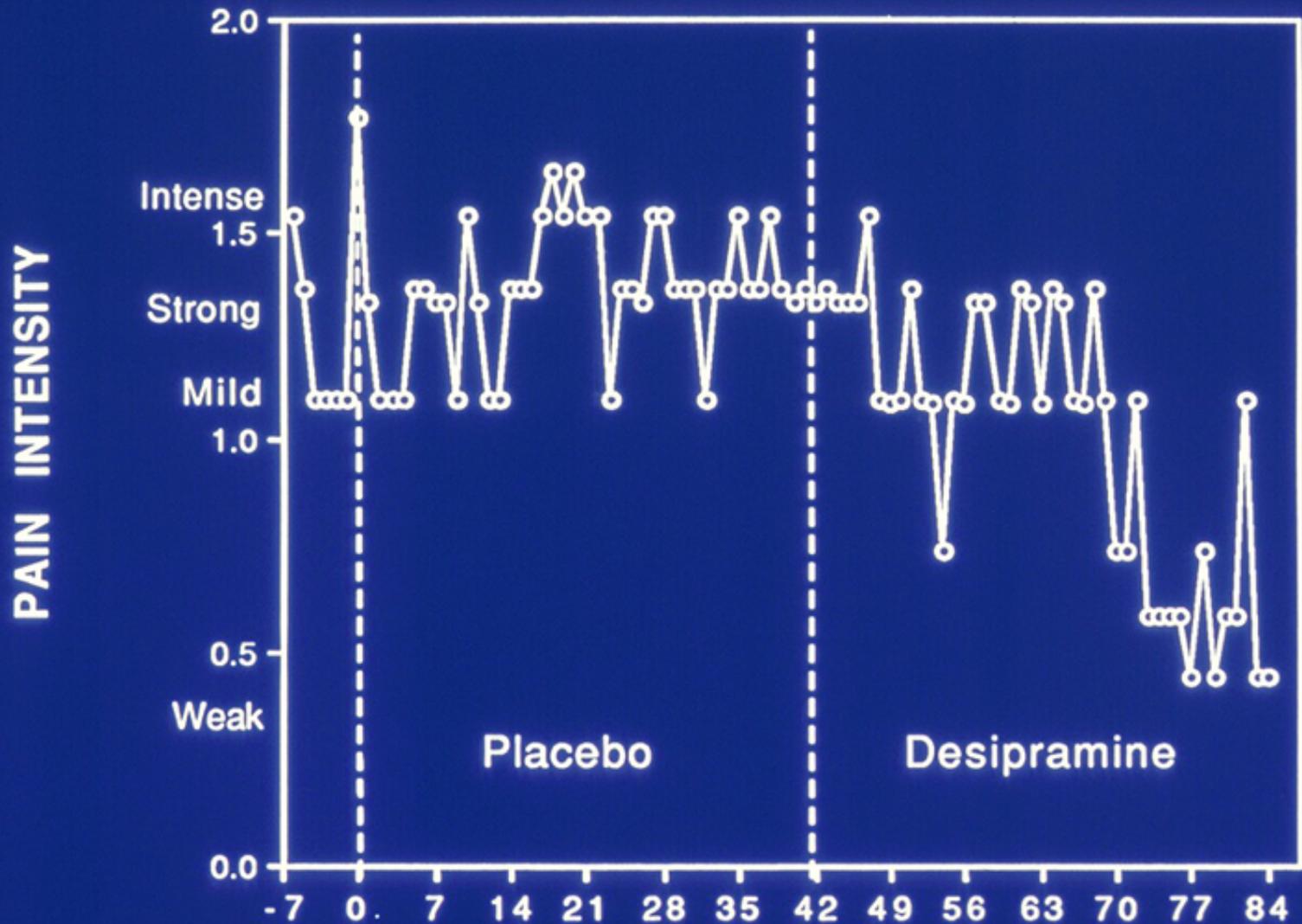
## *Comparison of pain scales in 124 patients:*

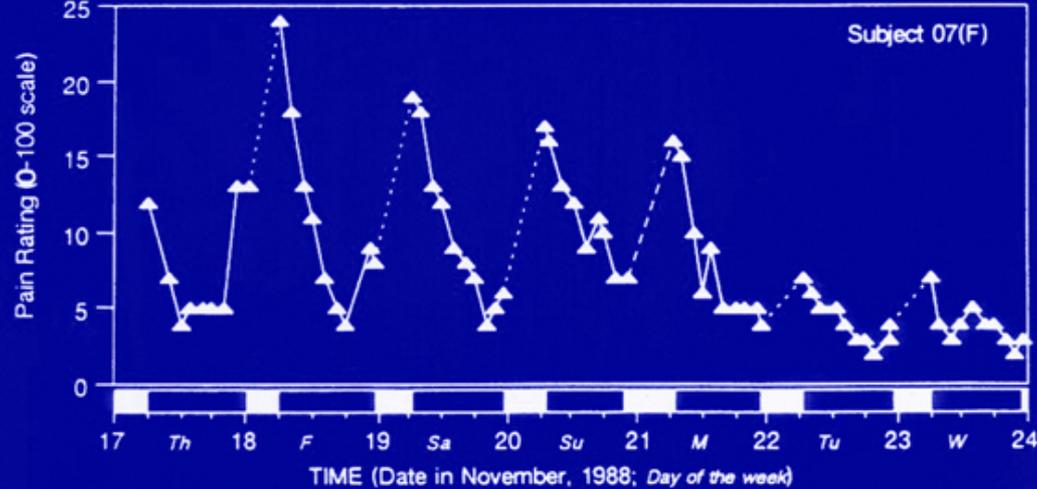
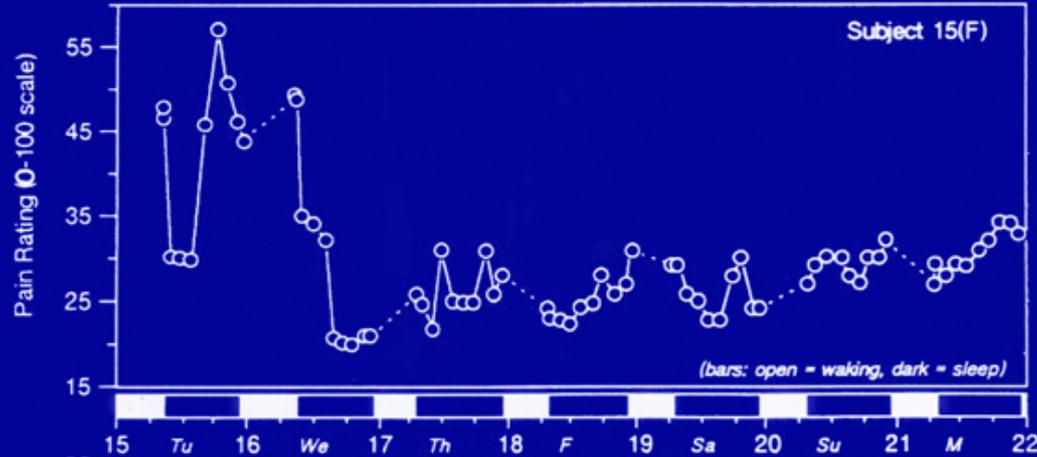
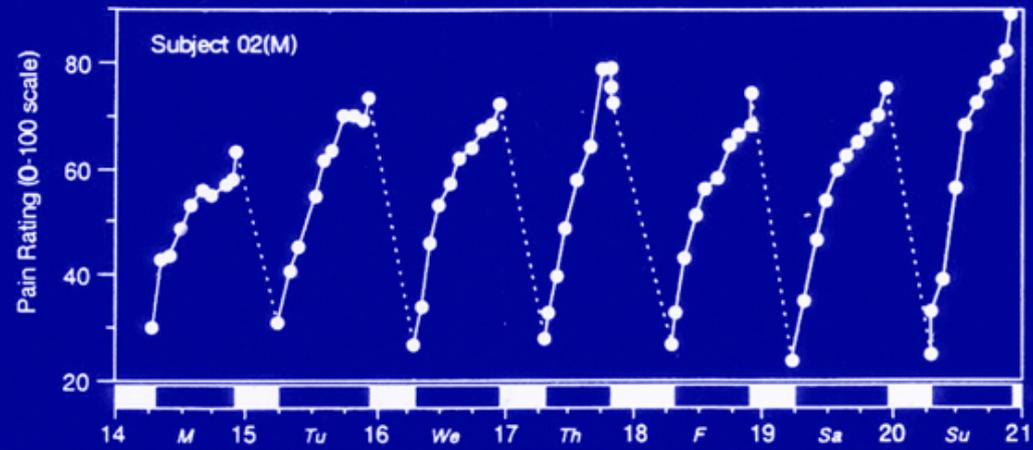
NSAID free baseline vs. 4 wks oxaprozin

Bellamy et al., Curr Med Res Opin. 1999;15:121-7

<b>Scale</b>	<b>Improvement/SD</b>	<b>N for identical power</b>
VAS	1.08	100
0-10 numerical	1.08	100
5 point pain category	0.97	120
Pain faces (Champion)	0.90	144
McGill (total)	0.68	256

# Pt #24, Painful Diabetic Neuropathy





# **Challenges of explanatory clinical trials**

## **Improving power of study**

**Maximize treatment effect**

**Minimize variance**

**pharmacokinetic adjustments**

**improve assessment methods**

**crossover designs**

# Crossover studies

## Advantages:

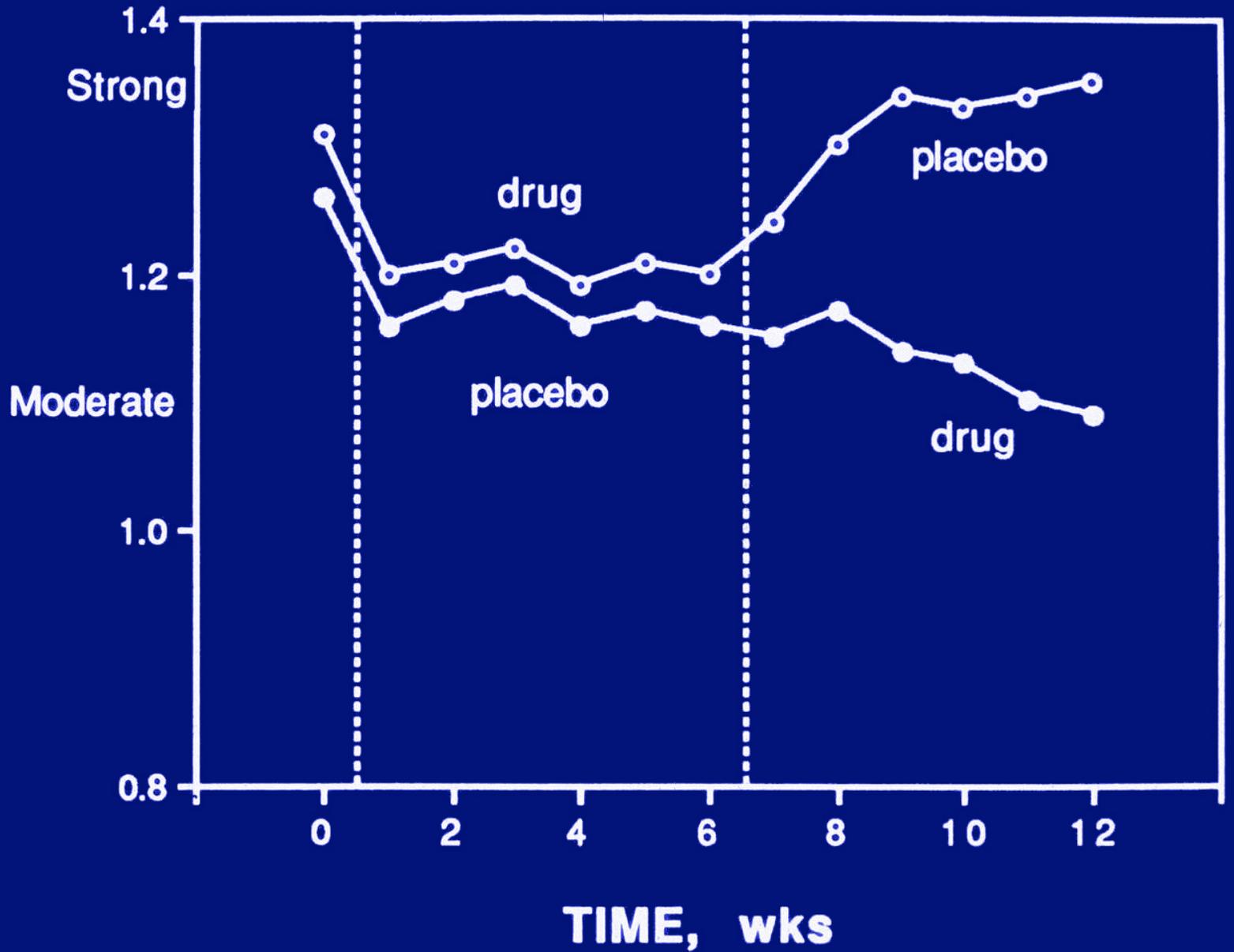
**Eliminates interpatient variability;  
can reduce sample size**

## Disadvantages:

**Carryover effects (may be difficult to  
detect)**

**Dropouts**

**PAIN INTENSITY**



# **Challenges of explanatory clinical trials**

**Heterogeneous mechanisms of  
chronic medical disorders**

**Distinguish using:**

**symptoms**

**physiological measures**

**response to drugs**

**genetic markers**

## Quality of Diabetic Neuropathy Pain in 29 Patients

<u>Sensory</u>		<u>Temporal</u>	
Burning	18	Steady	28
Cold	5	Brief	14
Aching	3		
Tight	2		
Throbbing	2		
Prickling	2		
Stinging	2		

## RELIEF OF FREQUENT BRIEF PAINS (n=8)

<u>Relief</u>	Treatment	
	<u>Amitriptyline</u>	<u>Placebo</u>
Complete	7	1
A lot	-	-
Moderate	1	2
Slight	-	1
None	-	4

# **Challenges of explanatory clinical trials**

**Heterogeneous mechanisms of  
chronic medical disorders**

**Distinguish using:**

**symptoms**

**physiological measures**

**response to drugs**

**genetic markers**

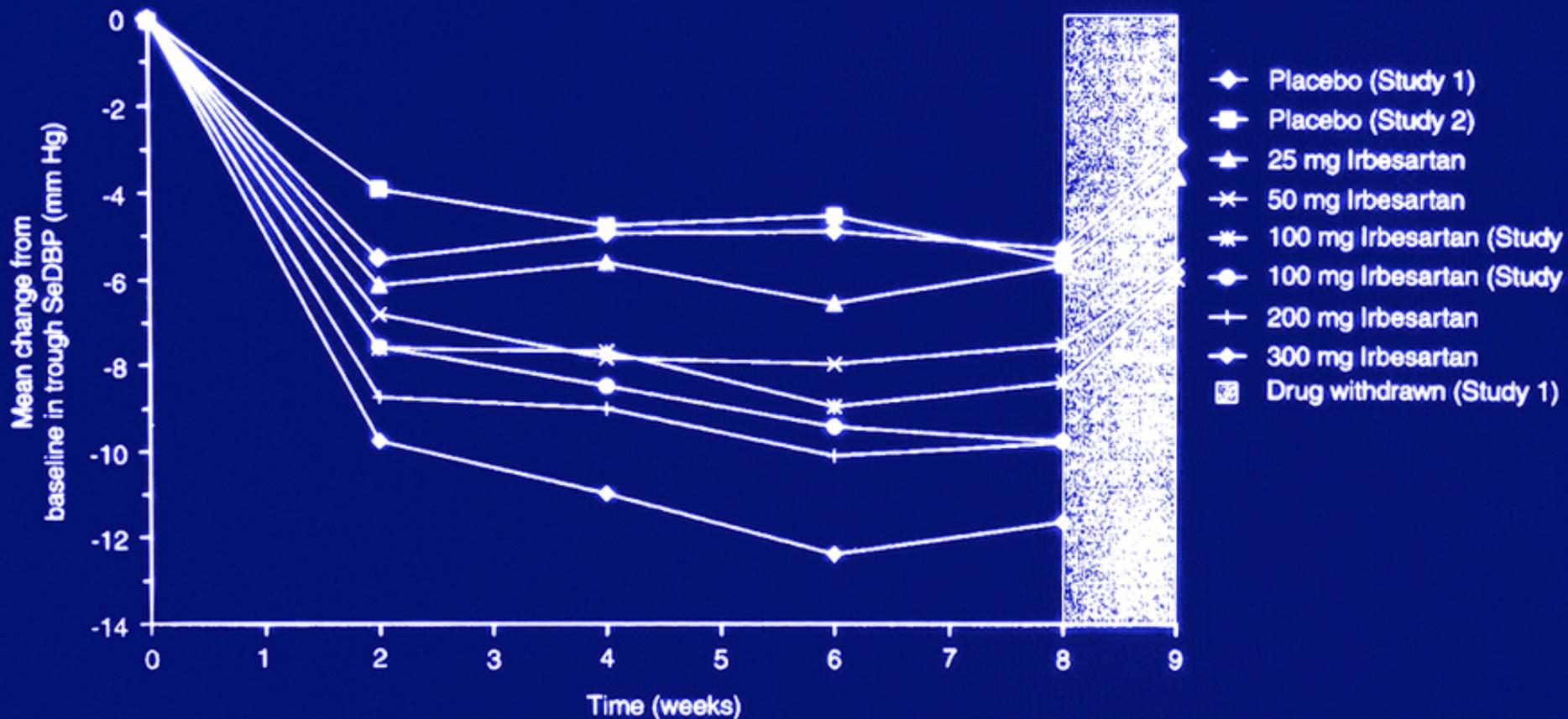
# Placebo response

**Occurs mainly in subjective responses or reversible physiological states (e.g. bronchospasm, high blood pressure); minimal effects on gross structural lesions.**

**Incidence and magnitude highly variable.**

**Distinguish from "regression to mean."**

**Makes blinding, measurement of assay sensitivity critical in studies of subj. responses**



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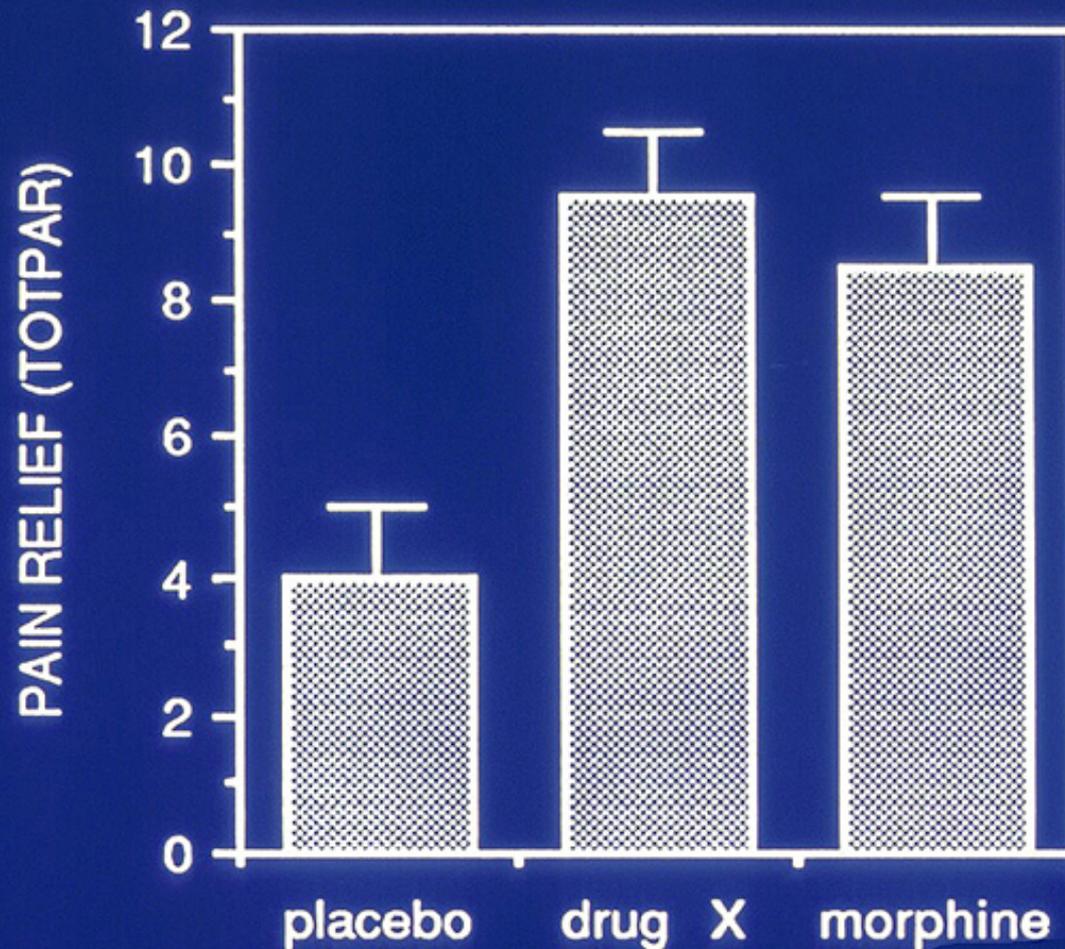
**Placebo response**

**Interpreting results of studies of  
symptom treatments**

**Conclusions:**

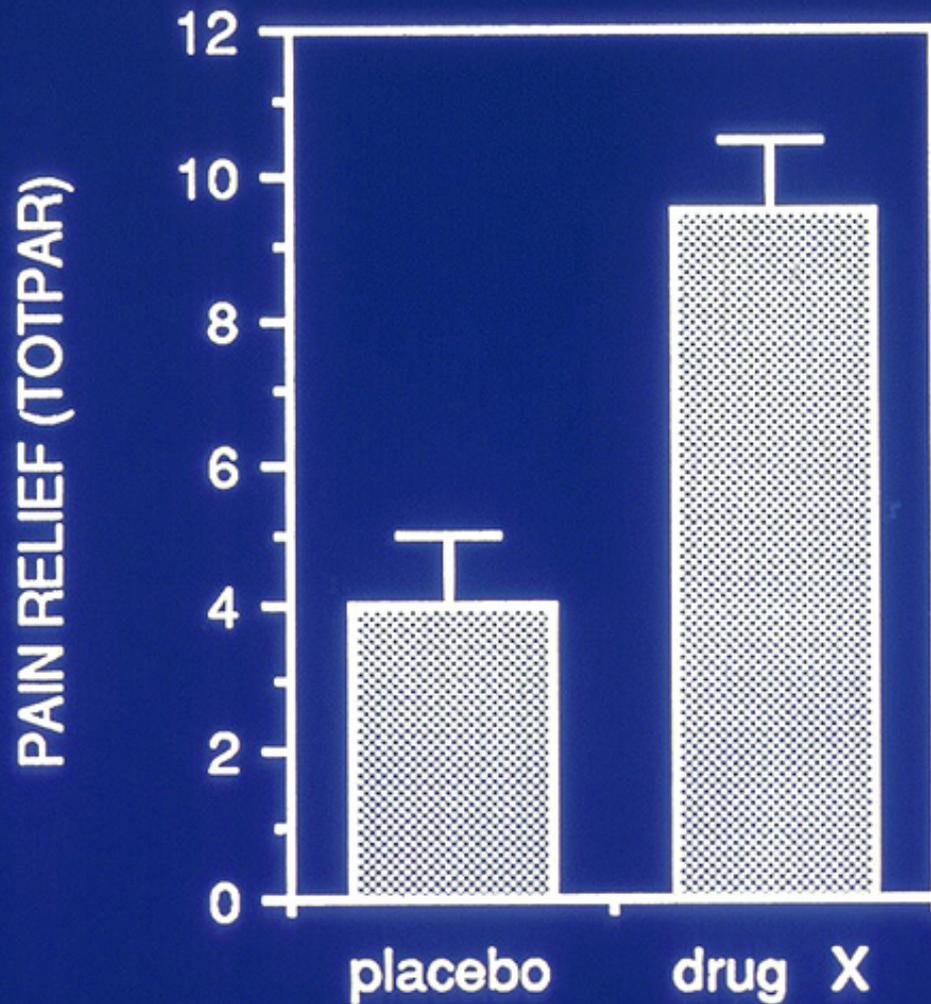
**Drug X = morphine > placebo.**

**Assay can detect morphine analgesia.**



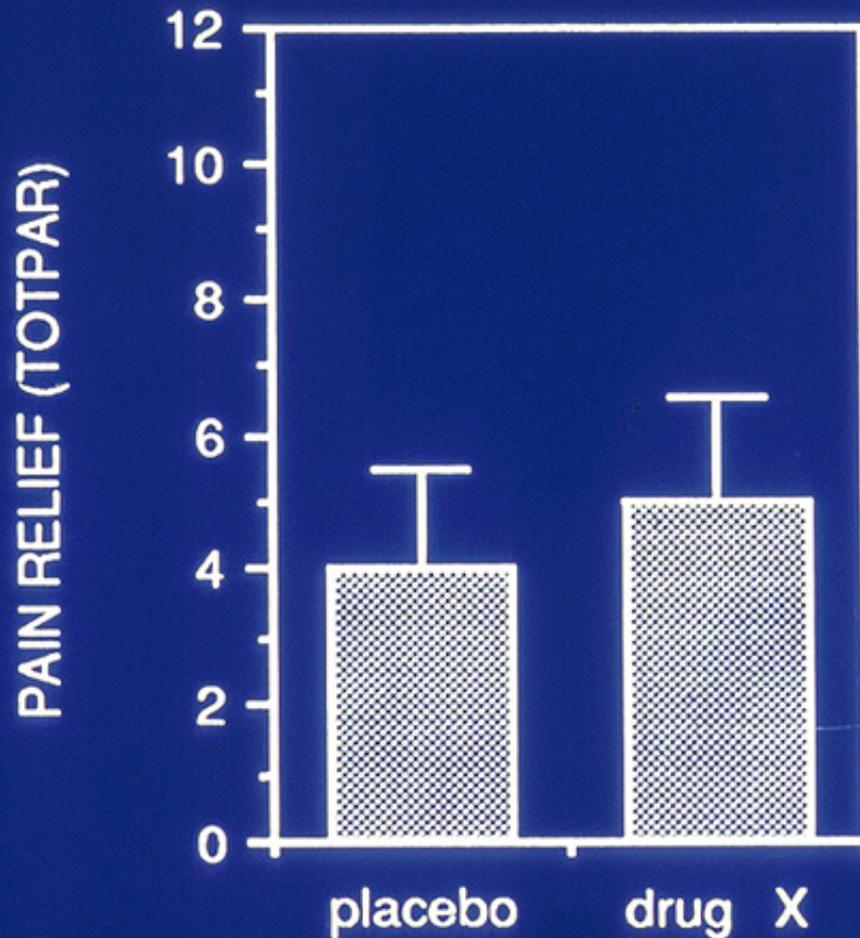
**Conclusion:**

**Drug X has at least some efficacy.**



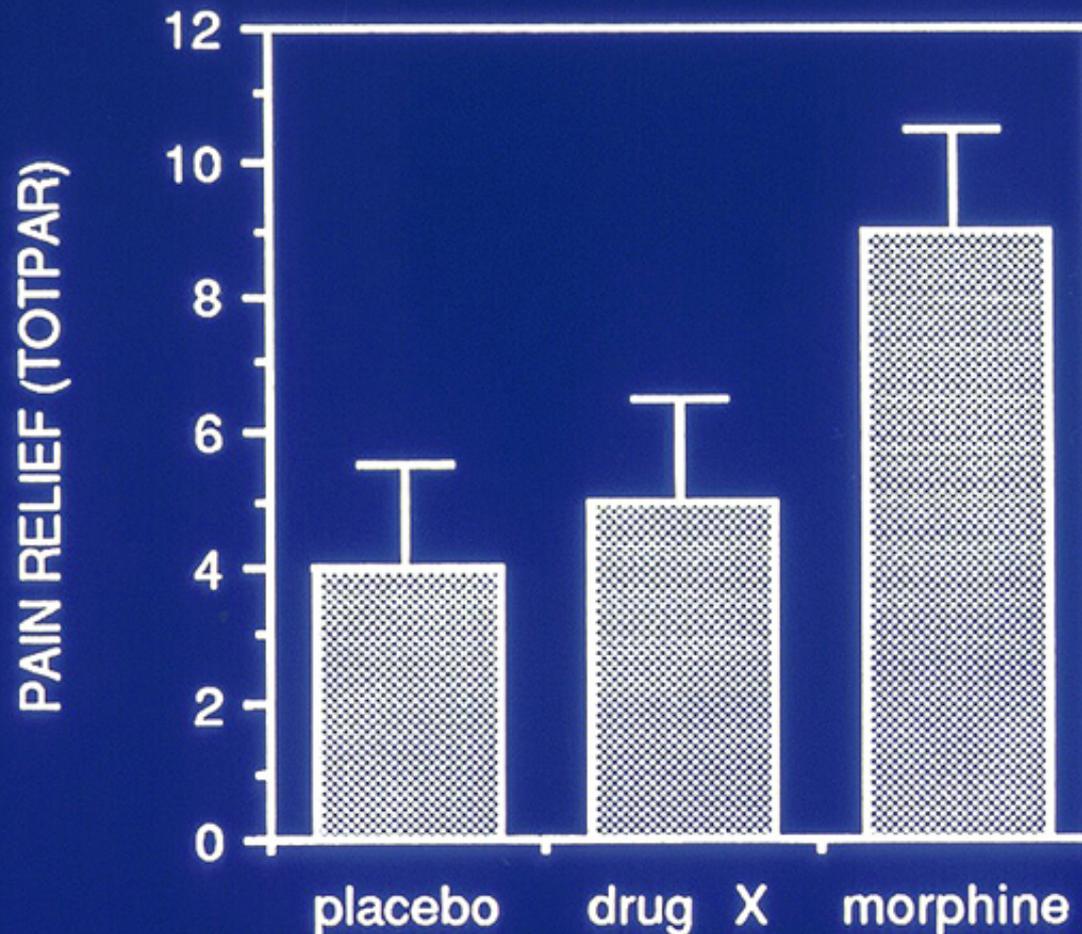
**Conclusions:**

**Drug X not analgesic in these pts, or  
study methods ineffective**



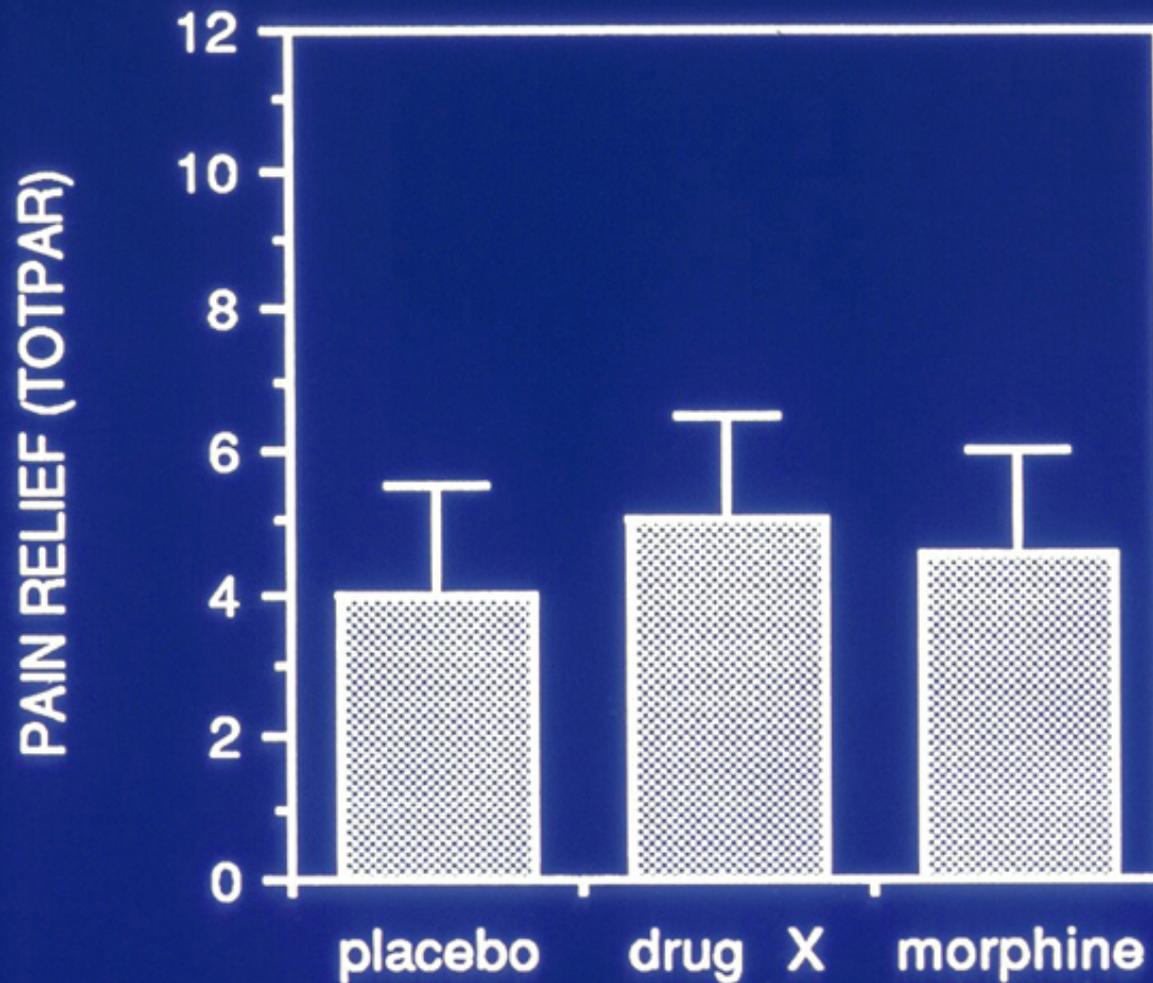
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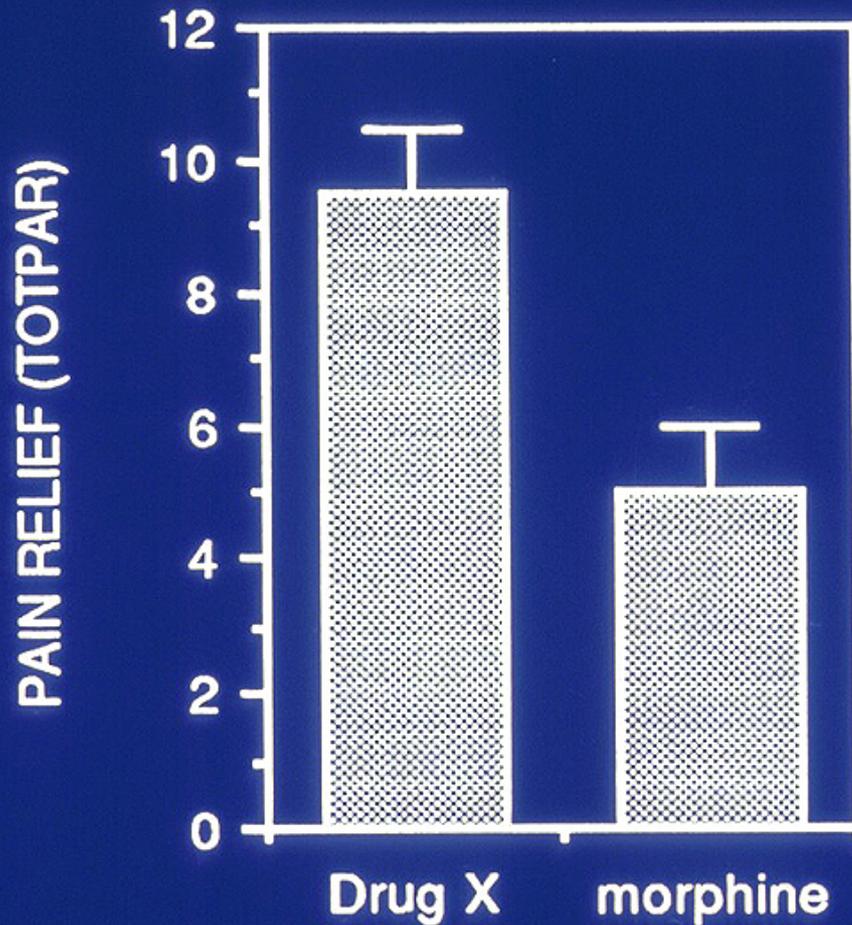
**Conclusion:**

**Study methods are ineffective.**



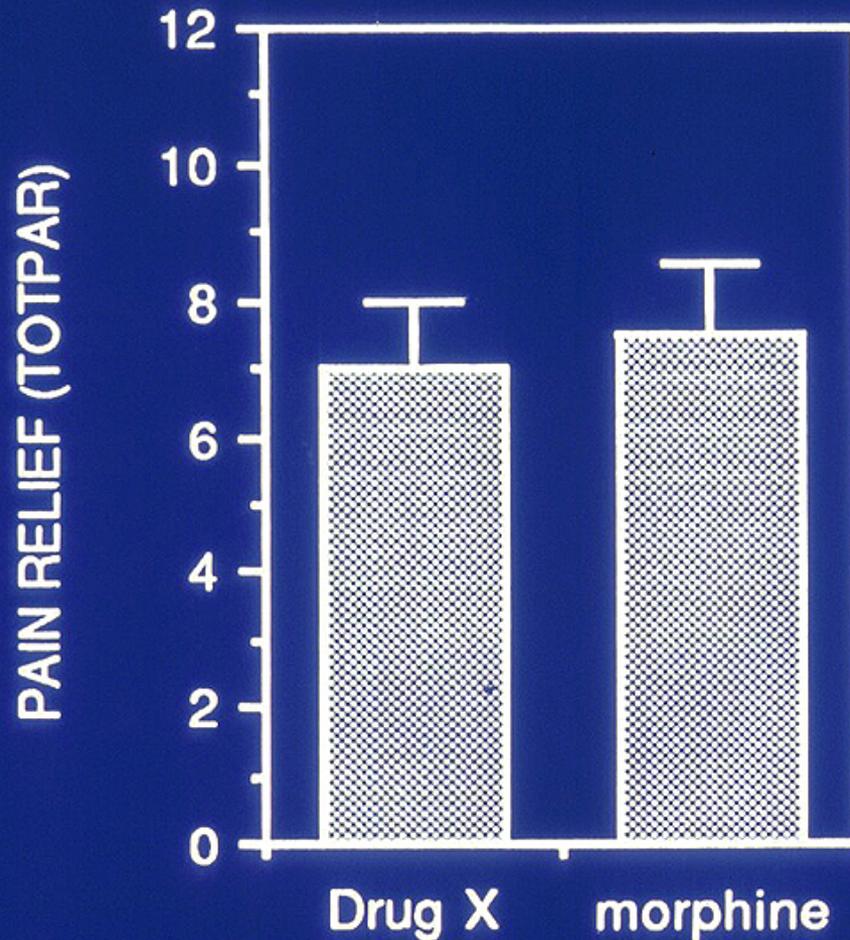
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**Conclusion:**

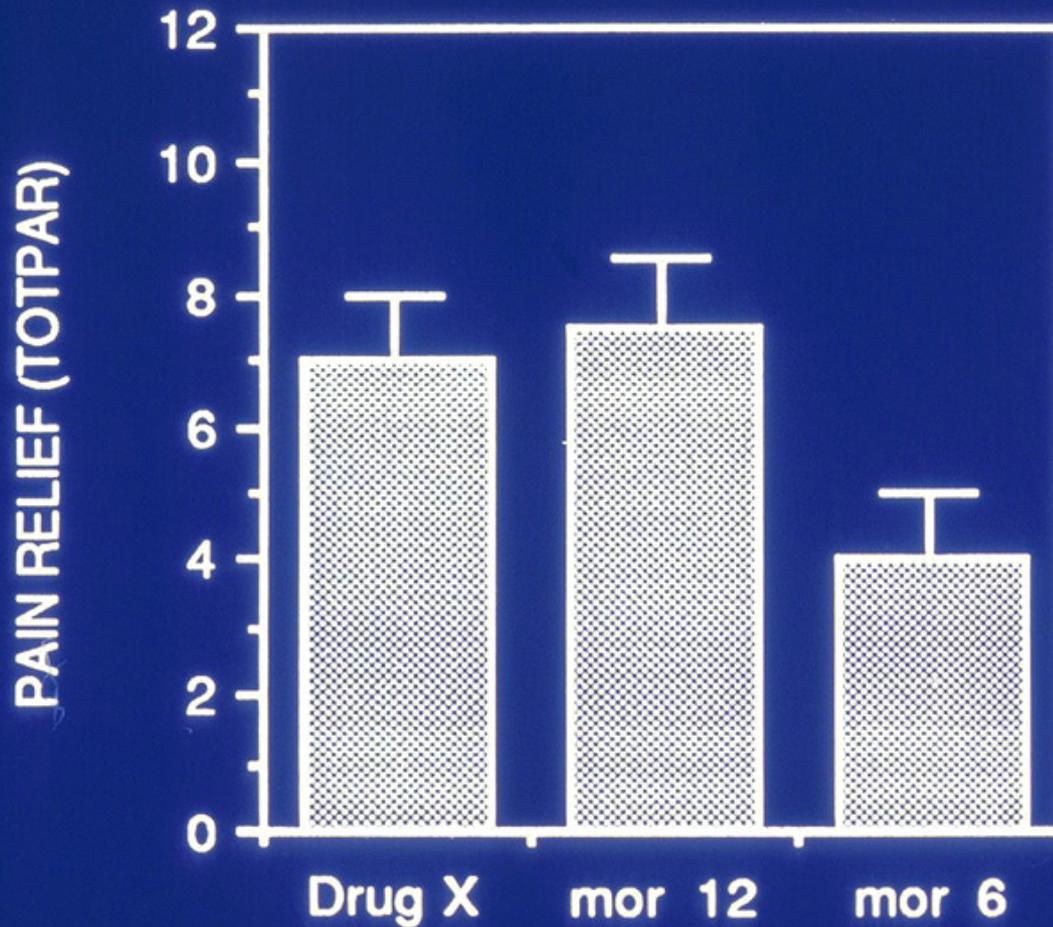
**Drug X = morphine; or neither effective,  
with large placebo effect.**



**Conclusions:**

**Drug X = morphine, 12 mg.**

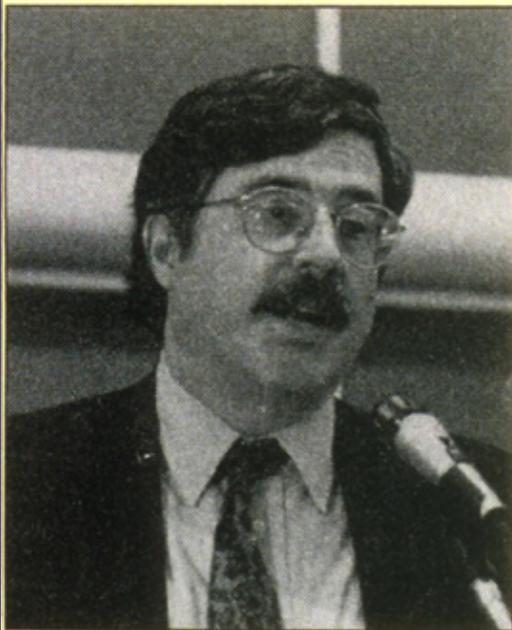
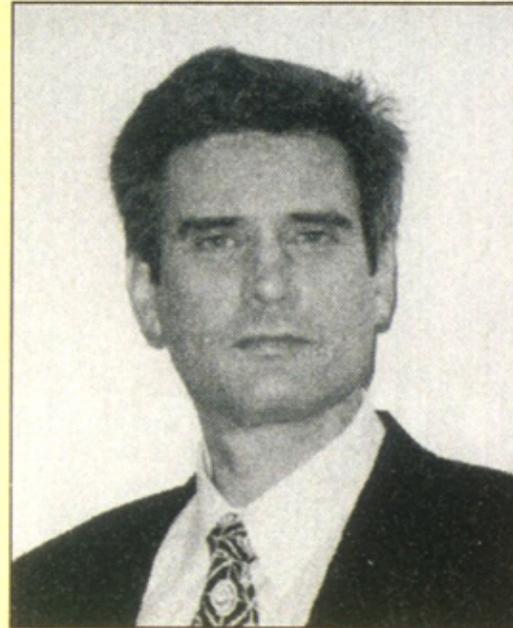
**Assay distinguishes morphine 6, 12 mg.**



The Declaration [of Helsinki]  
“is not obscure in its  
language. It doesn’t waffle,  
doesn’t allow for exceptions.”



Kenneth Rothman



“What [Rothman and Michels]  
write says they do not  
understand the difficulties that  
arise when researchers try to  
design” drug trials.



Robert Temple

# Factorial Design to Enhance Chance of Showing Differences

Deyo et al, NEJM 1990;322:1627 was skeptical of TENS in idiopathic low back pain.

2x2 factorial, TENS vs. sham TENS and exercise vs. no exercise, 145 pts.

*Mean VAS improvement*

- TENS, real 47 vs. sham 41 (NS)
- Exercise, 52 vs. no exercise 37 (p=.02)

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