Improving Clinical Pain Research: Past, Present, Future

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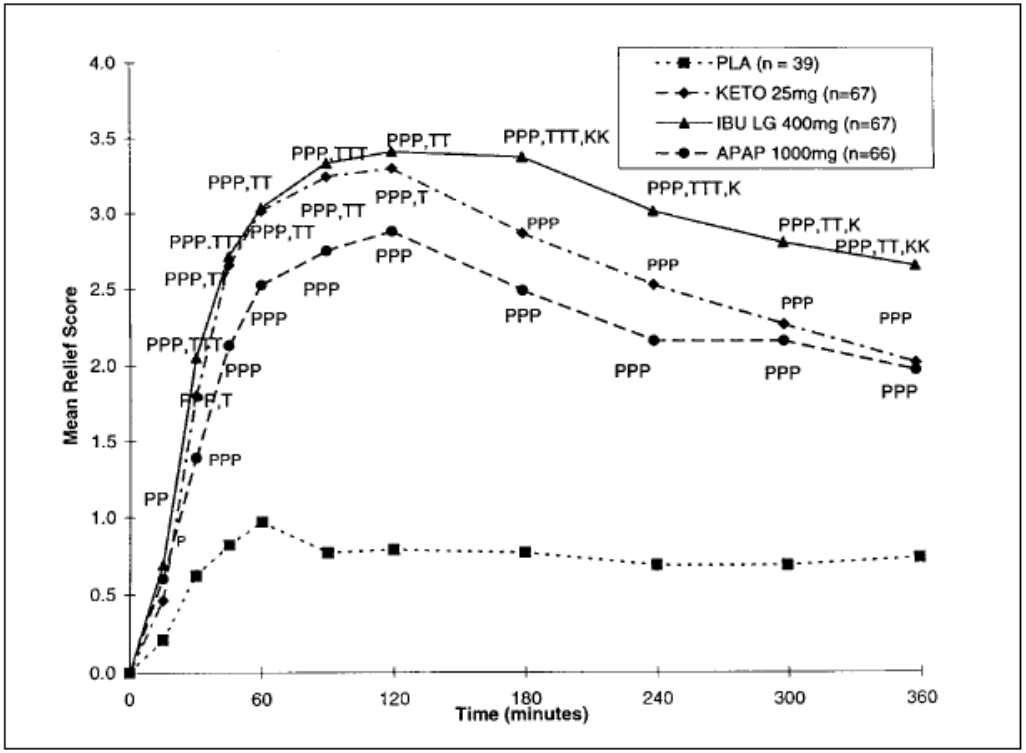
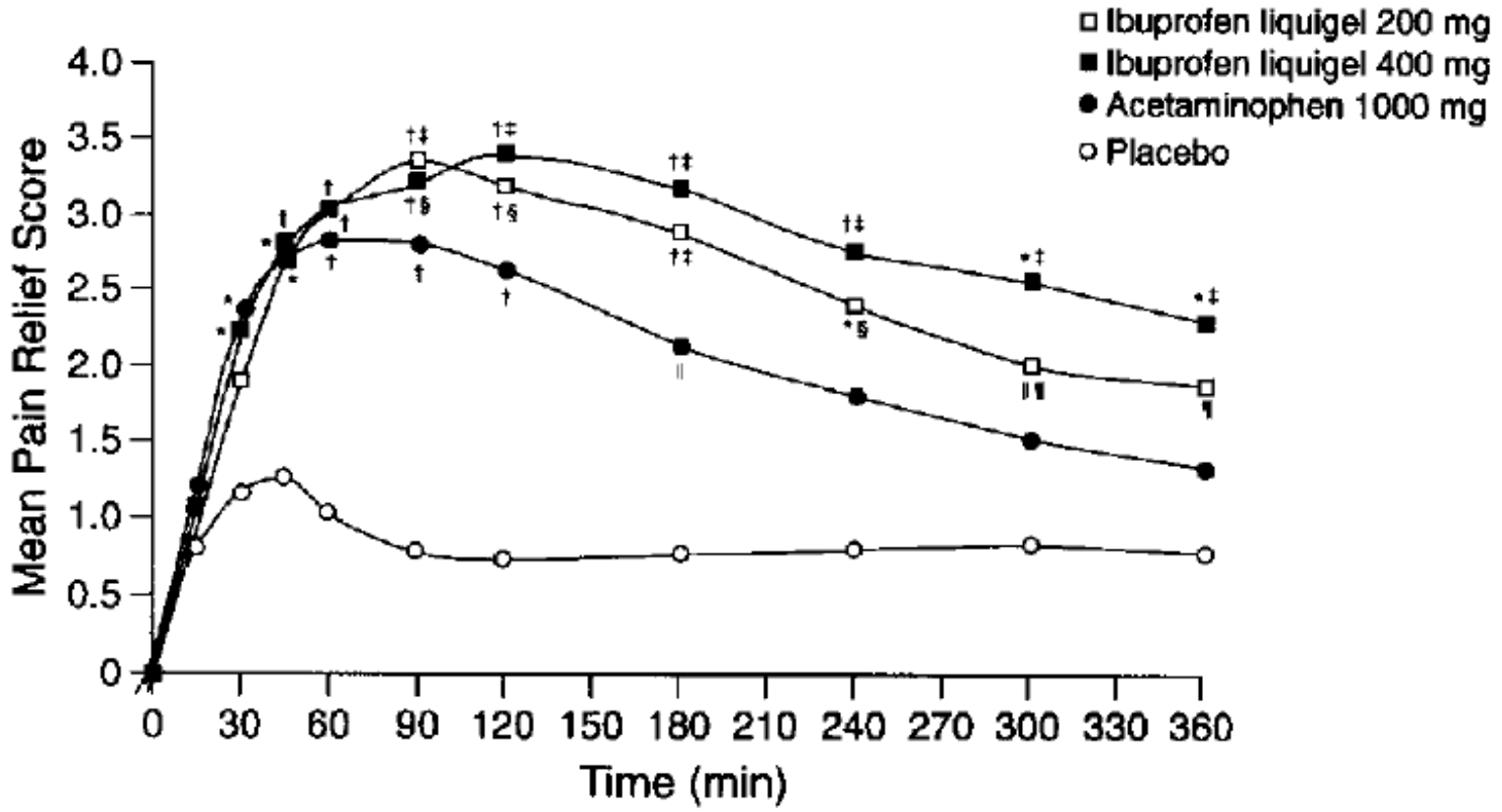
Abraham Sunshine
January 3, 1928–January 2, 2007



Olson N, et al, J Clin Pharm, 2001



Hersh E, et al, Clin Ther, 2000

ANALGESIC SOLUTIONS

Relative Standard Effect Size

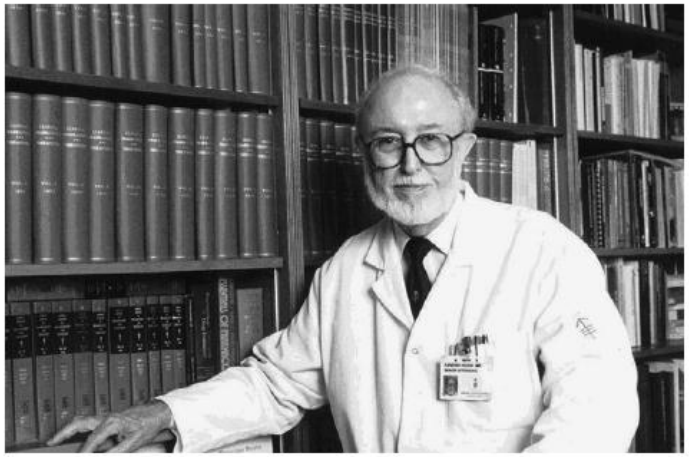
SPID6 Ibuprofen liquigel 400mg vs. placebo:

	Hersh	Sunshine
Delta	7.61	9.17
SD	4.85	4.5
SES	1.57	2.04

Sunshine has 30% higher SES
(Equivalent to reducing sample size from 100/arm to 60/arm)

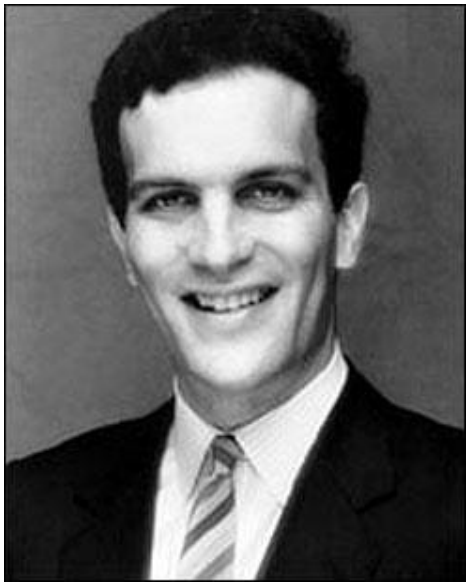
ANALGESIC SOLUTIONS

Ray Houde
(1916-2006)



Louis Lasagna
(1923-2003)

Mitchell B. Max
(1949-2008)



Case Study – Assay Sensitivity (Inguinal Hernia Data)

	Research Site A (n = 126)	All 24 Other Sites (n = 274)
Primary efficacy endpoint: mean difference between active and placebo (Δ)	0.81	0.56
Pooled standard deviation (SD)	2.25	2.56
Standardized effect size (Δ/SD)	0.360	0.219
N needed for 80% power at alpha = 0.05	244	658
Subjects enrolled per site per month (mean)	23.2	0.75
Overall Performance (time to 80% power)	10.5 months*	36.6 months **

***utilizing one site at Lotus** ****utilizing 17 non-Lotus sites in concert**

Case Study – Assay Sensitivity (Surgical Hemorrhoidectomy)

	Research Site A (n = 126)	All 24 Other Sites (n = 274)
Primary efficacy endpoint: mean difference between active and placebo (Δ)	55.9	32.6
Pooled standard deviation (SD)	192.93	205.46
Standardized effect size (Δ/SD)	0.29	0.159
N needed for 80% power at alpha = 0.05	376	1250
Subjects enrolled per site per month (mean)	14.2	.5
Overall Performance (time to 80% power)	26.5 months*	147 months**

***utilizing one site at Lotus** ****utilizing 17 non-Lotus sites in concert**

What did they do?

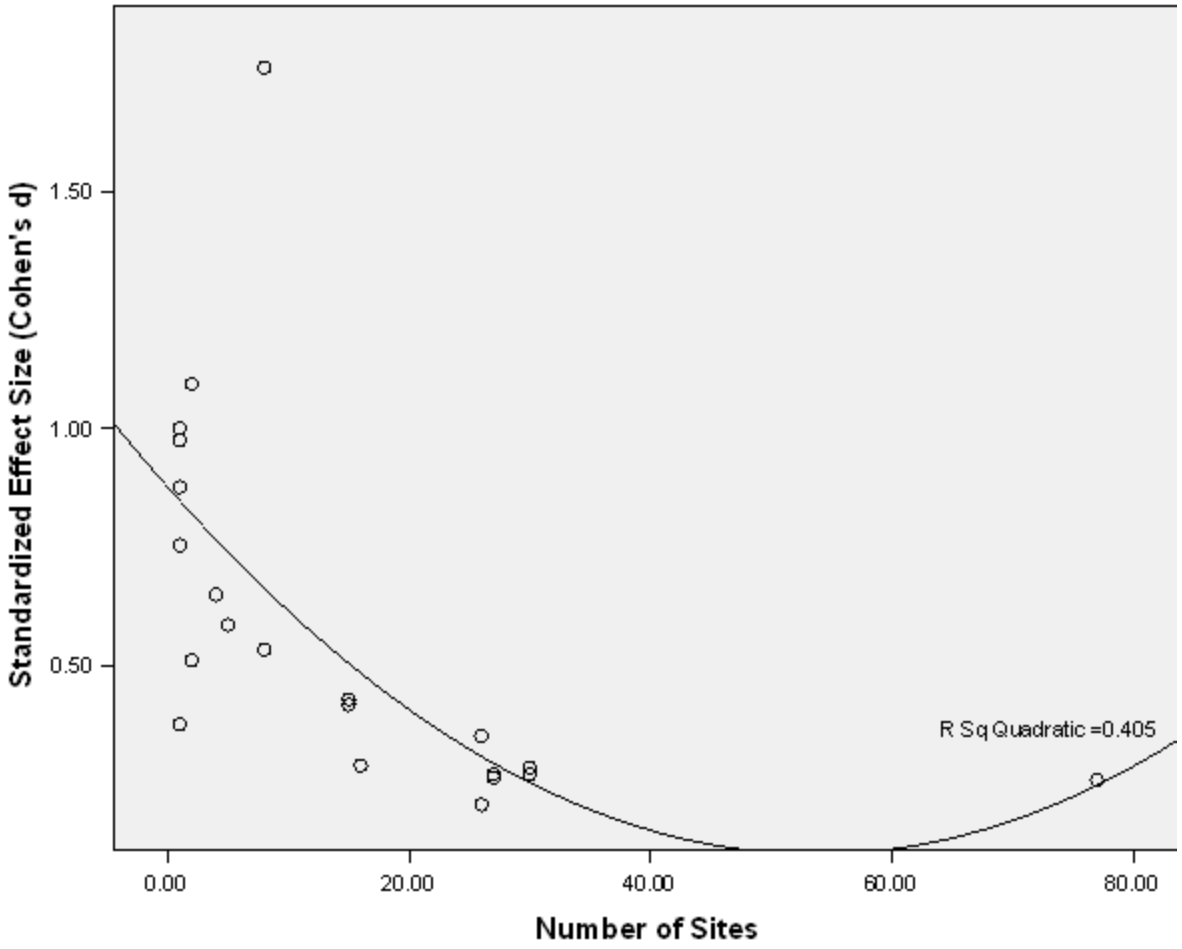
- Single sites
- Experienced investigators & nurses
- Accurate diagnosis
- Empiric patient qualification
- Empiric nurse qualification
- Repeated use of “good” patients
- Talking to the patients

Reasons for Failure: Opioid Trials

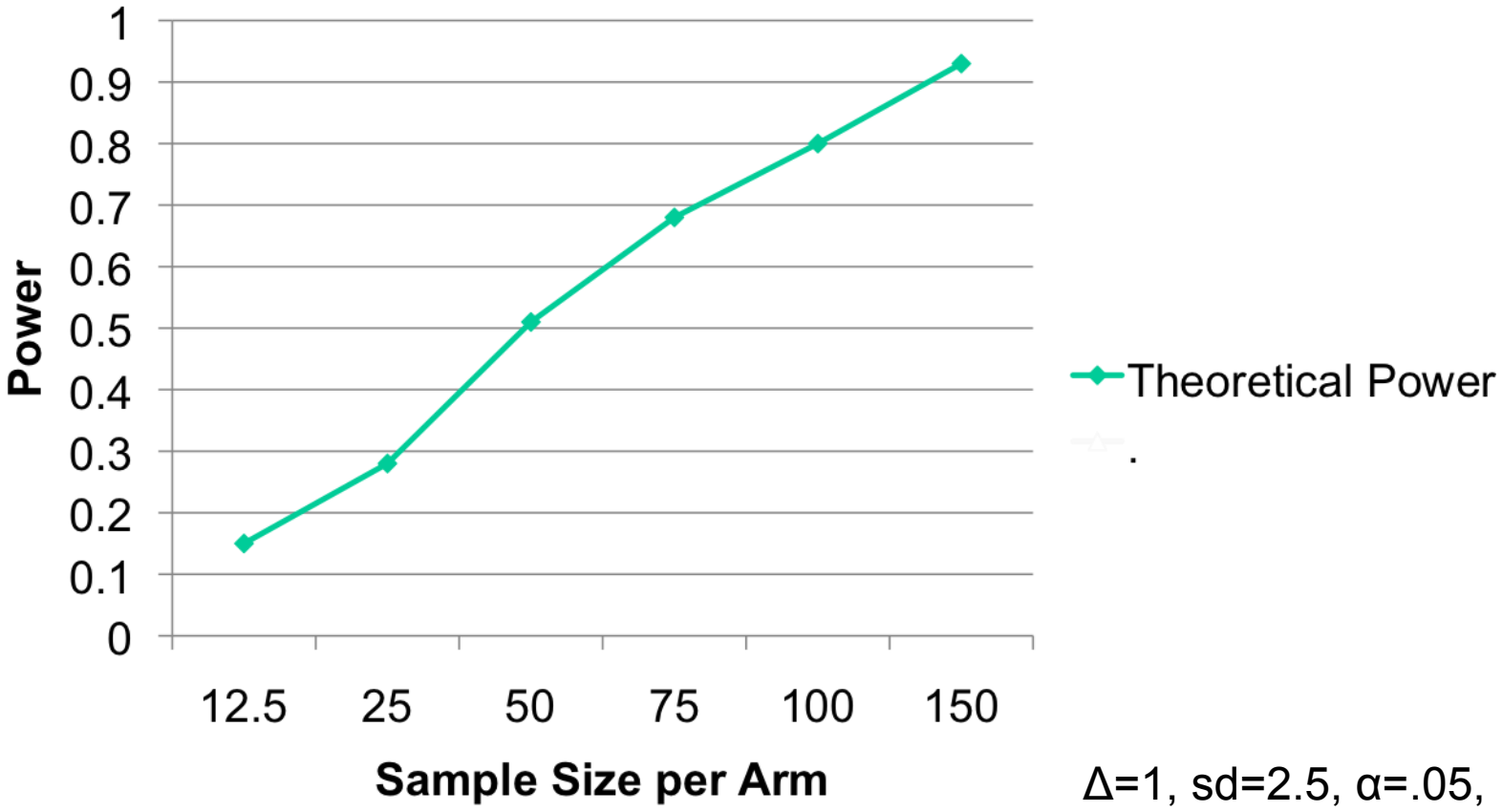
- Trial structure
  - Crossover and withdrawal better than parallel treatment
- Dosing
  - Titration better than non-titration
  - Flexible better than fixed
- Concomitant analgesics
  - Prohibited better than allowed
- Rescue
  - Prohibited better than allowed
- Primary endpoint
  - AUC better than landmark
- Number of sites
  - The fewer the better

Katz N, et al, Neurology, 2005

Standardized effect size vs. number of sites, opioid trials

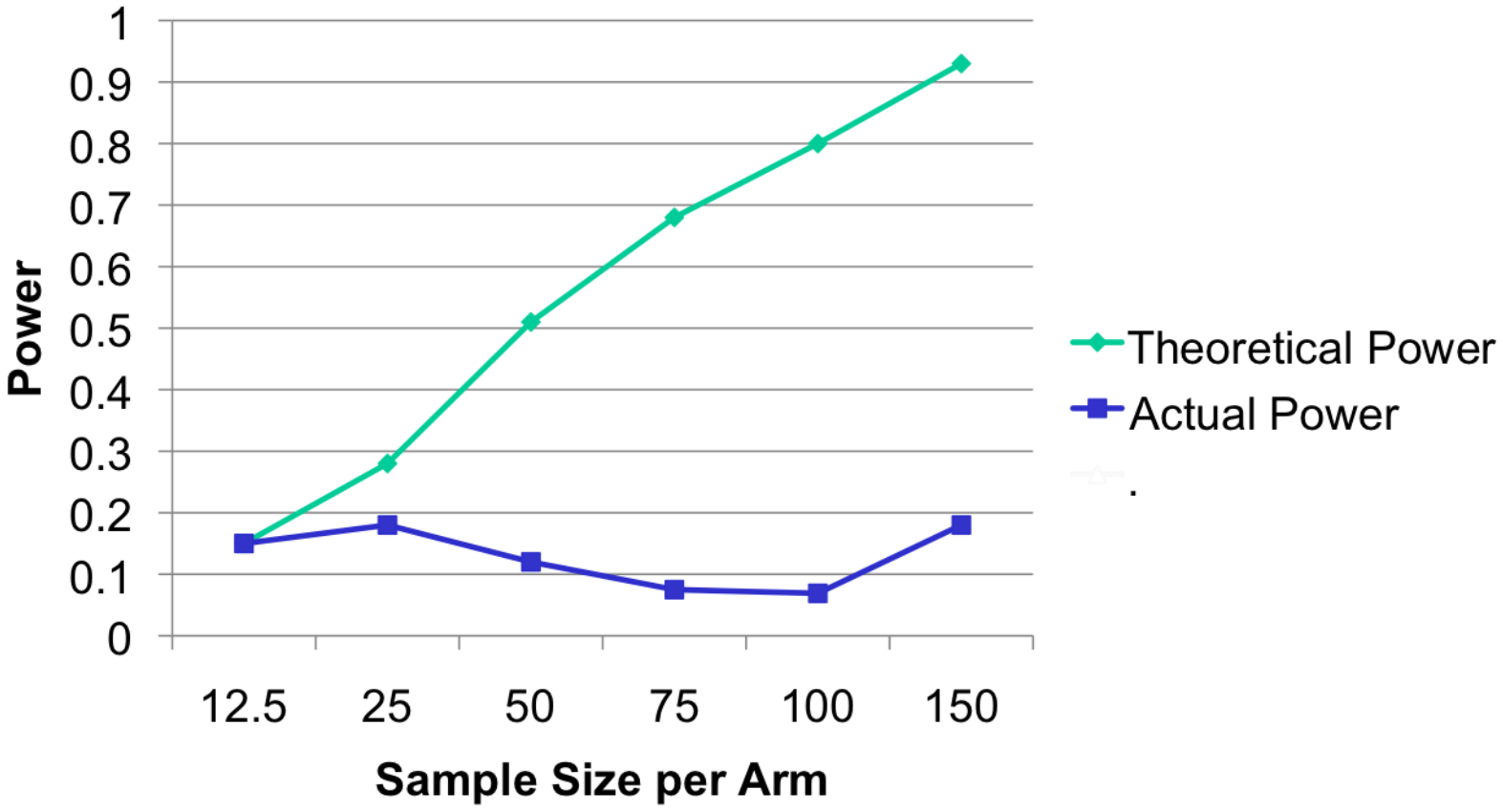


True vs. Actual Power



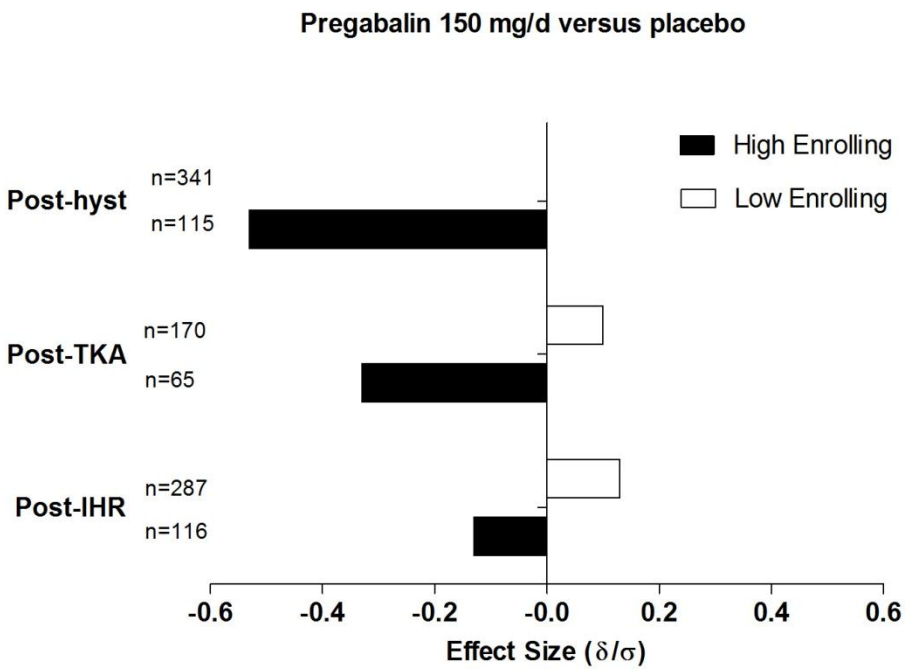
Δ=1, sd=2.5, α=.05, power=.8

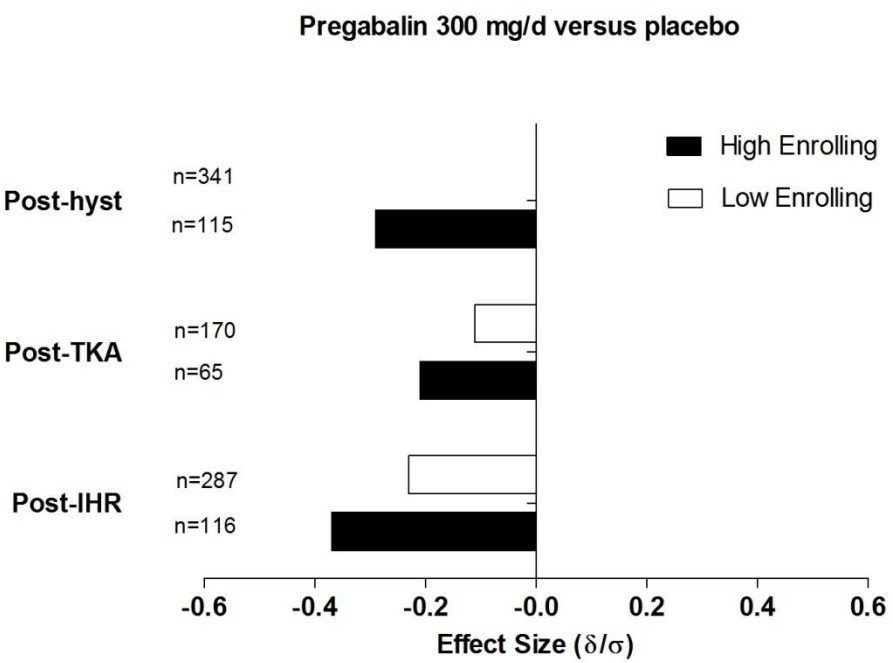
True vs. Actual Power



ANALGESIC SOLUTIONS

Low enrolling sites perform poorly





Negative effect size indicates greater pain relief in study drug vs. placebo.

Singla N et al, personal communication

Failure: Neuropathic Pain Trials

	Positive	Negative	P-value
Placebo response	15.8	26.3	0.002
Year (pub)	1995.2	1998.5	0.047
PHN	16	4	
Polyneuropathy	39	12	
Study design			0.006

Katz J, Neurology, 2008

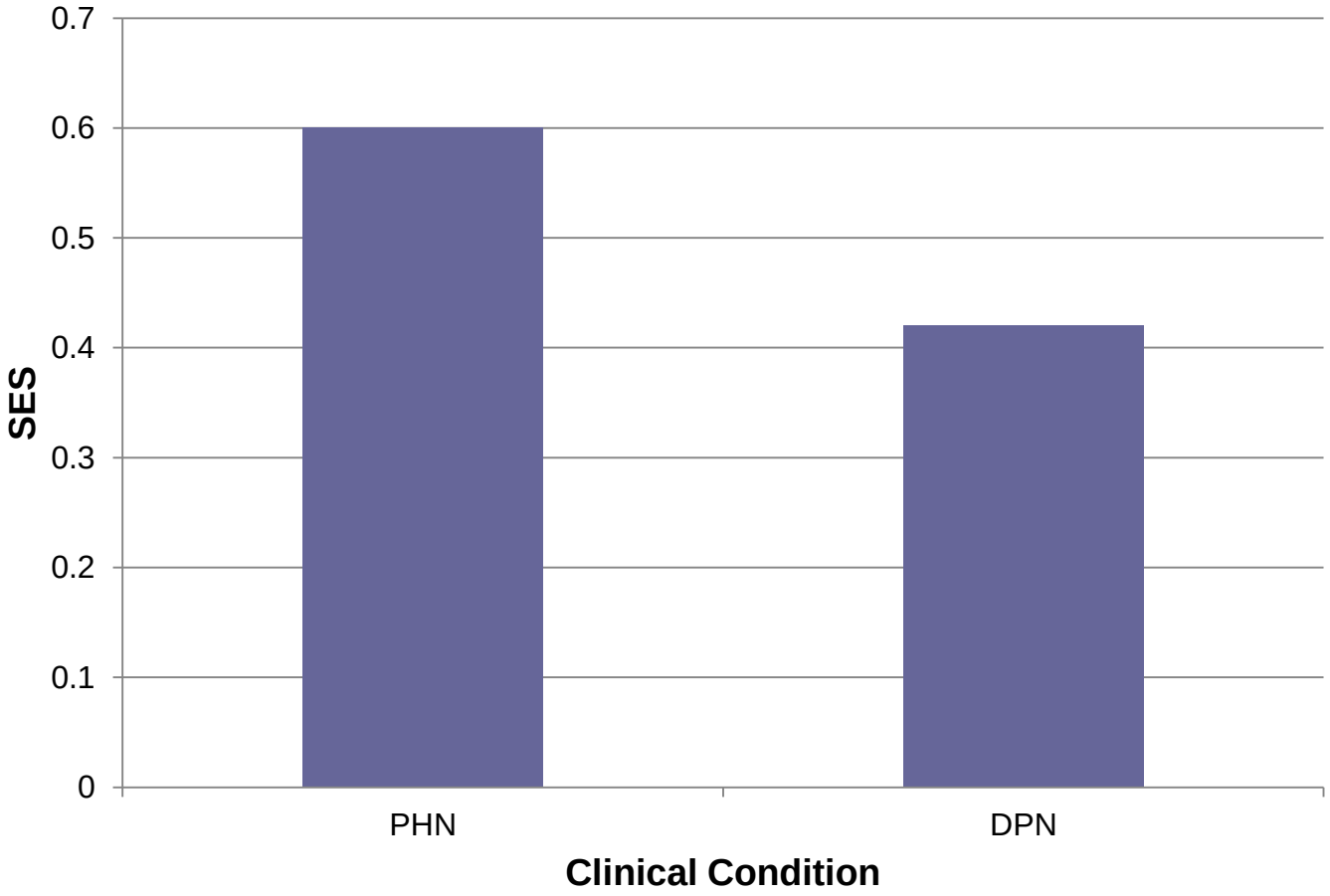
Failure: PDN Studies

Correlation between design feature and SES

- Longer duration of PDN (r = 0.80)
- Shorter treatment duration (r = 0.65)
  - Probably a proxy for earlier capture of primary endpoint
- Shorter titration (r = 060)
  - Probably a proxy for shorter trials
- Smaller sample size (r = 0.55)
  - Probably a proxy for fewer sites
- Fewer sites (r = 0.50)
- Fewer study visits per trial duration (r = 0.44)
  - May be due to less “nurturing nurse” effect or potentially higher dropouts
- Two arms (SES = 0.60) vs. >2 arms (SES = 0.40)
- No rescue medication (SES = 0.60) vs. rescue medication (SES = 0.40)

Dworkin R, Katz N, et al, unpublished

Clinical Condition Impacts SES

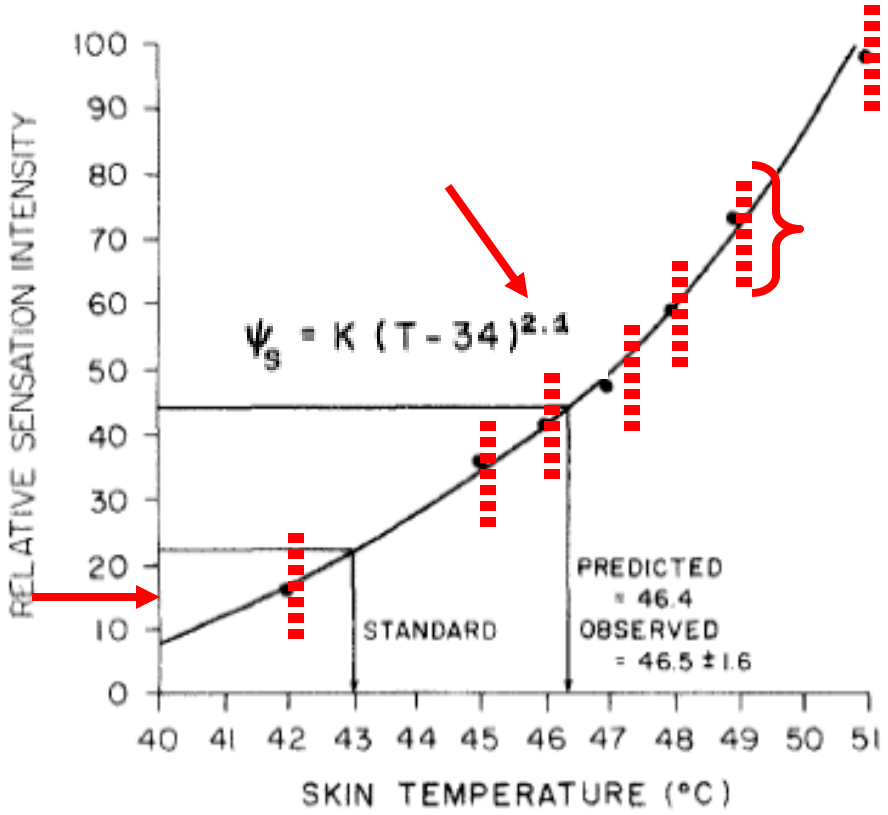


Dworkin RH, Pain, 2010

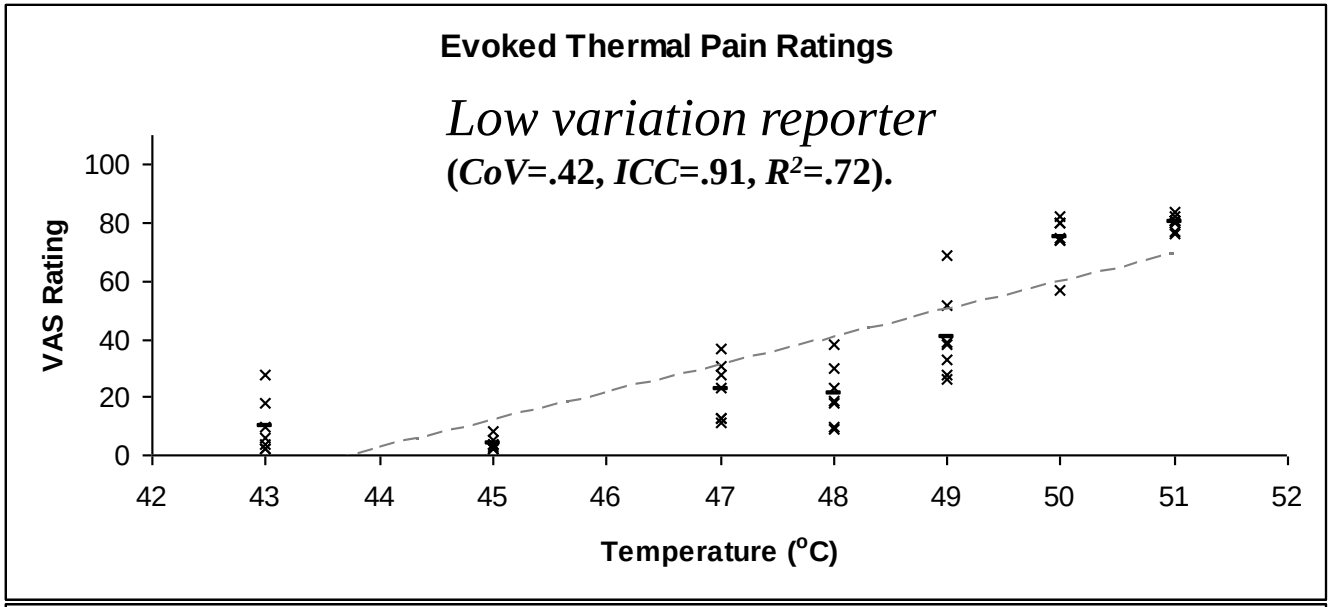
Psychophysical Assessment(Φ)

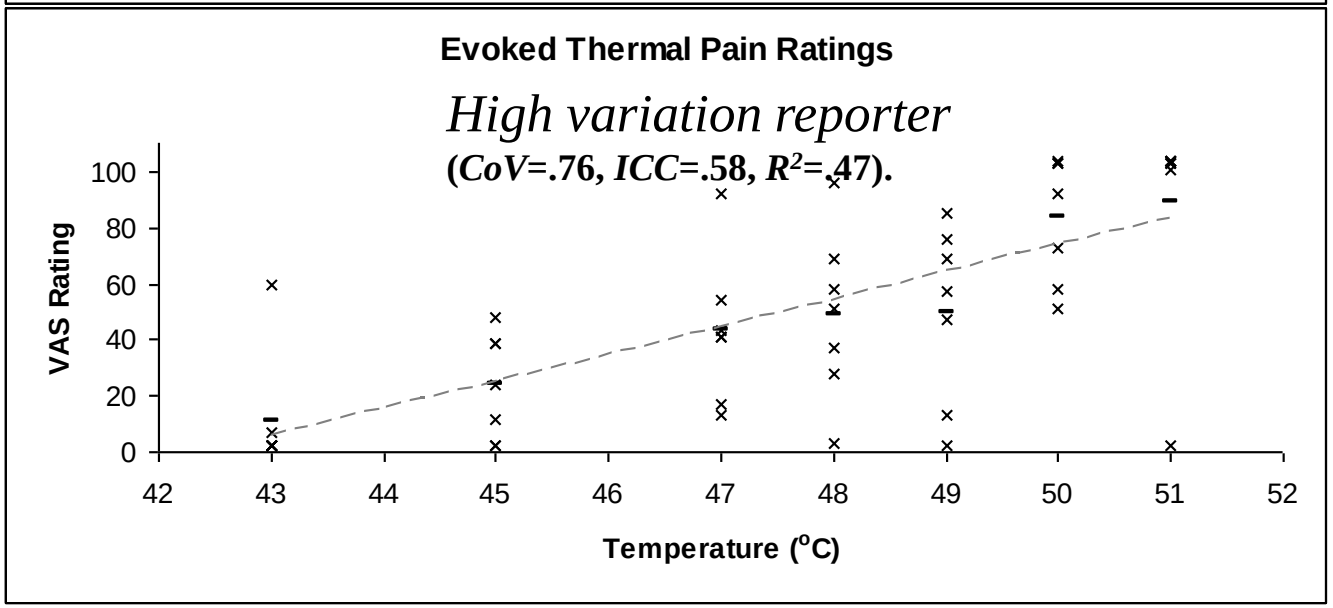
I. Experimental Pain Rating

Subjects rate 7 *temperatures* 7 times using VAS

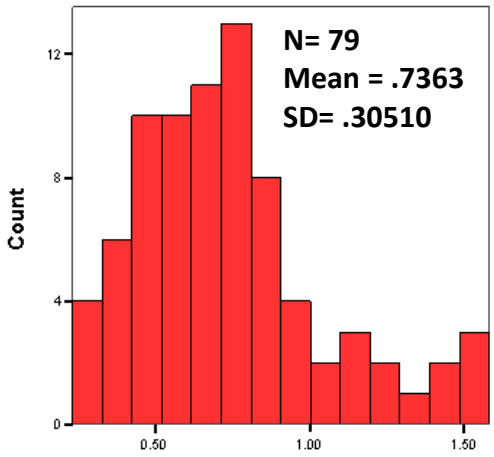


Psychophysical Profile Samples Φ

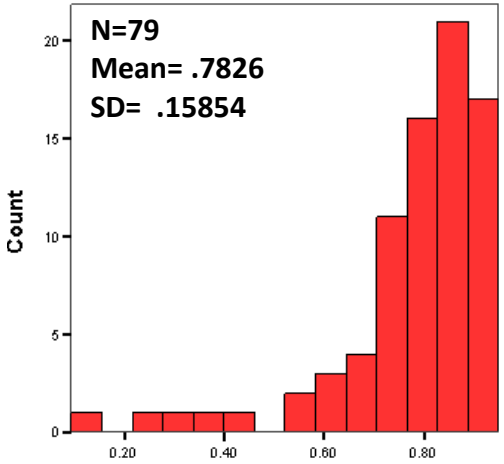




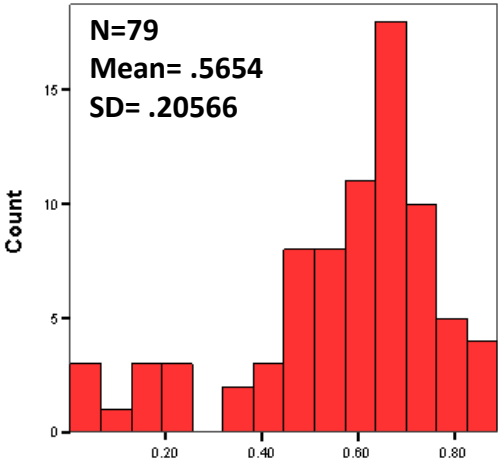
Frequency Plots for Pain Reporting Skill



CoV



ICC



R^2

Subjects demonstrated a large range of performance in pain reporting skill as indexed by CoV, ICC, and R^2.

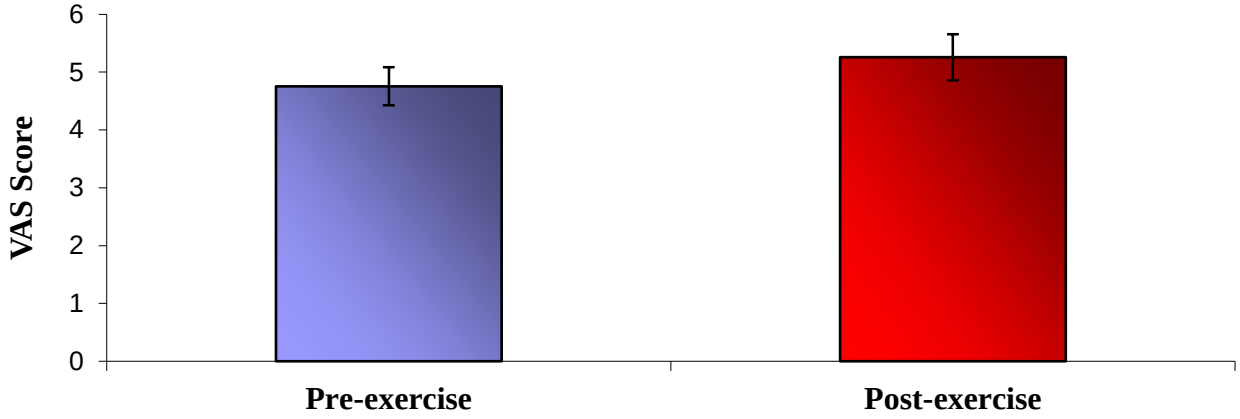
ANALGESIC SOLUTIONS

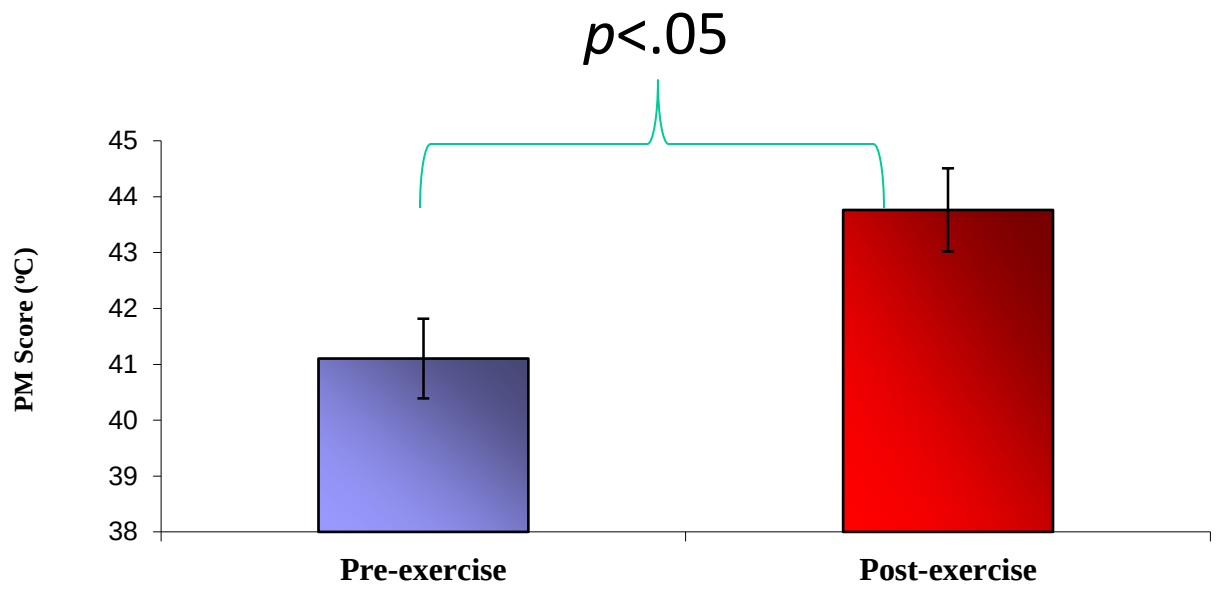
Pain Matching

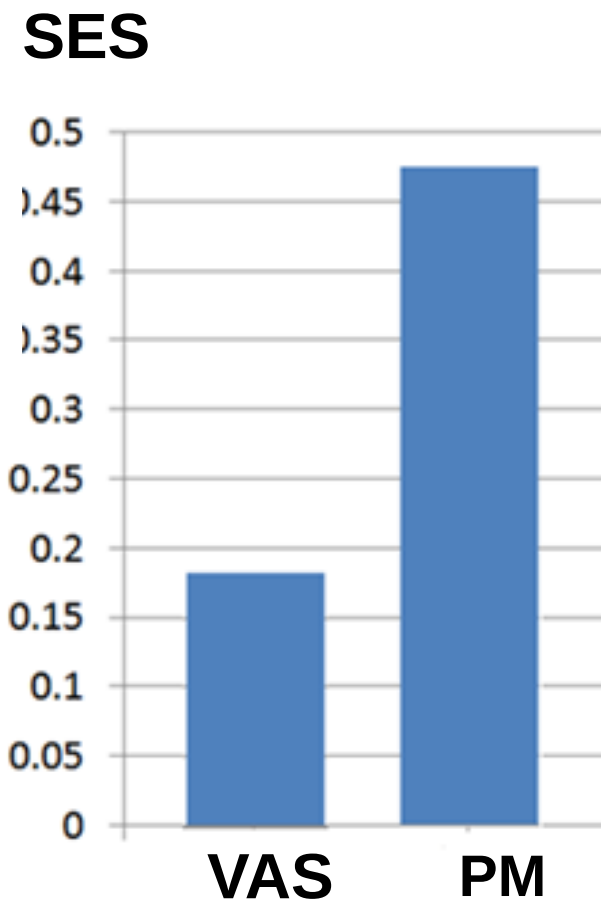
Subjects adjust thermode temp until $pain_{heat}$ = $pain_{OA}$ (forced choice staircase procedure)

Delta Exercise Pain Results:

Change in pain significantly different for PM not VAS







Placebo reduction training program

How do clinical trials help?

When some people take a new drug at the same time that other people take a placebo (fake drug), we can find out if:

- the new drug works at all.
- the new drug works better than placebo.
- the new drug works same or worse than placebo.

All "over-the-counter" and prescription medicines, like cough syrup or pain killers, were once tested in clinical trials. They now help thousands of people every day.

What is a placebo?

A placebo will be used in this clinical trial.

Placebos have ***no treatment benefit*** because they do not contain any medicines. The placebo will look, smell, taste, and feel like the new drug being tested.

Sometimes participants taking a placebo experience side effects, or their symptoms might get better. Many people assume this means they are taking the real drug.

Although this is possible, you might experience changes in symptoms because you:

- use other treatments or medicines.
- are hopeful about the study.
- feel worried about side effects.
- want to help the research staff.

Please complete the quiz below!

Circle **T** for true and **F** for false. Check back in this brochure if you aren't sure. When you finish, check your answers on the bottom of the page.

1. A placebo contains only inactive substances.	T/F
2. Participants in a clinical trial have a good chance of receiving placebo.	T/F
3. I should give the most accurate opinion of how I feel.	T/F
4. I should drop out of the study if I do not have any changes in my symptoms.	T/F
5. None of the study staff know if I am actually getting the real drug or a placebo.	T/F
6. If I feel a side effect, it must mean that I am in the real drug group.	T/F

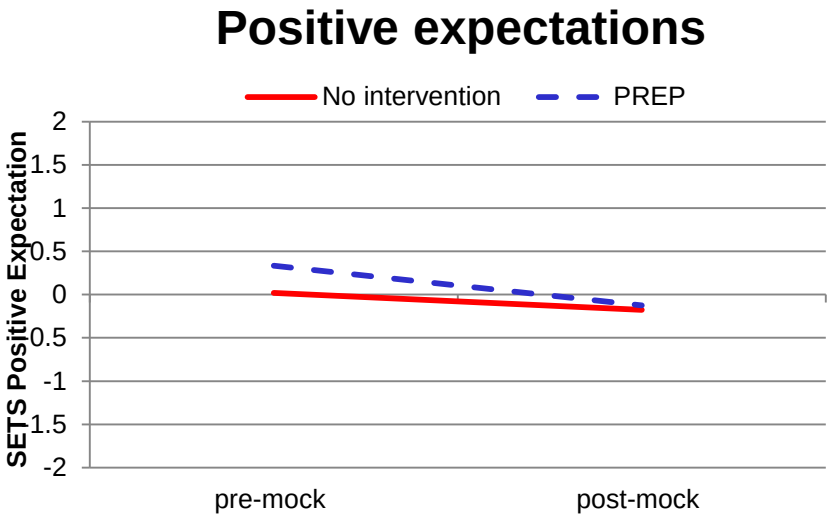
1-T; 2-T; 3-T; 4-F; 5-T; 6-F

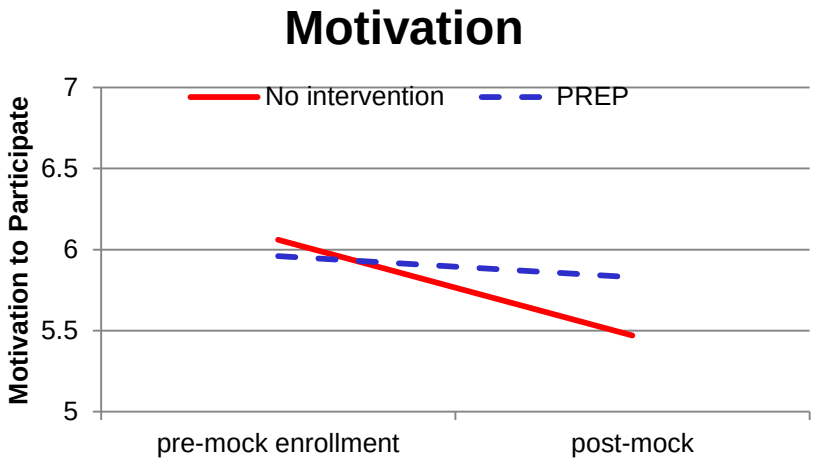
CLINICAL TRIALS

What you need to know as a research participant

ANALGESIC SOLUTIONS

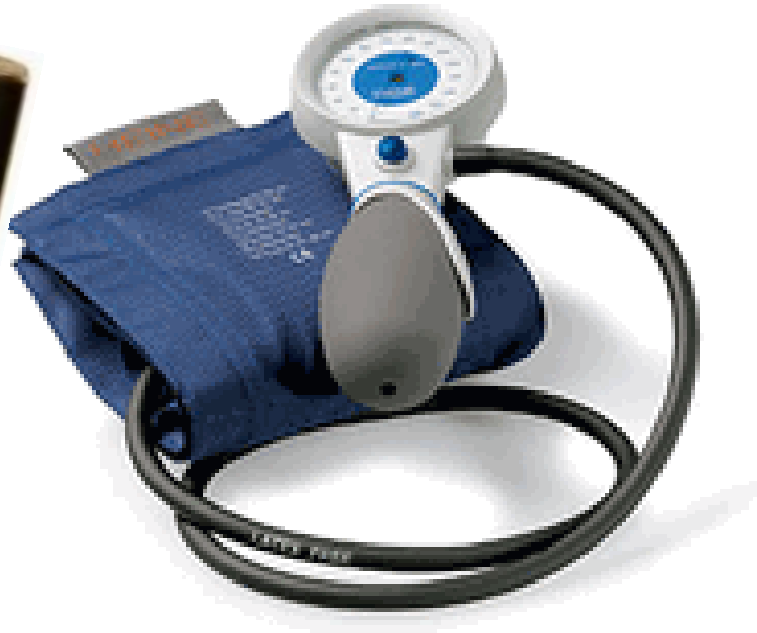
Preliminary Results

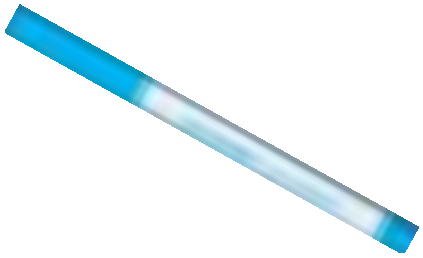




ANALGESIC SOLUTIONS

Bedside Sensory Testing Kit





Conclusions

- The old timers were probably doing something right
- We can quantify good research methods and standardize these approaches
- Doing so would accelerate the development of better analgesics