

Challenges in Interpreting Pain Research

Choosing Wisely
Presentation Prepped by EBM team with U of A & ACP

A story

- Marketing Authority ≈ Drug Approval
 - Required to promote a product for a particular condition
- The Manufacturer of Gabapentin was promoting the medication for chronic pain condition,...
- Unfortunately, they did NOT have marketing authority for that indication
 - It was Off-Label.
- Litigation ensued,.... Which led to release of all related documentation
- Our first look behind the curtain.

What did they find?

What happens to the RCTs they've done

```

    graph TD
      A[21 RCTs] --> B[8 never published]
      A --> C[13 Published (10 fully)]
      B <--> C
    
```

N Engl J Med 2009;361:1963-71. PLoS Med 2013; 10(1): e1001378.

What did they find?

What happens to the Primary Outcomes

```

    graph LR
      A[21 Primary Outcomes] --> B[10 Dropped]
      A --> C[11 Retained]
      B --> D[29% Positive]
      C --> E[28 Primary Outcomes]
      F[17 New Added] --> E
      E --> G[78% Positive]
    
```

Only 32% of the 180 secondary outcomes reported

N Engl J Med 2009;361:1963-71. PLoS Med 2013; 10(1): e1001378.

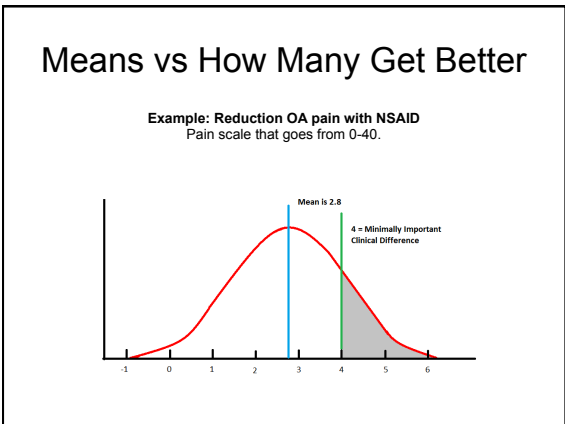
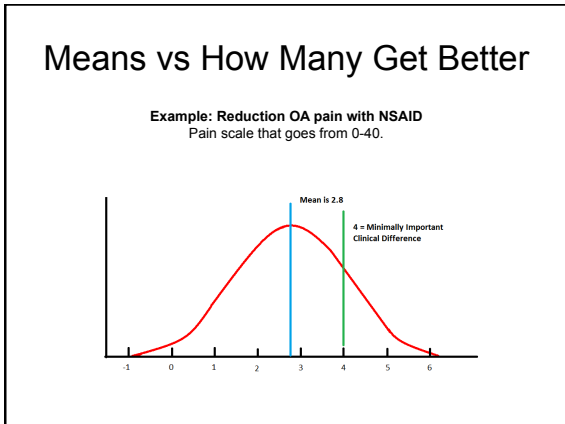
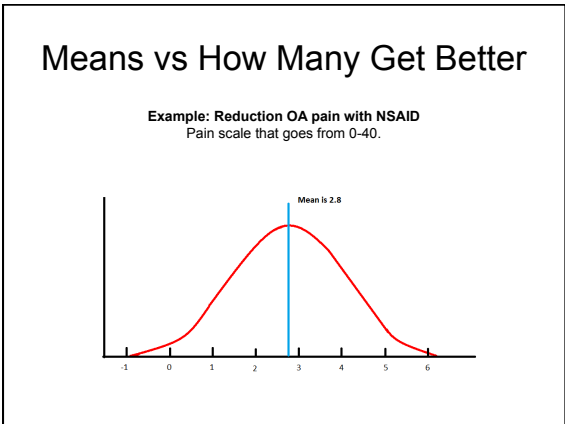
Sure, but is it all that bad,...

- 20 studies have looked at protocol to publication
 - 40–62% of RCTs have ≥1 primary outcome changed, introduced, or omitted
 - Significant result more likely to be fully reported (OR: 2.2 to 4.7)

PLoS ONE 2013; 8(7): e66844

Liars, Damn Liars & Scales

- Continuous variables can be reported many ways; and each can look different
- Scales = lots of numbers
- ↑ numbers = ↑ odds Statistical significance
- Statistical Significant ≠ clinical significance
- Let's look at two main ways to report effect



- ### How can you report Effect?
- Continuous Outcome: 4 examples
 - change in pain score,
 - percent change in pain score from baseline,
 - final pain score,
 - percent of final score compared to baseline.
 - Dichotomous Outcome: >3 examples
 - Proportion that attain a defined pain reduction,
 - Proportion that attain a defined pain score
 - Proportion that attain a defined percent reduction

- ### How can we report Effect?
- Consider the different number of outcomes
 - Pain, quality of life, function, disability, working, use of other analgesia, etc
 - Consider the huge number of scales for each
 - Pain: VAS (x3), WBS Rating, NRS, Likert, WOMAC, etc
 - Consider the variety of cut-offs.
 - 10%, 20%, 30%, etc. 1 pt, 2 pts, 10pts, 12 pts, etc
 - Is it any wonder that 12 gabapentin studies had >200 outcomes.

Example of a Cheat

- Goal: prove pregabalin gets more people to VAS pain scale of ≤ 3 .
- Control Randomization:

Pregabalin (10)	Placebo (10)
5.5	5.6

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Pregabalin (10)	Placebo (10)
5.5	5.6
4, 4, 5, 5, 4, 5, 9, 5, 10, 4	6, 7, 4, 4, 7, 6, 7, 3, 6, 6
80% can get to 3	30% can get to 3

- If Pregabalin ended up with more pts with higher scores, change your outcome to percent reduction

Summing Up

- Studies of Pain are easily manipulated
- Studies of Pain are often manipulated
- Ideally we look at lots of results, using similar endpoints
- In perfect world, reporting both mean continuous effect and proportion (NNT) attaining a meaningful cut-off.