Improving Assay Sensitivity in Analgesic Proof-of-Concept Studies: Osteoarthritis

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Objectives

- To present a conceptual framework for approaching the problem of assay sensitivity
- To provide examples of efforts to improve assay sensitivity, focusing on osteoarthritis
Why do effect sizes of identical treatments differ across studies?

- Actual biological effect of drug differs when studied by different authors
- Random chance: God rolls dice in our studies
- Aspects of study design or conduct influence observed effect size

Zhang et al, Osteoarthritis & Cartilage, 2010
“a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment”

\[
\frac{\text{Pain}_{\text{ACTIVE}} - \text{Pain}_{\text{PBO}}}{\text{Std Dev}_P}
\]
Abraham Sunshine

Ray Houde
(1916-2006)

Louis Lasagna
(1923-2003)

Mitchell B. Max
(1949-2008)
Ibuprofen Liquigel 400 mg for Dental Pain

## Relative Standard Effect Size

**SPID6 Ibuprofen liquigel 400mg vs. placebo:**

<table>
<thead>
<tr>
<th></th>
<th>Hersh</th>
<th>Sunshine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta</td>
<td>7.61</td>
<td>9.17</td>
</tr>
<tr>
<td>SD</td>
<td>4.85</td>
<td>4.5</td>
</tr>
<tr>
<td>SES</td>
<td>1.57</td>
<td>2.04</td>
</tr>
</tbody>
</table>

Sunshine has 30% higher SES  
(Equivalent to reducing sample size from 100/arm to 60/arm)
## Pregabalin vs. Placebo in Inguinal Herniorrhaphy

<table>
<thead>
<tr>
<th></th>
<th>Lotus Research (n = 126)</th>
<th>All 24 Other Sites (n = 274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint: $\Delta$</td>
<td>0.81</td>
<td>0.56</td>
</tr>
<tr>
<td>SD</td>
<td>2.25</td>
<td>2.56</td>
</tr>
<tr>
<td>SES ($\Delta$/SD)</td>
<td>0.360</td>
<td>0.219</td>
</tr>
<tr>
<td>N for 80% power, alpha = 0.05</td>
<td>244</td>
<td>658</td>
</tr>
<tr>
<td>Subjects enrolled per month</td>
<td>23.2</td>
<td>0.75</td>
</tr>
<tr>
<td>Overall Performance (time to 80% power)</td>
<td>10.5 months*</td>
<td>36.6 months **</td>
</tr>
</tbody>
</table>

*utilizing one site at Lotus             **utilizing 24 non-Lotus sites in concert

Singla N, American Pain Society, 2010
Implications

• The standardized effect size of a treatment is not fixed, but elastic depending on methodologic factors that determine assay sensitivity

• We can figure out what those methodologic factors are

• We can intentionally implement them in clinical trials to increase assay sensitivity
Approaches

• Meta-analysis
  – By study
  – Within-patient

• Experimental
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

- Decreasing SES from 1 to 0.25 can increase sample size requirements from 20 to 250 patients/arm

Adapted from Katz N, et al, Neurology, 2005
# Methodologic Factors

## Study Level
- Study structure
- Number of arms
- Duration
- Number of visits
- Baseline duration
- Dose, administration
- Rescue meds
- Concomitant analgesics
- Protocol concealment
- Site training
- Investigator experience

## Patient Level
- Diagnosis
- Pain duration
- Co-morbidities
- Psychiatric status
- Concomitant analgesics
- Demographics
- Baseline pain intensity
- Baseline pain variability
- Diary compliance
- Expectation of pain relief
- Previous experience
Predictors of positive studies: neuropathic pain, n=90 studies

Table 3: Logistic regression model predicting clinical trial outcomes from study characteristics (n = 90)*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>Std. Error</th>
<th>z value</th>
<th>p value</th>
<th>Exp(B)</th>
<th>CI Lower</th>
<th>CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo response added to initial model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication response</td>
<td>0.15</td>
<td>0.04</td>
<td>0.001</td>
<td>116</td>
<td>1.07</td>
<td>1.07, 1.25</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>0.03</td>
<td>0.01</td>
<td>0.003</td>
<td>1.03</td>
<td>1.01</td>
<td>1.01, 1.05</td>
<td></td>
</tr>
<tr>
<td>Year of publication</td>
<td>-0.08</td>
<td>0.08</td>
<td>0.292</td>
<td>0.92</td>
<td>0.78</td>
<td>0.78, 1.08</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>-0.84</td>
<td>0.99</td>
<td>0.400</td>
<td>0.43</td>
<td>0.06</td>
<td>0.06, 3.04</td>
<td></td>
</tr>
<tr>
<td>Pain condition</td>
<td>0.91</td>
<td>1.27</td>
<td>0.474</td>
<td>2.48</td>
<td>0.21</td>
<td>0.21, 29.76</td>
<td></td>
</tr>
<tr>
<td>Placebo response</td>
<td>-0.24</td>
<td>0.06</td>
<td>0.001</td>
<td>0.79</td>
<td>0.70</td>
<td>0.70, 0.89</td>
<td></td>
</tr>
</tbody>
</table>

Sample size requirements to detect differences in SES by methodologic feature

<table>
<thead>
<tr>
<th>Difference in SES</th>
<th>Total N of studies</th>
<th>Total N of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>74</td>
<td>12561</td>
</tr>
<tr>
<td>0.2</td>
<td>20</td>
<td>3142</td>
</tr>
<tr>
<td>0.3</td>
<td>12</td>
<td>1398</td>
</tr>
<tr>
<td>0.4</td>
<td>8</td>
<td>787</td>
</tr>
<tr>
<td>0.5</td>
<td>6</td>
<td>505</td>
</tr>
</tbody>
</table>

Increasing SES from 0.3 to 0.4 can decrease sample size requirements **per arm** from 175 to 100
Meta-analytic methods

- Meta-analysis can shed light on the relationship between methodologic features and study outcome.
- Databases will need to be large, and include within-patient data.
- We should be looking for trends and testing candidate approaches experimentally.
Experimental Approaches

What generates a pain score?

- Experimental Noise
- FAST
- Pain Matcher
- Random Error

= Reported Pain Score

Validity
Reliability
Responsiveness

Single Site Studies

“True” Pain Score +

Patient Innate Reporting Capability

Measure Error
Psychophysical Assessment ($\Phi$)

**Experimental Pain Rating**

Subjects rate 7 *heat* stimuli for pain level 7 times using VAS.

\[
\Psi_g = K (T - 34)^{2.4}
\]

- No pain
- Worst pain imaginable

**Plot:**
- Relative sensation intensity vs. skin temperature.
- Predicted $= 46.4$
- Observed $= 46.5 \pm 1.6$

![Graph showing relationship between skin temperature and relative sensation intensity with data points and equations.]
Evoked Thermal Pain Ratings

Low variation reporter
\( (CoV=.42, ICC=.91, R^2=.72). \)

Evoked Thermal Pain Ratings

High variation reporter
\( (CoV=.76, ICC=.58, R^2=.47). \)
Subjects demonstrated a large range of performance in pain reporting skill as indexed by CoV, ICC, and $R^2$. 

- $N = 79$
- Mean = .74
- SD = .31
Pre- vs. post-exercise VAS scores in “good” vs. “bad” pain reporters
Stay Tuned

- Single-site POC study in knee OA recently completed
- FAST assessment demonstrated to be reliable
- After excluding “high variability” pain reporters, NSAID separated from placebo in 31 subjects on primary endpoint of staircase-evoked pain
Pain Matching

Subjects adjust thermode temp until $\text{pain}_{\text{heat}} = \text{pain}_{\text{OA}}$ (forced choice staircase procedure)
Delta Exercise Pain Results:

Change in pain significantly different for PM not VAS

$p<.05$
Other explorations of alternative pain measures

Pain-Activity Composites

Actiwatch®-Score
Pain-Activity Composites in an OA RCT, Celecoxib vs. Placebo, n=43

Pain alone: ≥20% improved from baseline; liberal: pain improved ≥20% OR activity improved ≥10%; conservative: pain pain improved ≥20% OR activity improved ≥10% WITHOUT deterioration in the other measure.
Bedside Sensory Testing Kit - OA
# Sensory Categories in OA: Pilot Study

<table>
<thead>
<tr>
<th></th>
<th>No hyperalgesia</th>
<th>1° hyperalgesia</th>
<th>2° hyperalgesia</th>
<th>1° and 2° hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intact DNIC</strong></td>
<td>N=3</td>
<td>N=1</td>
<td>N=2</td>
<td>N=2</td>
</tr>
<tr>
<td><strong>Dysfunctional. DNIC</strong></td>
<td>N=0</td>
<td>N=1</td>
<td>N=2</td>
<td>N=9</td>
</tr>
</tbody>
</table>

**Alpha = .59 - .72**
Conclusions

• Meta-analytic methods can be used to shed light on the impact of methodologic factors on study outcome

• Experimental methods can be used to develop and test study design methods to increase assay sensitivity

• Success will require resources, perseverance, and patience: hitting home runs on the first swing is unlikely