Placebo Response in Chronic Pain: What Have We Learned

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Changing the State of the Brain

What do you see?
“Placebo Response” Versus Placebo Group Response

- Response in a placebo treated group
  - Natural history of disease
  - Regression to the mean
  - Brain-body effect (placebo effect)

- Response in a drug treated group
  - Natural history of disease
  - Regression to the mean
  - Brain-body effect (placebo effect - maybe)
  - Specific effect of the therapy
Factors That Affect Individual Response

- Natural history
- Regression to the mean
- Brain-body effect
  - This is the only truly individual characteristic “placebo” effect
- Specific effect of therapy
Why Do We Care

• RCTs are important for medical therapy

BUT.. Not all RCTs are a problem

• No RCT needed for penicillin treatment of Pneumococcal pneumonia
  – No penicillin - Last week 9/10 people died
  – With penicillin – This week 1/10 people died

• Importance of the placebo group response depends on the size of the specific effect
Potential Reasons to Reduce Placebo Group Response Rate

- **Statistical** – Comparison of change in group levels is harder to detect the closer the underlying group response is to 0.5 or 50%
- **Measurement** – Ceiling affect
- **Reduction in size of the detectable difference between groups (more efficient)**
Does the Placebo Response Affect the Success Rate of RCTs

- Larger placebo response is associated with lower likelihood of a statistically positive study*
- This does not prove that the higher placebo group rate causes the study failure
- Also does not prove that excluding placebo responders would change the results

*Katz, Finnerup, Dworkin: Neurology 2008
Thoughts About Reducing Placebo Response Rate

• Exclude placebo responders? (which type?)
• Conduct longer trials – placebo response may not last as long (controversial)
• Select patients with worse pain
  – Lower placebo response in severe pain (maybe)
  – Larger response to placebo
  » (Regression to the mean?)

Placebo Rates in Neuropathic Pain Clinical Trials

• Placebo response level increased with time up to 19 weeks
• Calendar time (since 1990s)  
  – placebo rates have been flat
• Placebo response by disease:  
  – PHN average 15%  
  – DPN average 26%

*Quessy, Rowbotham: Pain 2008
Problems in Placebo “Responder” Exclusion

- **Placebo run-in responder**
  - Does not definitively identify brain-body placebo responders

- **Placebo run-in non-responder**
  - Does not definitively identify brain-body placebo non-responders

- **Natural history/ Regression to the mean**
  - If you remove those getting better may be left with only those getting worse
  - And those may be likely to get better again in the next period
REPORT Study Findings

• Change in placebo group larger in DPN (1.5) versus PHN (0.9)
• Change in active treatment groups were similar DPN (2.4) versus PHN (2.3)
• Positive studies DPN (60%) versus PHN (80%)

Analysis of Lamotrigine RCT’s

- Characteristics of studies that were statistically significant
  - Higher baseline pain
  - Higher site recruitment rate

- These results suggest that both patient and study site characteristics can influence the response in the placebo arms of neuropathic pain studies.

Design Considerations

- Placebo run in – may not make a difference in depression studies*
- Elimination of all analgesics before enrollment has limited benefit – ethics?
- Suppressing placebo response may not be helpful or may even be counter productive**

**Quessy, Rowbotham: Pain 2008
No Advantage
Placebo Responder Exclusion

- Treatment Response
- Placebo Response
- Non-responders
Advantage for Placebo Responder Exclusion

- Treatment Response
- Placebo Response
- Non-responders
So How Do We Approach This?

- Overall study design issues
- Populations to study
- Individual characteristics of patients
Overall Study Design Issues

- Randomization
- Blinding
- Choice of outcome
- Appropriate timing for therapy
- Analysis
- Interpretation
Populations/ Patients to Study

• Have the disease of interest (phenotype)

• Likely to be responsive
  – Newly diagnosed may be best
  – Unresponsive to all other therapies may not be responsive

• Appropriate personality and affect

• Ability to accurately report change

• Appropriate expectation of benefit
Things That May Affect The Placebo Group Response

- Natural history - Selection of patients
  - Must have the right disease process
  - Preferably relatively stable disease and pain
  - Must have propensity for response
    » Disease at a treatable stage
    » Able to ingest, absorb, metabolize and excrete drug

- Regression to the mean
  - Select patients with relatively stable pain

- For both - Do not select patients with too high a level of pain
Things That May Affect the Placebo Group Response

- Those less likely to have brain-body response
  - Multiple responses to placebo
  - Predictive patient characteristics?
  - Functional imaging
Model of Pain

Physical State

Nociception

Reflex Action

Perception

Memory and Expectations

Affect (mood)

Evaluation

Response

Actions

Symptoms and Signs

Environment
Things That May Affect the Brain-Body Placebo Effect

- **Expectation** – Belief in a response
- **Conditioning** – Previous experience
- **Current experience** – “Side-effects”
- **Traits of the patient**
  - Insight to notice and record change
  - Not overly optimistic/pessimistic
- **State of the brain**
  - Not overly depressed or manic
Things That May Affect The Placebo Group Response

• Brain-body placebo effect
  – Blinding
  – Enroll patients with reasonable expectations
  – Keep level of expectation appropriate
    » Consent form issues
    » Standardize staff => subject interaction protocols

• Consider influence of brain-body response
  – Appropriate brain-body response may also facilitate response to drug
Specific Design Suggestions

- Select population homogeneous for the propensity for response to a drug
  - Randomized withdrawal studies in those who respond
  - Prediction of response from baseline characteristics
- Standardize information conveyed to subjects to regularize expectation
- Limit subject/staff interaction to reduce study effect
Specific Design Suggestions (cont)

• Appropriate design (# of groups) and timing (pharmacodynamics)
• Appropriate measures and baseline inclusion criteria
• Reduce overall group variability as much as possible
• Everything else
Thank you

If these don’t work, come back and I’ll prescribe you a stronger placebo