Placebo Response in Chronic Pain: What Have We Learned

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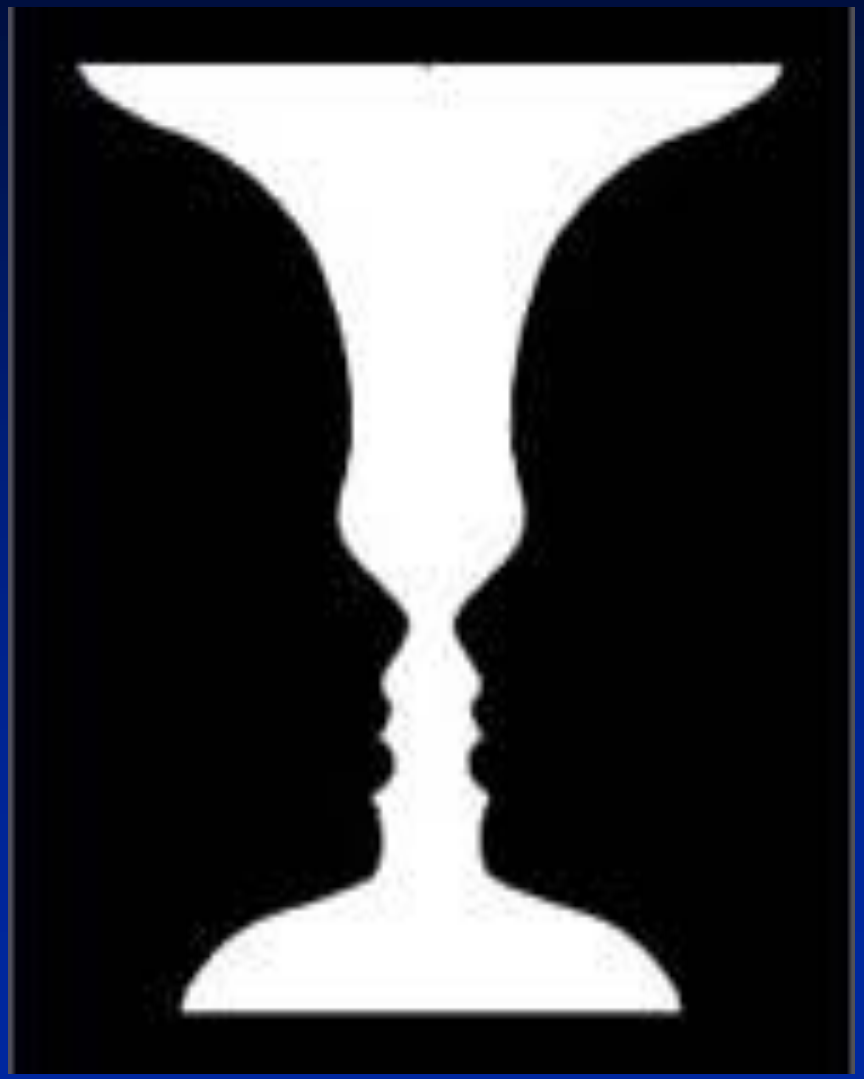
Changing the State of the Brain

What do you see?



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"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

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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

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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?)

1.Dworkin RH, Turk DC, Peirce-Sandner S, et al. Placebo and treatment group responses in postherpetic neuralgia vs. painful diabetic peripheral neuropathy clinical trials in the REPORT database. *Pain. Jul 2010;150(1):12-16.*

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

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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

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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%)

1.Dworkin RH, Turk DC, Peirce-Sandner S, et al. Placebo and treatment group responses in postherpetic neuralgia vs. painful diabetic peripheral neuropathy clinical trials in the REPORT database. *Pain. Jul 2010;150(1):12-16.*

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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.

Irizarry MC, et al: Clinical Journal of Pain. 2009

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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**

*Lee S, et. al. Depression and anxiety 19 (1) p10 -19 2004

**Quessy, Rowbotham: Pain 2008

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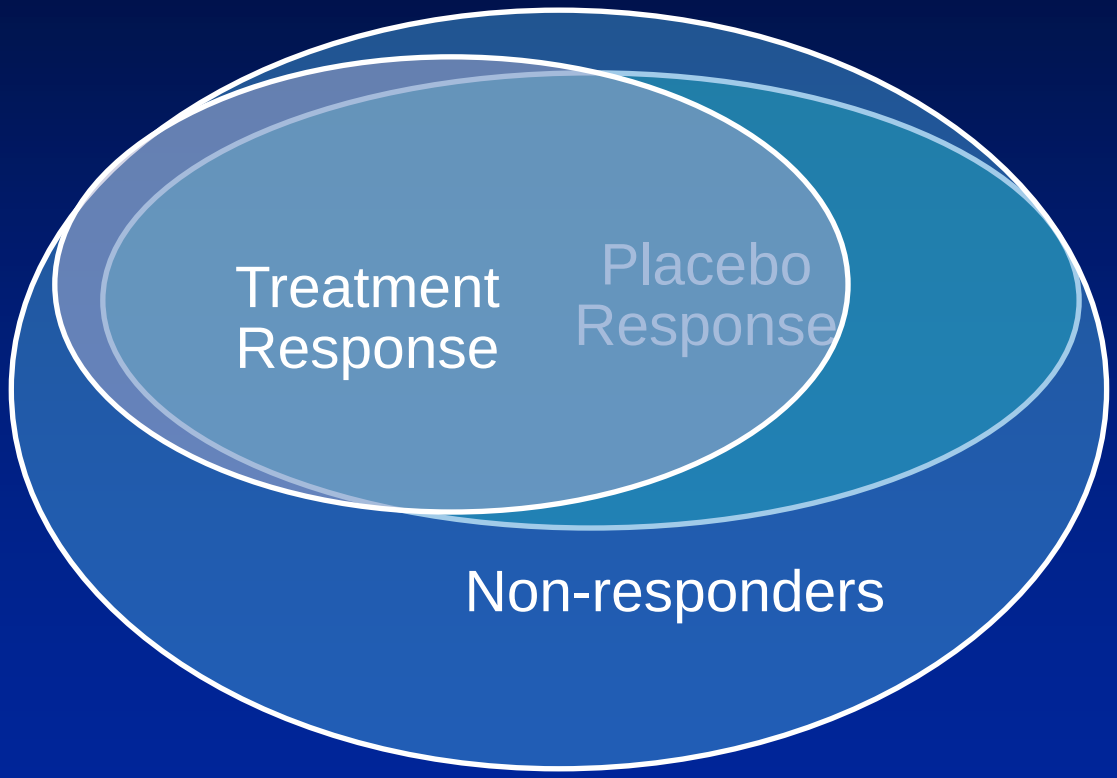
No Advantage
Placebo Responder Exclusion



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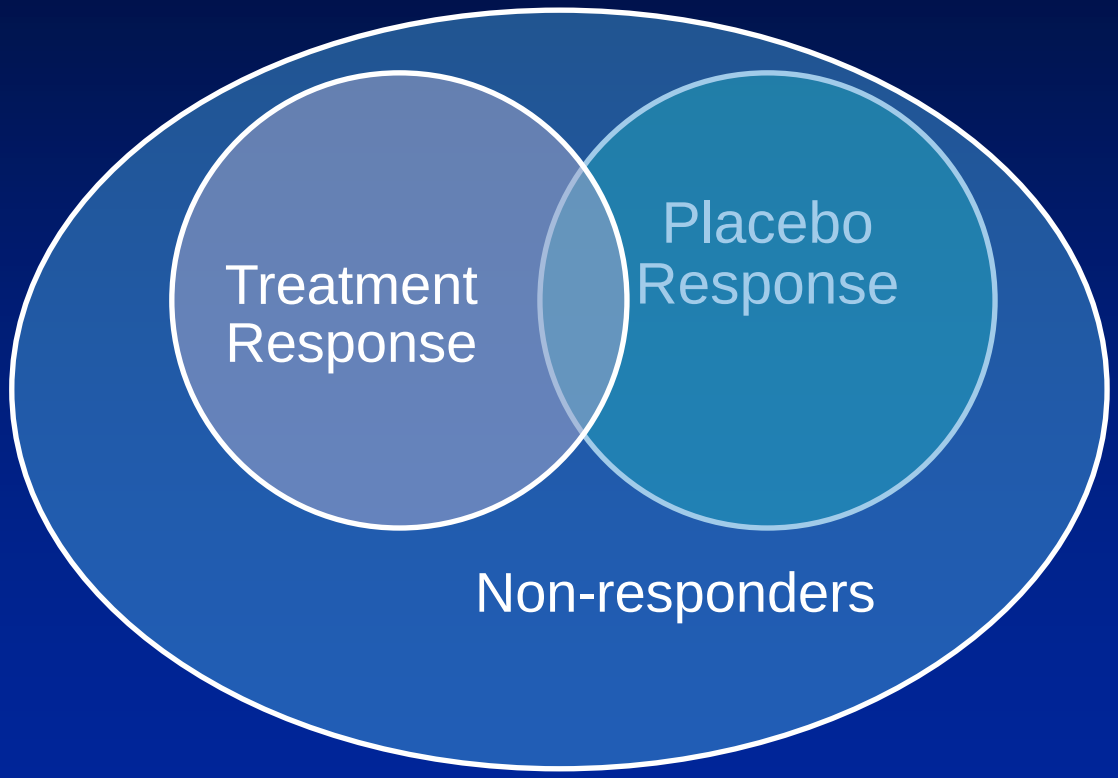
Advantage for Placebo Responder Exclusion



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So How Do We Approach This?

- Overall study design issues
- Populations to study
- Individual characteristics of patients

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Overall Study Design Issues

- Randomization
- Blinding
- Choice of outcome
- Appropriate timing for therapy
- Analysis
- Interpretation

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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

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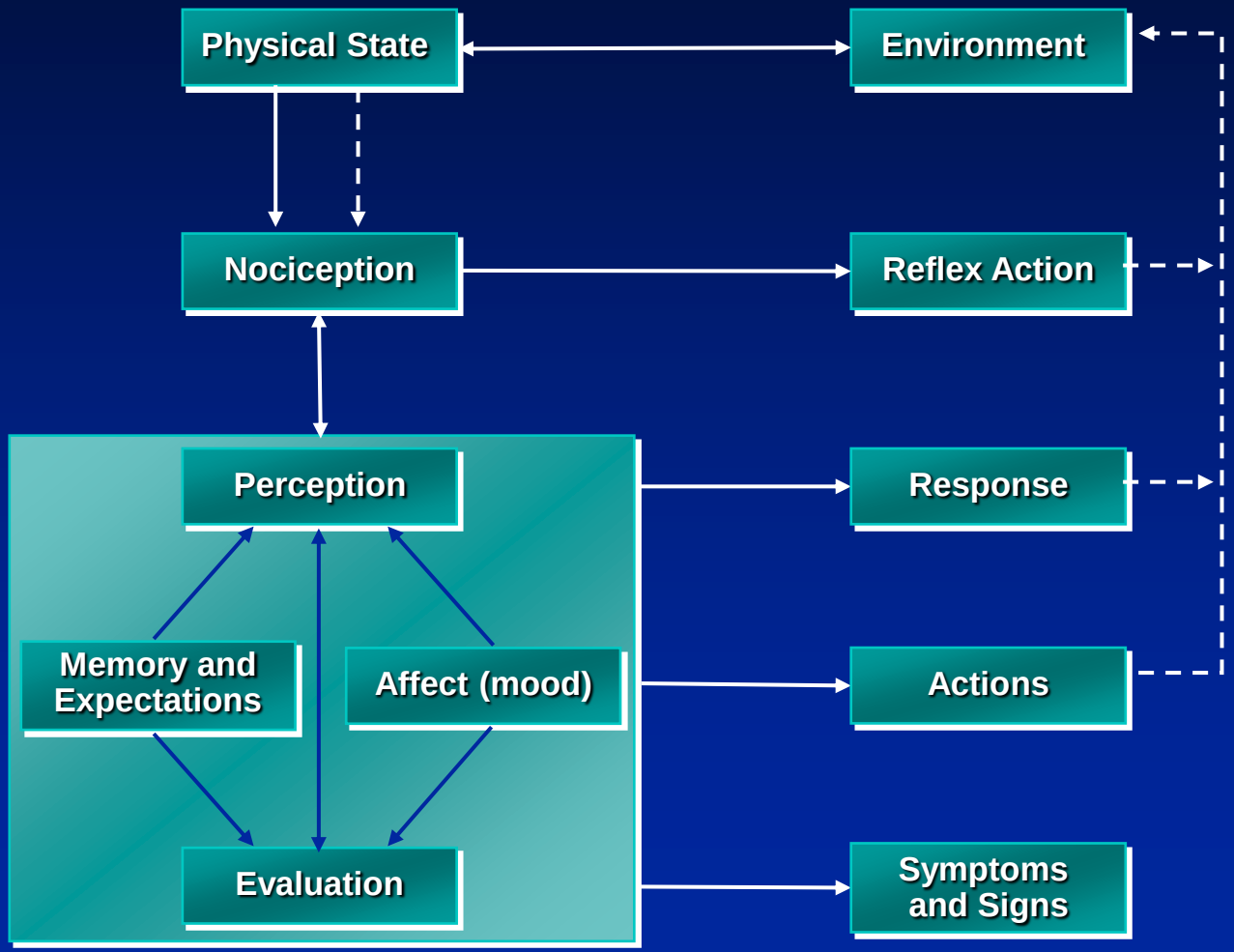
Model of Pain



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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

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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

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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

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