

Integrating New Information Increasing our Understanding of Placebo Response and Implications for Drug Development

Teodora (Dora) Pene Dumitrescu¹, Ph.D

Virginia (Ginny) D Schmith², Ph.D.

¹ GSK and ²Nuventra Pharma Sciences

Objectives

- Gain an understanding of the placebome (a group of genome-related mediators that affect an individual's response to placebo treatments) and of the neurological evidence that multiple neurotransmitter and molecular pathways mediate placebo effects.
- Gain an understanding of how placebo response influences Phase 3 failures and describe traditional and novel clinical study design and pharmacometric strategies to optimize drug-placebo differences.

Speakers

- Ginny Schmith: Collaboration Across Fields to Minimize Placebo Response and Maximize the Potential for Positive Phase 3 Outcomes (20 min)
- Kathryn Hall: Genetics of the placebo response: what can we learn from the placebo? (25 min)
- Julie Passarell: Case Study in Placebo Modeling and its Effect on Drug Development (25 min)
- Yaning Wang: Application of Placebo Model in Drug Development-A Regulatory Perspective (25 min)
- Panel Discussion (25 min)

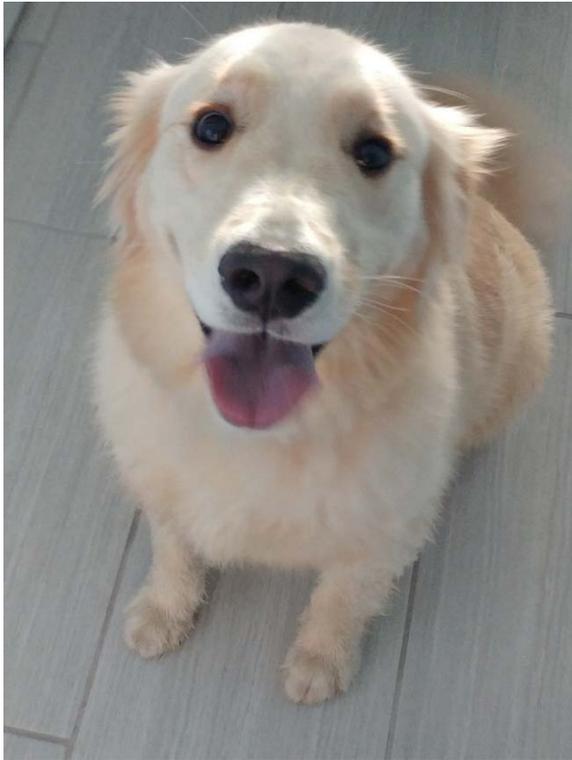
Collaboration Across Fields to Minimize Placebo Response and Maximize the Potential for Positive Phase 3 Outcomes

Ginny Schmith¹ and Dora Pene-Dumitrescu²

¹Nuventra Pharma Sciences

²GlaxoSmithKline

Placebo Response



- Placebo-controlled study of new NSAID in 58 dogs with arthritis.
- 50% of caregivers and 40% of veterinarians stated that dog lameness decreased with placebo

Conzemium Evans. Journal of the American Veterinary Medical Association 2012; 241:1314-1319.

Is Placebo Response Responsible for Many Phase 3 Failures?

- 90% of drugs for the treatment of neuropathic and cancer pain were dropped between 1990 and 2013^a
- In 2011, clinicaltrials.gov listed 4152 pain trials, yet over 3 years only 3 drugs were approved (duloxetine, oxycodone, fentanyl as new formulations)^a
- Patient expectancy is a key component in placebo response
- Once efficacy is achieved in Phase 2, physician and patient expectancy increases, with the potential for an increase in placebo response
- Placebo response differs by indication, with high placebo response in functional disorders (e.g., IBS) and those with imprecise measures of endpoints (e.g., Crohns Disease), but are lower for diseases like rheumatoid arthritis
- Phase 3 trials tend to include subjects from a large number of countries with differing access to healthcare and differing physician-patient relationships

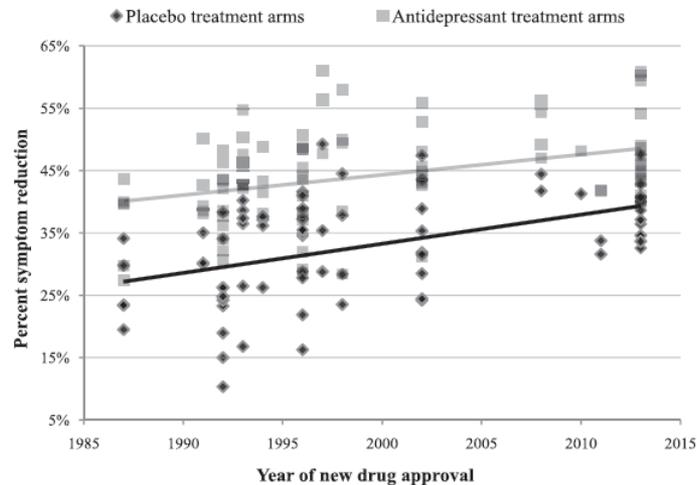
^aBenedetti, Carlino, Piedimonte Lancet Neurology 2016;15:736-47

Is Placebo Response Responsible for Many Phase 3 Failures?

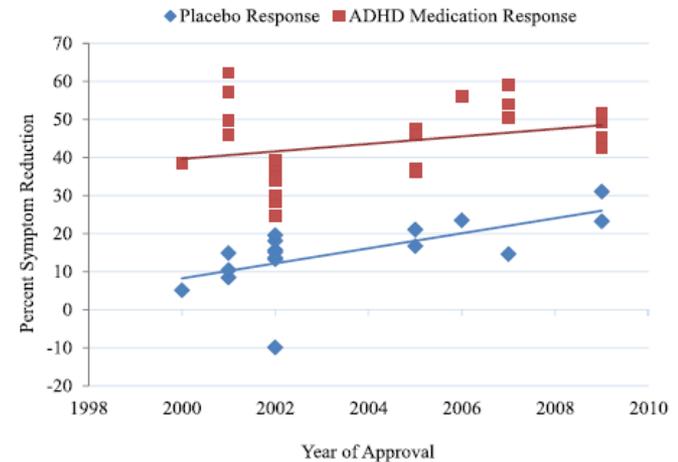
- FDA summarized 22 cases where Phase 2 and Phase 3 trials had divergent results including drugs, vaccines and other biologics, and devices
- Reason for Phase 3 failures included:
 - Use of biomarkers in Phase 2 that did not predict Phase 3 outcome (e.g., oncology, CV)
 - Untested mechanism of action
 - Changes in placebo response not mentioned, but could be reason for 4 drugs:
 - Bitopertin for add-on therapy in schizophrenia
 - Capsaicin topical patch for HIV induced nerve pain
 - Dexmecamylamine for depression
 - Imiquimod cream for molluscum contagiosum

Is Placebo Response Responsible for Many Phase 3 Failures?

Depression



ADHD



Placebo response has steadily grown over the years. A similar increase in treatment response has occurred, and the magnitude of treatment-placebo has been the same in depression and in ADHD

Factors Affecting Placebo Response

- Placebo response appears to be related to
 - Patient expectancy
 - Number of treatment arms (less with 1:1 than with 2:1 randomization)
 - Therapeutic encounters (empathetic witnessing, emotional support, medical rituals, symbols, and paraphernalia (e.g., placebo pill))
 - Genetics
 - Time

The Effects of Therapeutic Encounters on Placebo Response

- 122 healthy volunteers exposed to the cold pressor test from a doctor (actor) using two different scripts:
 - Standard doctor patient encounter (treatment A)-where doctor acts busy and volunteer has to wait, statements are “facts only”
 - Attentiveness and strong suggestion (treatment B)-where doctor is empathetic and strongly suggests that this individual cream will work for you
- There was a 60% increase in pain threshold after treatment B
- Thus, patient-physician encounter can have large effect on placebo response

New Society to Evaluate Placebo Response

- SIPS: Society for Interdisciplinary Placebo Studies
- Goals are to use multidisciplinary tools (neuroscience, psychology, cognitive science, history, anthropology, and philosophy) to examine the physiological and psychological mechanisms underlying placebo effects, and to develop ethically acceptable methods to harness the placebo effect to improve treatment outcome
- First official conference of SIPS held, April 2-4, 2017, Leiden, The Netherlands

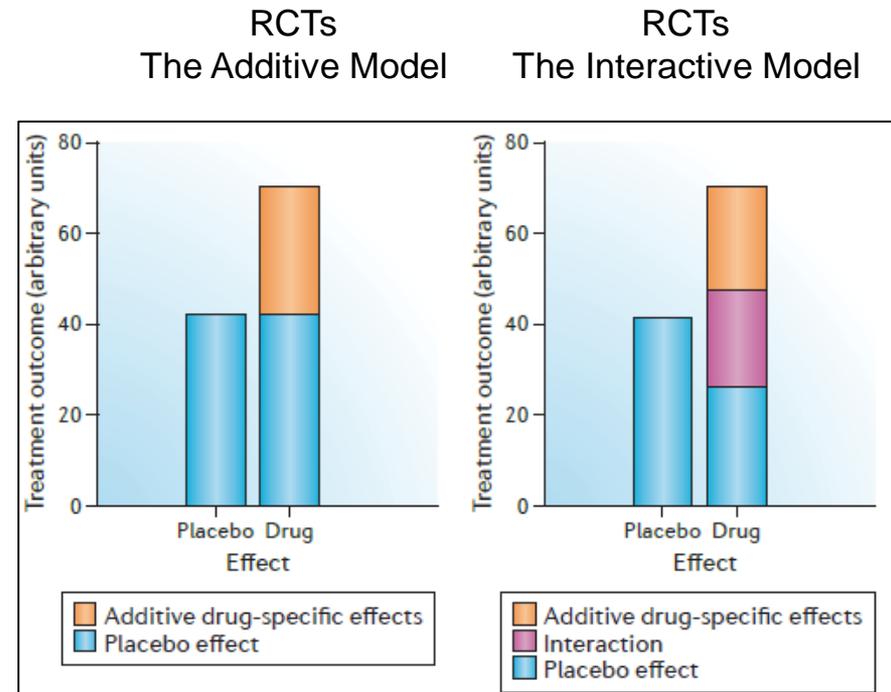
Is Placebo Response the Same for Each Treatment Group?

- Implicit assumption is that the placebo response is the same in drug arm and placebo arm
 - If not, then the effect size could be over- or under-estimated
- If you eliminate placebo responders, do you also eliminate drug responders?
- Is there an interaction between drug and placebo mechanisms?

Genetics of Placebo Response Challenges

Interpretation of RCTs

- Genome-related mediators that affect the response to placebo – the “Placebome”
- Evidence suggests overlap between placebo, drug treatment and disease networks
- Drug could change a placebo response and a placebo response could modify a drug response
- Is the key assumption of RCTs that placebo effects in placebo group are identical to placebo effects in the drug group valid?



P. Enck et al. Nature Reviews| Drug Discovery 2013;12:191-204

Neurological-based complex interactions between placebo and active treatment responses: Brain imaging may be used to predict placebo responders and subjects with higher propensity to active drug response

Study 1:

- Baseline resting –state fMRI (rs-fMRI) in patients with knee osteoarthritis (OA) followed by 2 week placebo treatment
- Placebo responders had significant higher connectivity from the right midfrontal gyrus to the rest of the brain.
- Placebo Response model of brain connectivity developed and tested in Study 2

Study 2:

- Baseline rs-fMRI in knee OA patients followed by randomization to placebo or active treatment
- Placebo response of brain connectivity model accurately (95%) predicted placebo responders and non-responders
- Comparison of model-predicted placebo response in subjects receiving active treatment with the actual response showed 3 subsets:
 - Active drug enhanced predicted placebo response
 - Active drug had no effect relative to predicted placebo response
 - Active drug diminished predicted placebo response

Can Study Designs Help Reduce Placebo Response?

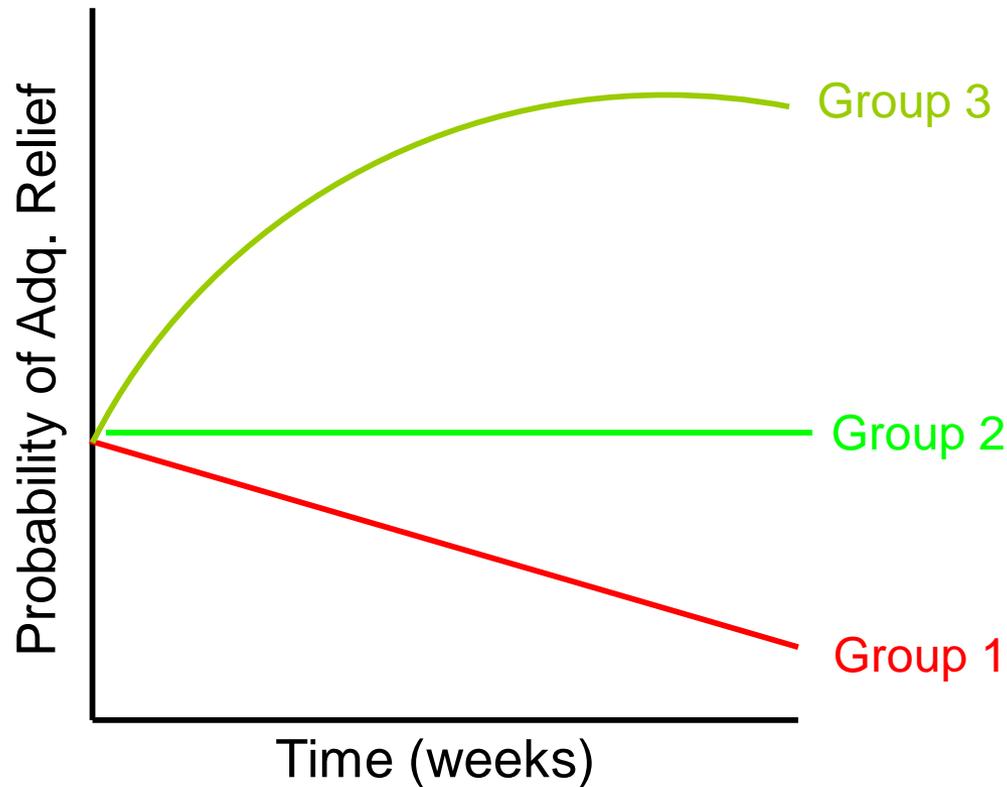
- Study designs to reduce placebo response :
 - Run-in (eliminate placebo responders and noncompliant subjects, then randomize 1:1 to treatment)
 - Sequential parallel comparative design (first half of study more than 50% assigned to placebo, second half placebo non-responders randomly assigned 1:1 to placebo or active)
 - Double-blind, variable duration, placebo run-in
 - Using inclusion/exclusion criteria that eliminate subjects more likely to be placebo responders (e.g., low baseline score)
 - Randomized withdrawal
 - Hidden vs open dosing
 - Hidden dosing silences expectation mechanism

Alternative Methods for Analysis

- Model placebo response and drug response
- Evaluate factors affecting placebo response (e.g., genetics)
- Analyze the outcomes of a trial using the center-specific level of placebo response as weighting factor to estimate the treatment effect
 - data generated in centers with high placebo response - considered as less informative than data generated in the other centers
- Control for some factors (e.g., baseline score, genetics) that affect placebo response

Describing Placebo Response

Time Course of Adequate Response in Patients Receiving Placebo



Conclusions and Next Steps

- Understanding placebo response has a potential to reduce Phase 3 failures
- Placebo response has physiological and psychological mechanisms that need to be considered
- Eliminating all placebo responders may also decrease the probability of demonstrating efficacy for a drug
- Characterizing placebo response over time and controlling for some factors may improve the ability to show a treatment effect
- Characterizing the genetic and neurobiological mechanisms of interaction between active treatment and placebo may minimize the potential confounding effects of placebo on randomized controlled trials
- Collaboration across disciplines (including SIPS) will help in advancing the science