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# Disclosures

In the past 3 years Dr. Sanacora has served as consultant to Ancora, Aptinyx, Atai, Axsome Therapeutics, Biogen, Biohaven Pharmaceuticals, Boehringer Ingelheim International GmbH, Bristol-Myers Squibb, Clexio, Daiichi Sankyo, Denovo Biopharma, EMA Wellness, Embark, Engrail Therapeutics, Freedom Biosciences, Gilgamesh, Intra-Cellular Therapies, Janssen, KOA Health, Levo therapeutics, Lundbeck, Merck, MiCure, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Otsuka, Perception Neuroscience, Praxis Therapeutics, Relmada Therapeutics, Sage Pharmaceuticals, Seelos Pharmaceuticals, Taisho Pharmaceuticals, Tetricus, Transcend Therapeutics, Usona Institute, Valeant, Vistagen Therapeutics, and XW Labs; and received **research contracts** from Johnson & Johnson/Janssen, Merck, and the Usona Institute over the past 36 months. Dr. Sanacora **holds equity** in Biohaven Pharmaceuticals, Freedom Biosciences, Gilead, Relmada, and Tetricus. He is a co-inventor on a **US patent** (#8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by Yale University Office of Cooperative Research. **Yale University has a financial relationship** with Janssen Pharmaceuticals and may receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office.

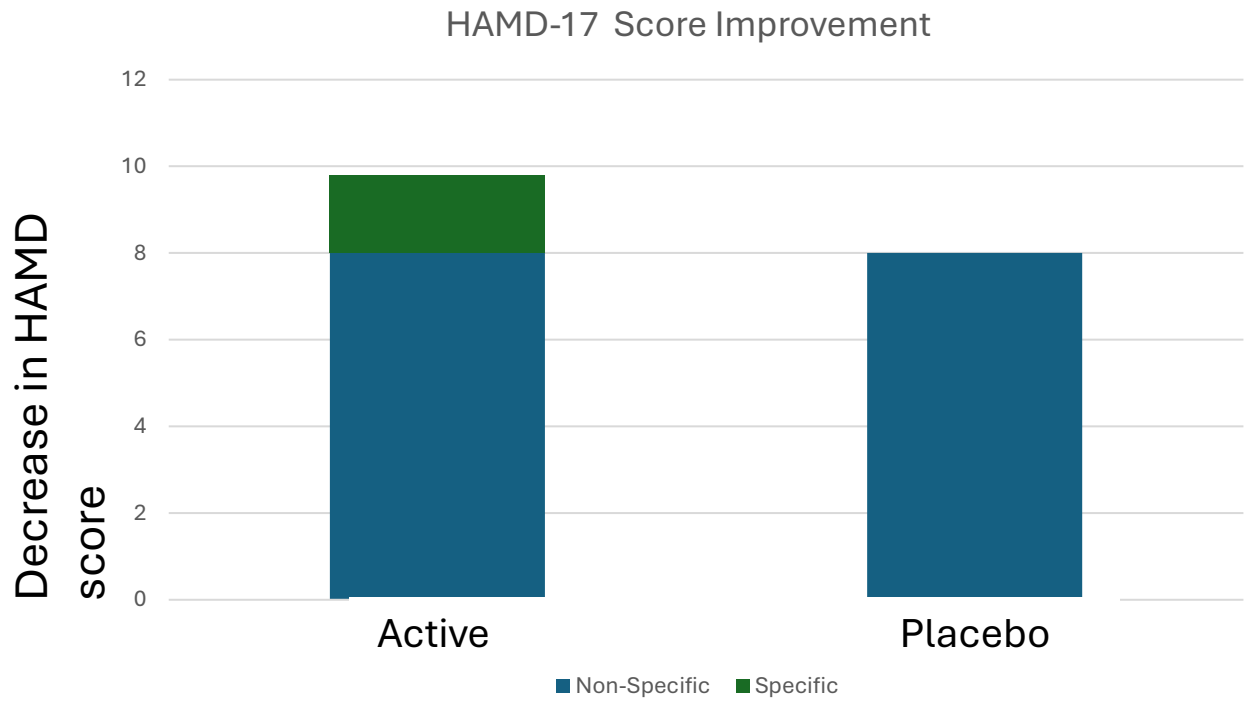
# Balancing Act

- Speed and cost of trial
- Insuring appropriate participant selection

- Optimal study design to answer specific questions for approval and support marketing
- Attracting the right patients/participants
- Burden on clinical sites

# Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis

Marc B Stone,[1] Zimri S Yaseen,[1] Brian J Miller,[2] Kyle Richardville,[3] Shamir N Kalaria,[4] Irving Kirsch[5]




Stone et al., BMJ. 2022 Aug 2;378

**ABSTRACT**

**OBJECTIVES**

To characterize individual participant level response distributions to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration from 1979 to 2016.

**DESIGN**

Individual participant data analysis.

**POPULATION**

232 randomized, double blind, placebo controlled trials of drug monotherapy for major depressive disorder submitted by drug developers to the FDA between 1979 and 2016, comprising 73 388 adult and child participants meeting the inclusion criteria for efficacy studies on antidepressants.

**MAIN OUTCOME MEASURES**

Responses were converted to Hamilton Rating Scale for Depression (HAMD17) equivalent scores where other measures were used to assess efficacy. Multivariable analyses examined the effects of age, sex, baseline severity, and year of the study on improvements in depressive symptoms in the antidepressant and placebo groups. Response distributions were analyzed with finite mixture models.

**RESULTS**

The random effects mean difference between drug and placebo favored drug (1.75 points, 95% confidence interval 1.63 to 1.86). Differences between drug and placebo increased significantly (P<0.001) with greater baseline severity. After controlling for participant characteristics at baseline, no trends in treatment effect or placebo response over time were found. The

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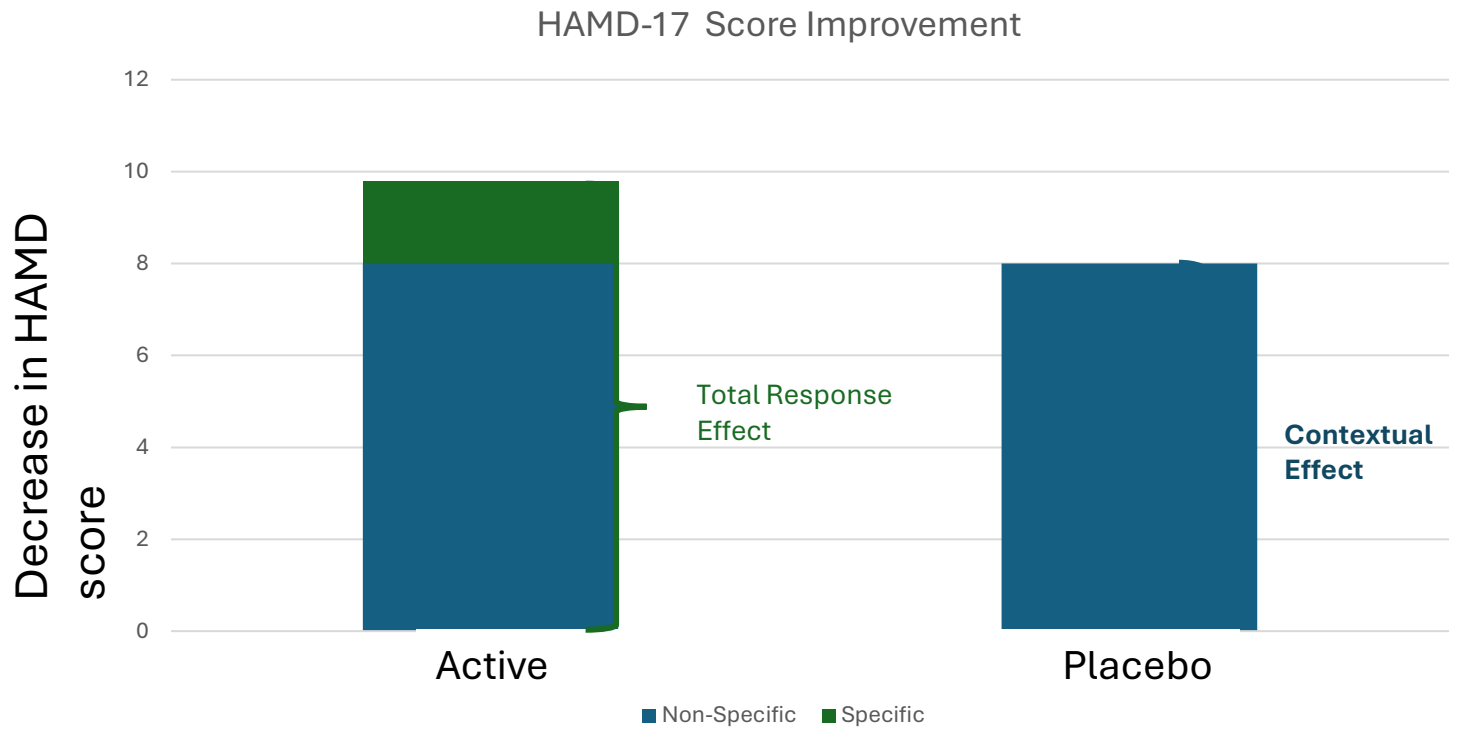


Proportional Contextual Effects (PCE)

PCE=CE/TRE

TRE=9.8 points
CE=8 points

PCE = .82

82% of the effect could be attributed to Contextual Effects

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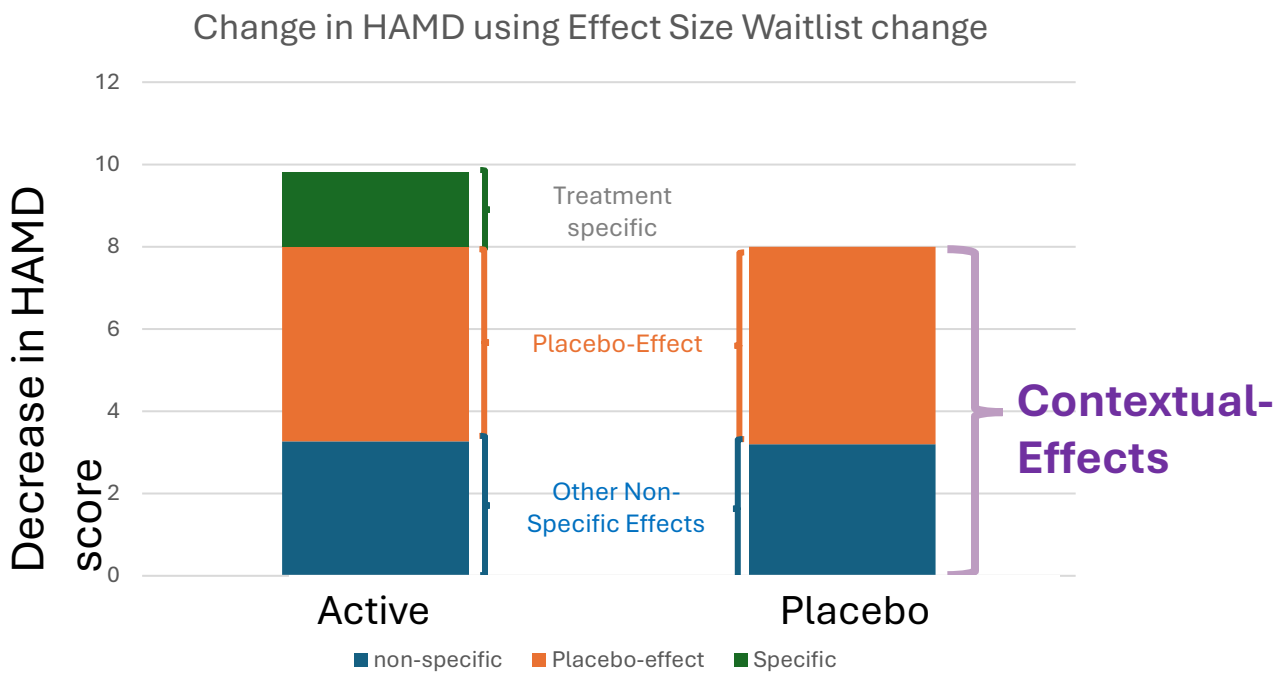
# What Constitutes the Proportion Attributed to Contextual (Non-specific) Effect?




Placebo Effects

- Expectations
- Conditioning
- Therapeutic Alliance

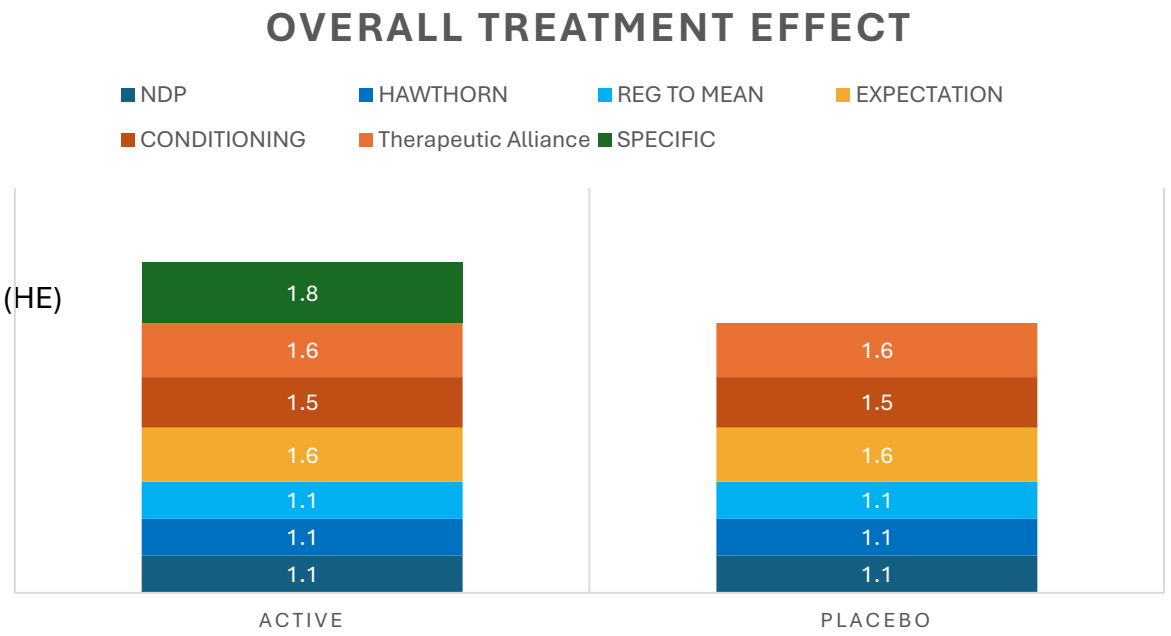
Non-Specific Effects

- Natural Progression of Disease
- Regression to the Mean
- Hawthorne Effect

Accounts for ~1/3 the overall response from wait-list studies in MDD, Rutherford et al. J Psychiatr. Res. 2021

# Complexity of Treatment Response

- $\text{Response} = SE + [SDE_{[NDP+RM+HE]} + EXP_{[ExC + ExU]} + CND_{[CdS + CdG]} + TA_{[BnG+EDF+PEB][Pcpet+Pcas+PP+PS\}}]$




Response = Specific Effect (SE) + Non-specific Effect (NE) + (SExNE)

NE = Study and Demographic Effects (SDE) + Placebo Effects (PE)

SDE = Natural History of Disease (NHD) + Regression to the Mean (RM) + Hawthorne Effect (HE)

PE = Expectations (Ex) + Conditioning (Cd) + Therapeutic Alliance (TA)

EXP = Conscious Ex (Cex) + Unconscioius Ex (Uex)

Cd = Specific (CdS) + Generalized (CdG)

TA = Patient Characteristics (PC) + Clinician Characteristics (CC) + (PCxCC)

PC = Biological and Genetic (BnG) + Ethnic and Demographic Factors (EDF) + Previous Experiences and Beliefs (PEB) [MindSet]

CC = Projected Competence (PCpet)+ Projected Compassion (Pcpas) + Projected Presence (PP) (time of visits, attentitiveness) + Physical Setting (set)

$\text{Response} = SE + SDE_{[NHD+RM+HE]} + EX_{[ExC + ExU]} + Cd_{[CdS + CdG]} + TA_{[BnG+EDF+PEB][Pcpet+Pcas+PP+PS\}}$

# Attracting the Right Participants

- Severity
  - More Severe patients typically afford greatest signal detection
    - However, usually a less pristine population with con-meds, multiple treatment failures and comorbidities
- Stability
  - Patients with more stable conditions usually afford greater signal detection
    - However, more stable patients with fewer socio-economical challenges also usually have more treatment options
- Enthusiasm for the study (Would I refer my Mother, Brother, Wife, or Child to this study?)
  - This can dramatically help with recruitment and may even attract a more severe population
    - However, may also increase expectations and barring a high degree of functional unblinding may increase the placebo response rate

# Study Conduct

- More-Strict Eligibility Criteria
  - This could improve the signal and decrease proportion of contextual effects
    - However,  the hurdles could limit the involvement of more severely ill patients
- Decreased Visits
  - Shown to reduce placebo response rates
    - However, more severe patients may be hesitant to participate or have increased risks that require closer observation
- Centralized Raters.
  - Can increase consistency across sites and decrease chances of functional unblinding
    - However, can be difficult for some of the more severely ill patients to complete centralized ratings. A caveat, functional unblinding could work in favor of separating active treatment.

# Purposefully Addressing Placebo Response

## Attempts to Mitigate Placebo Response

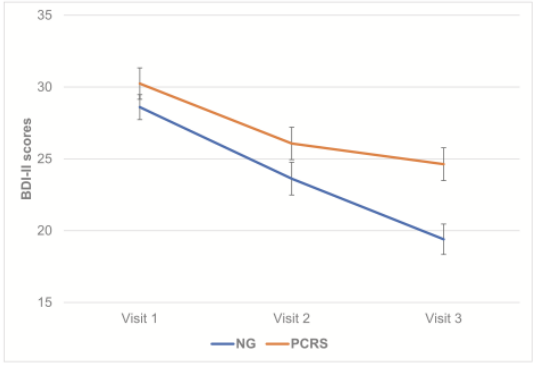



**Fig. 2 Mean BDI-II scores across visits.** The overall linear decrease was significantly smaller in the PCRS group than the NG. BDI Beck Depression Inventory, PCRS Placebo Control Reminder Script, NG Non-intervention Group. Note: Error bars reflect standard errors.

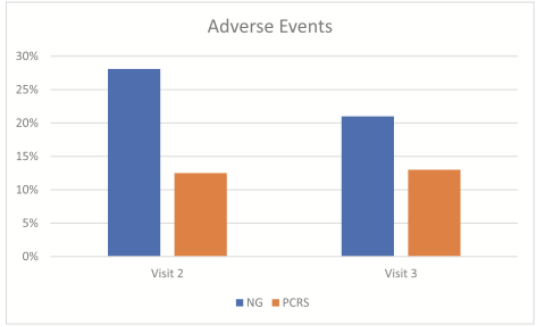



**Fig. 3 Adverse events reported at Visit 2 and at Visit 3.** The percentage of reported adverse events was significantly lower in the PCRS group than the NG at Visit 2. The percentage of reported adverse events did not significantly differ between groups at Visit 3. PCRS Placebo Control Reminder Script, NG Non-intervention Group.

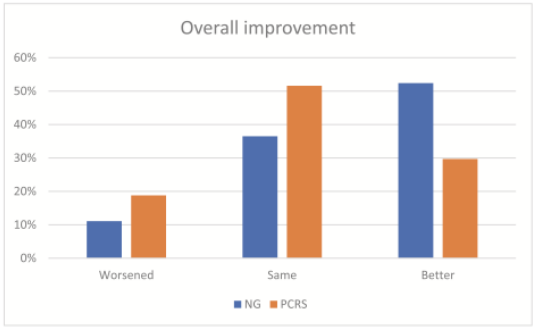



**Fig. 4 Subjective beliefs about performance.** Compared to the NG, a significantly larger proportion of the PCRS group reported staying the same and a significantly smaller proportion of the PCRS group reported getting better. PCRS Placebo Control Reminder Script, NG Non-intervention Group.

Cohen EA, Hassman HH, Ereshefsky L, *et al.* Placebo response mitigation with a participant-focused psychoeducational procedure: a randomized, single-blind, all placebo study in major depressive and psychotic disorders. Neuropsychopharmacology (2021) 46:844 – 850

# Pulling the Signal out of the Noise

- Study Recruitment
  - Target Appropriate Patients
    - Make study appealing to more severe patients
    - Chose sites that have appropriate access to desired patient population
  - Screen to Insure Appropriate Patients
  - Attempt to Accurately Predict Proportional Contextual Effects and Include in Power and Sample Size Calculations

- Study Conduct
  - Attempt to Minimize Proportional Contextual Effects
    - Reducing Expectations
    - Reducing Therapeutic Alliance
    - Acknowledging Conditioning Effects
  - Attempt to decrease variability in ratings