Considerations on choosing the appropriate setting from which to enroll patients

Gerard Sanacora M.D., Ph.D.

George D. Gross and Esther S. Gross Professor of Psychiatry, Yale University School of Medicine

Director Yale Depression Research Program

Co-Director Yale New Haven Hospital Interventional Psychiatry Service

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.

Target Population of Study

Specific Inclusion Criterion (Is this a study specifically Targeting SI?)

vs

Specific Exclusion Criterion (Is this a broader study hoping not to exclude patients with SI?)

Range of Suicidal Ideation and Behavior Inclusion Considerations

- **Demographic Risk**
  -Age, gender, socio-economic factors
- **Personal History Risk**
  -Specific History of Suicide Ideation, Attempt
- **Current Ideation Risk**
  -Assessment by C-SSRS, MADRS, or Other SI specific Measures
  -Categories of SI Active, Passive, Intent, Plan

Challenges for Studies Aiming to Study Patients Considered at Serious Risk for Suicidal Behavior Population and Determination of Appropriate Setting

Special Considerations related to the fact that high level of SI commonly requires hospitalization

- Ethics
  - Overall Appropriateness (Do patients have the capacity to make the decision to participate?)
  - RTC with use of placebo
- Assessing level of Care Needed
- Timeline of risk
  - Transientness of intent and behavior
  - Longer-term risks

Pragmatic concerns

- Difficulty in matching clinical sites seeing these patients and research sites participating in clinical trials
- What is in it for the participants?

Determination of Appropriate Sites

Special Considerations related to the fact that high level of SI commonly requires hospitalization

- Do the Sites have the Appropriate Level of Direct Access to Emergency Room Setting For Recruitment?
- Do The Sites have the Appropriate Level of Access to Inpatient Units for admission if/when needed?
- Is there an Appropriate Level of Access access to stepdown care facilities?

Pragmatic Challenges in Recruiting this Population that Influence the Choice of Setting

What is the level of Suicidal Ideation or Suicidal Behavior that is being considered for the study

- SI is not really on a linear-scale but we try to make it such and Risk goes beyond SB.
  - What are we really asking/studying in terms of SI and SB
  - What is our real concern related to SI and SB

Will the patients be considered at Imminent risk of self-harm

- Need of an inpatient setting for rapid access to inpatient hospitalization if necessary
  - Not typical sites for clinical trials

Examples and characteristics of trials successful in recruiting this population

- Industry (Aspire Trials, add-on to SoC treatment)
- NIH (Wilkinson, Price)

- **Examples and characteristics of trials that have struggled**

- ***What is in it for the participants?***

Complicating Factors Related to Setting and the Interpretation of Studies in this Population

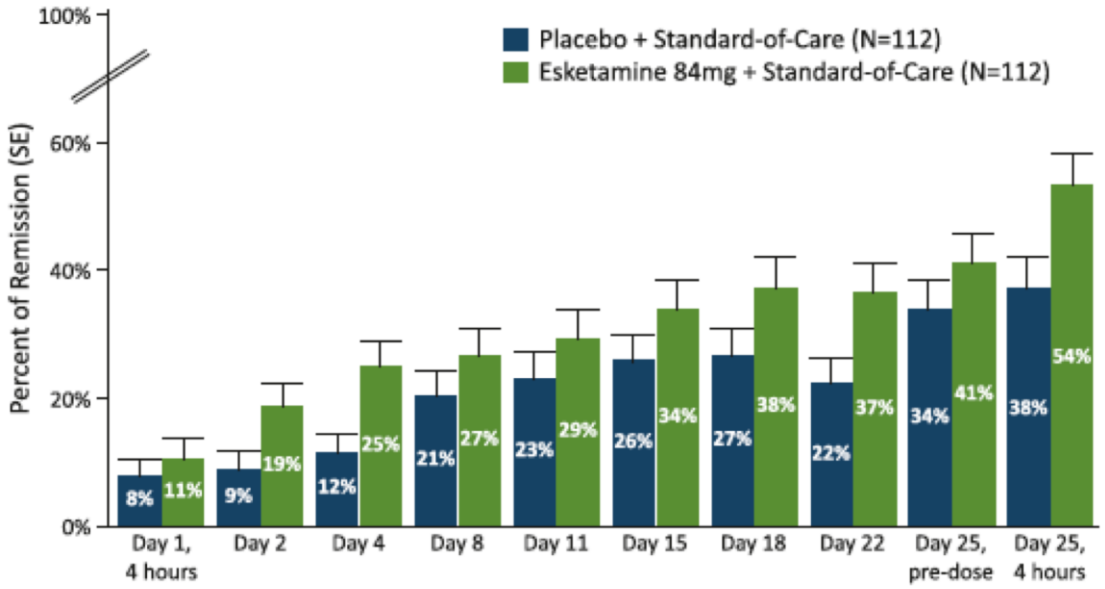
- **Relationship of study design with study outcome**
  - Inpatient stays can lead to extremely large magnitude contextual effects

  - **What is the outcome measure**
    - Item-10 MADRS, Specialized Suicide assessments, Behaviors…
  - **Time of outcome measurements**
    - Immediate response, weeks out, months out

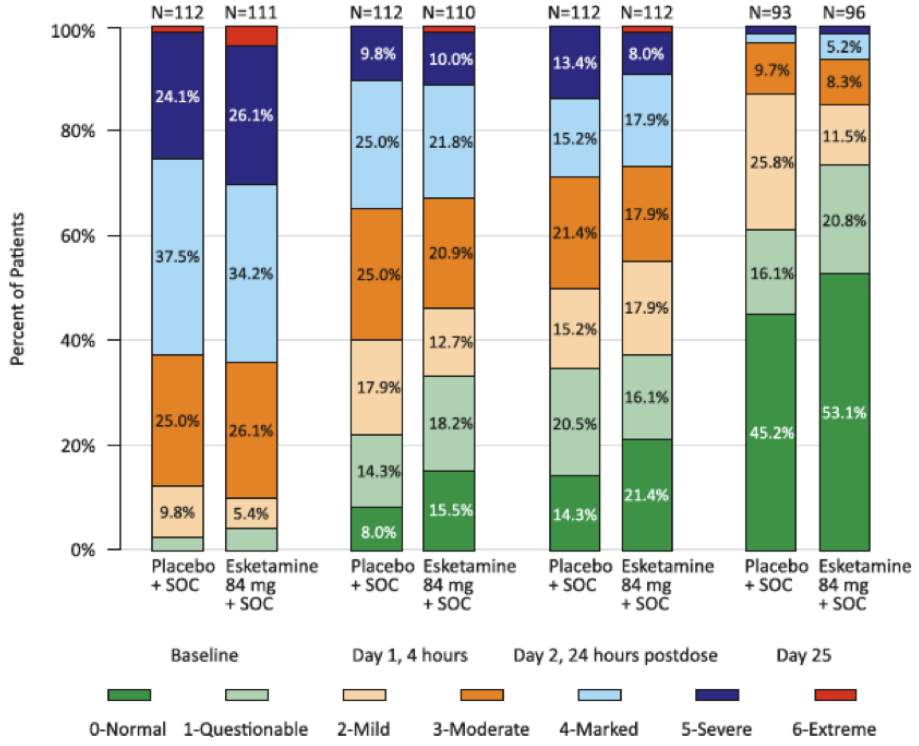
- **Inpatient studies can be extremely expensive which can influence treatment course and outcome**

Example from the Spravato Aspire I trial

Supplementary Figure 4. MADRS Remission Rate During the Double-Blind Treatment Phase



Supplementary Figure 6. Frequency Distribution of CGI-SS-r Score at Baseline, 4 and 24 Hours Post First Dose, and Day 25 (Observed Cases)



CGI-SS-r = Clinical Global Impression – Severity of Suicidality – Revised; SOC = Standard-of-Care

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Complicating Factors Related to Setting and the Interpretation of Studies in this Population

- **Relationship of study design with study outcome**
  - Inpatient stays can lead to extremely large magnitude contextual effects
    - Examples from Aspire studies showing markedly decreased SI in most all patients
  - **What is the outcome measure**
    - Item-10 MADRS, Specialized Suicide assessments, Behaviors…
  - **Time of outcome measurements**
    - Immediate response, weeks out, months out

- **Inpatient studies can be extremely expensive which can influence treatment course and outcome**

Implementing Appropriate Mitigation Measures to Reduce the Risk in This Population

What have we learned about the actual risks of including this population in clinical trials.

- **Changes in suicidal ideation and behavior as related to trial participation**
  - "Now that I am getting all this support and care by your staff, I am feeling more hopeful and less like I want to end my life"
- **High rates of SAEs**
  - Rates of SAEs can top 50% if these studies include longer follow up periods. Is that tolerable?
- **Likelihood of hospitalization or re-hospitalization.**
  - Rates of re-hospitialization is high in these studies. Who assumes the costs?
- **Level and allowance of transition care**
  - Importance of considering the various methods of managing transition care/ IOP, requiring Outpatient care prior to enrollment.
- **Need for inpatient setting or for rapid access to inpatient setting**
  - Not typical sites for clinical trials