Developing pharmacological treatments for the rapid reduction of suicidal ideation in depression

Unique Methodological Considerations in this Novel Indication

Methodological Considerations in this Novel Indication

1. Defining what are we really hoping to achieve

2. Relevance of short-term outcome measures to longer-term outcomes

3. Challenges related to the interpretation of commonly used data ascertainment methods

What Issue are we Actually Hoping to Address

- **Behavior**

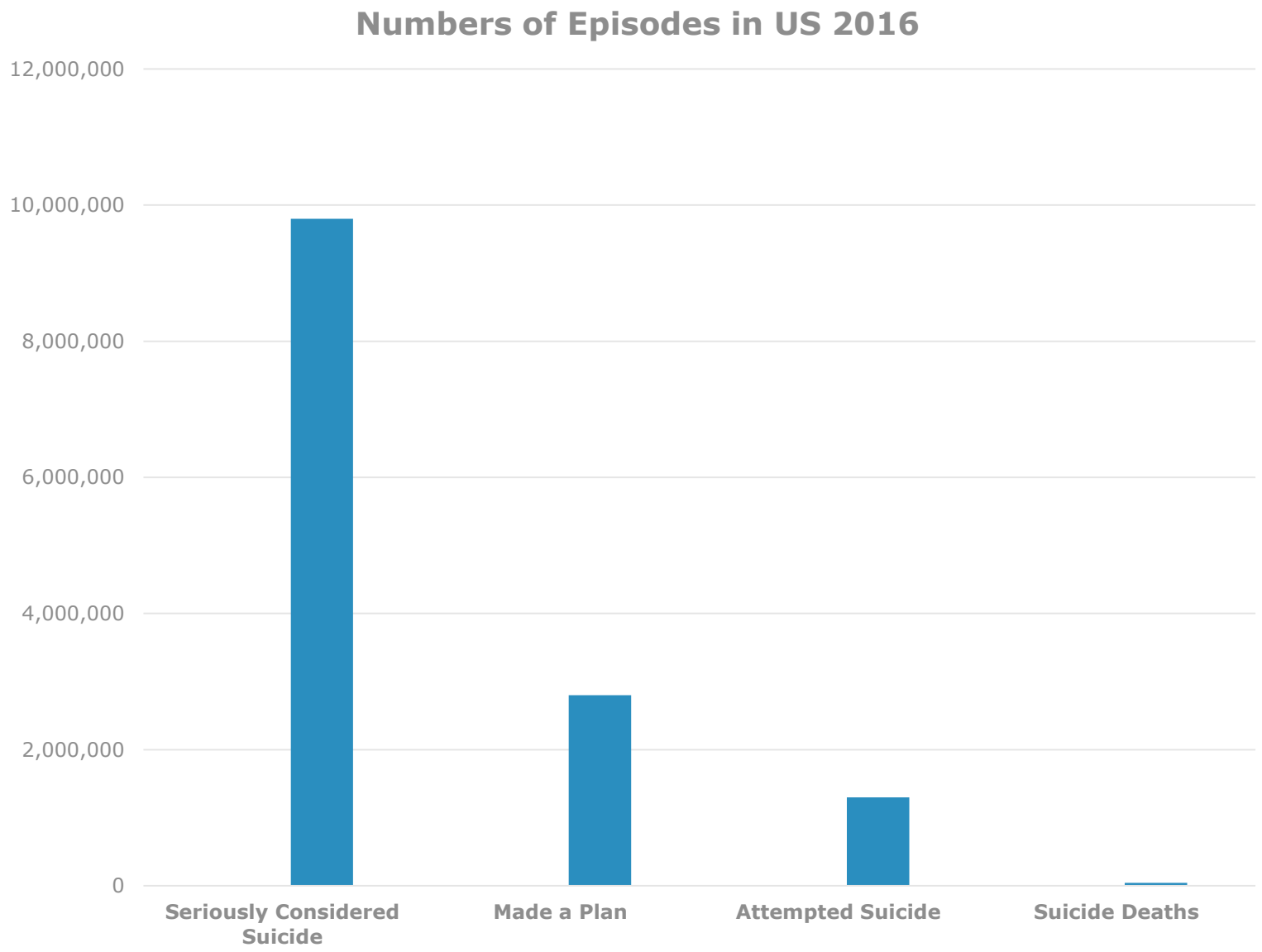
- Age standardized suicide rate worldwide was 12 per 100,000 individuals in 2015[1]
- There were more than 800,000 deaths from self harm, the 14 leading cause of global mortality
- The global 12-month prevalence of nonfatal suicide attempts is approximately 0.3 to 0.4%, and the lifetime prevalence is 3%.
- In the United States, there are more than 30 suicide attempts for each suicide death

- **Ideation**

- WHO community surveys in 21 countries (n >100,000 individuals) found the 12-month prevalence of suicidal ideation was approximately 2%, and that lifetime prevalence was 9%
- Individuals with a lifetime history of suicidal ideation, have approximately a 30% probability of ever making a suicide attempt
- In 2013, suicide ideation constituted nearly 1% of all adult ED visits in US, conservative costs of $2.2 billion

1. GBD 2015 Mortality and Causes of Death Collaborators. Lancet 2016; 388:1459., 2 Borges G, et al. J Clin Psychiatry 2010; 71:1617., 3 Han B, , et al. J Psychiatr Res 2016; 77:125, 4. Nock MK, Br J Psychiatry 2008; 192:98, 5. Owens PL, STATISTICAL BRIEF #220 https://www.hcup-us.ahrq.gov/

Relative Numbers and Costs of Suicidal Ideation and Behavior in US



Calculated annual public cost of suicide attempts and suicides in the United States is approximately $93.5 billion in 2013. Similar calculations in other industrialized countries. Shepard DS et al. **Suicide** Life Threat Behav. 2016 Jun;46(3):352-62

/www.cdc.gov/violenceprevention/suicide/fastfact.html

Risk Factors Associated with Suicide

- A **prior history of attempted suicide-** the strongest single factor predictive of suicide
  - Risk of dying by suicide is approximately 100 times than that of the general population within one year of an index attempt
- **Previous Psychiatric Hospitalization-**lifetime risk of suicide is 8.6 percent in patients who have had a psychiatric inpatient admission involving suicidal ideation
  - Up to 41 percent of those who committed suicide had been psychiatric inpatients within the previous year, and as many as 9 percent of suicides occurred within one day of discharge from psychiatric inpatient care
- **Other Identified Risk Factors include**, Marital Status, Belonging to a Sexual Minority, Occupation, Military Service, General Medical Comorbidities, Diagnosis of Personality Disorder, Chronic Pain, Traumatic Brain Injury, Childhood Abuse, Location of Residence, Access to Lethal Means (Firearms), and Family History of Suicide.

1 World Health Organization. Preventing Suicide: A Global Imperative. Geneva, Switerland. 2014. www.who.int, 2. Hawton K, Handbook of Affective Disorders, 2nd ed, Pa nkel, ES (Ed), Guilford, New York 1992. p.635., 3. Bostwick JM et al. Am J Psychiatry 2000; 157:1925, 4. Pirkis J, Burgess P. Br J Psychiatry 1998; 173:462. 5. Schreiber J, Culpepper L, Suicidal ideation and behavior in adults – UpToDate 2019

Protective Factors

- Social Support
- Being a Parent
- Religiosity

Identified Risk Symptoms

- Feelings of **worthlessness and hopelessness**
- Combination of **depression and anxiety**
- **Psychosis** (delusions, command auditory hallucinations, paranoia) regardless of the specific diagnosis

1. Rubio JD et al. Br J Psychiatry 2018; 212:279, 2. Bolton JM et al. Clin Psychiatry 2008; 69:1139. 3. Bolton JM et al., Depress Anxiety 2008; 25:477, 4. Schreiber J, Culpepper L, Suicidal ideation and behavior in adults – UpToDate 2019

Scales

- **Attempts to Predict Future attempts based on Identified Risk Factors**
  - **MINI suicidality module**-19 item instrument, largely historical with time references
  - **SAD PERSON scale-**(Sex, Age, Depression, Previous attempt or psychiatric care, Excessive drugs, (ir)Rational thinking, Separate/divorced/widowed/organized attempt, No social supports, Stated intent
  - **Manchester Self Harm Rule and Sodersjukhuset Self Harm Rule-** designed for ED triage
  - **Motto's Risk Estimator for Suicide-** queries 15 empirically derived variables predicting suicide
  - **Suicide assessment scale (SUAS)-**20 items assessing suicidality over time, evaluating both observed and reported symptomatology and designed to to be sensitive to change in suicide-related symptoms over time. (i.e. Hypersensitivity, resourcefulness, frustration tolerance)
  - **Suicide Intent Scale (SIS)-**15 items mix of objective and subjective geared largely to assessing intended lethality of event after an attempt as predictor of future attempts.
- **Attempts to use Theoretical Constructs related to suicidal behavior**
  - **Beck Hopelessness-** 20 Questions
  - **Beck Scale for Suicidal Ideaton-19** Questions (2 additional descriptive questions)-measures active and passive suicidal desire as well as suicidal preparation
  - **Adult Suicidal Ideation Questionnaire (ASIQ**)-25 items self-report considers mainly ideation as a risk factor for behavior
  - **Reasons for Living Inventory-** various versions Focuses primarily on protective factors, geared to monitoring chronic suicidal ideation
  - **Interpersonal Theory of Suicide-** 3 fundamental domains affection, behavior, cognition.

FDA proposed categories as the standard for classifying suicidal ideation and behavior events.

Suicidal ideation

1. Passive
2. Active: Nonspecific (no method, intent, or plan)
3. Active: Method, but no intent or plan
4. Active: Method and intent, but no plan
5. Active: Method, intent, and plan

Suicidal behavior

1. Completed suicide
2. Suicide attempt
3. Interrupted attempt
4. Aborted attempt
5. Preparatory actions toward imminent suicidal behaviors

Self-injurious behavior, no suicidal intent

Scales

- **Attempts to measure/capture changes in suicidal ideation and behavior**
  - **Columbia-Suicide Severity Rating Scale** (C-SSRS)-Considers Worst-point as major factor, considers SI and SB frequency and intensity as well as lethality
  - **Sheehan Suicidality Tracking Scale**-prospective assessment of treatment emergent-suicidal thoughts and behaviors self report, aim to have higher sensitivity. The clinically meaningful change version of the S-STS developed to test the anti-suicidal properties of new medications.

None of the assessment scales have proven to be extremely useful clinically

- Among patients who have presented to an emergency department after an episode of self harm, assessments by psychiatrists and emergency department staff have low sensitivity and specificity for predicting who will repeat self harm.

- A number of standardized scales have been proposed to evaluate suicide risk, but none is associated with a high predictive value.
  - "In the current review, we found no scientific support for the use of suicide risk instruments for predicting suicidal acts." but " The addition of an instrument in the suicide risk assessment may help to elicit more information, with relevant and uniform content, if integrated into a dialogue in which the clinician is able to provide ample space for the patient's narrative." Runeson et al. 2017

1. Runeson et al. PLoS ONE 12(7): e0180292., 2. Abarca C et al. **Medwave**. 2018 Sep 20;18(5):e7246

Suicide Ideation and Assessment Tool (SIBAT)

- A novel instrument for the assessment of suicidal ideation and behavior
  - Developed in collaboration with ~30 experts in suicide, psychometrics and statistics (the SIBAT Consortium) over a period of 4 years
- Computerized tool with patient-reported and clinician-rated components
- Patient components inform clinician assessments (including "CGI"-type endpoints)
- To be used as both an efficacy and safety measure
- Designed to detect rapid change
- Ongoing validation in adults and adolescents

Alphs L and the SIBAT Consortium

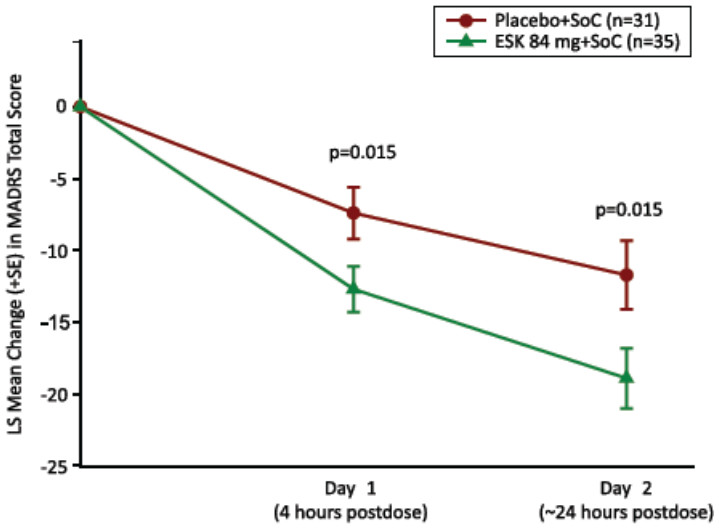
SIBAT: CGI-SS-R and Guide to Rating

CGI-Severity of Suicidality – Revised	
Considering your total clinical experience with suicidal patients and all information now available to you, how suicidal is this patient at this time?	
RATING	**GUIDE TO RATING**
0 Normal, not at all suicidal	• Not suicidal
1 Questionably suicidal	• Minimal ideations; little if any impulsivity for suicide, few risk factors and many protective factors ; and no impact on function.
2 Mildly suicidal	• Occasional ideations; little if any impulsivity for suicide; few risk factors; adequate protective factors and no or minimal impact on function
3 Moderately suicidal	• Intermittent ideations; with possible impulsivity for suicide; may or may not have plan or recent attempt*; several risk factors; protective factors may outweigh risk factors and some impact on function.
4 Markedly suicidal	• Regular ideations with intent or potential for impulsive actions for suicide; may or may not have plan or recent attempt*; multiple risk factors out weigh protective factors; and marked impact on function.
5 Severely suicidal	• Frequent ideations with intent; well worked out suicide plan; may or may not have recent attempt*; multiple risk factors out-weigh protective factors; and major impact on function.
6 Among the most extremely suicidal patients	• Nearly constant suicidal ideations and intent; well worked out plan and preparations underway or recent attempt*; and severe impact on function.

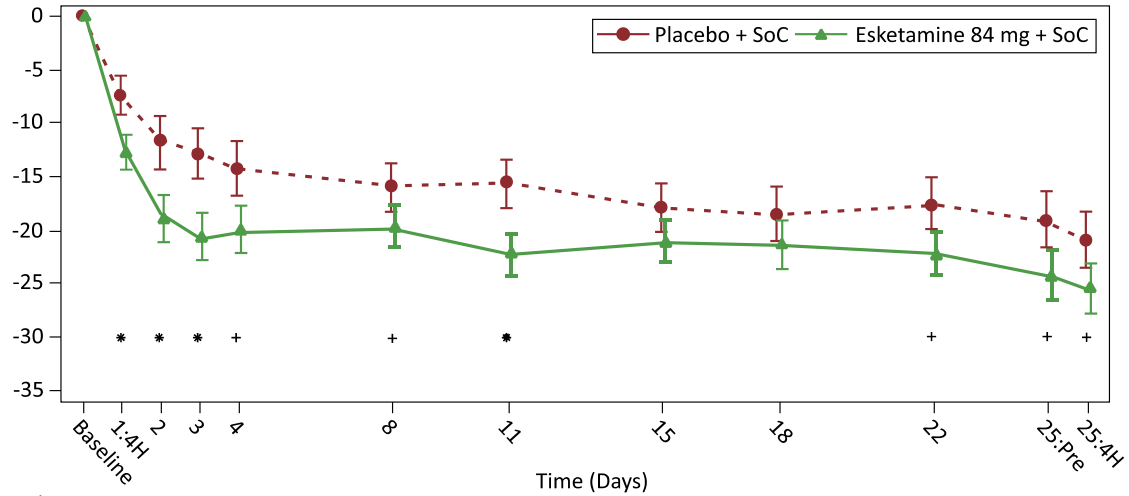
* Consider seriousness/lethality of any plan or suicide attempt in overall rating

Effects of Esketamine in Acutely Suicidal Patients

MADRS change from baseline to 4hr. and 24hr: ITT

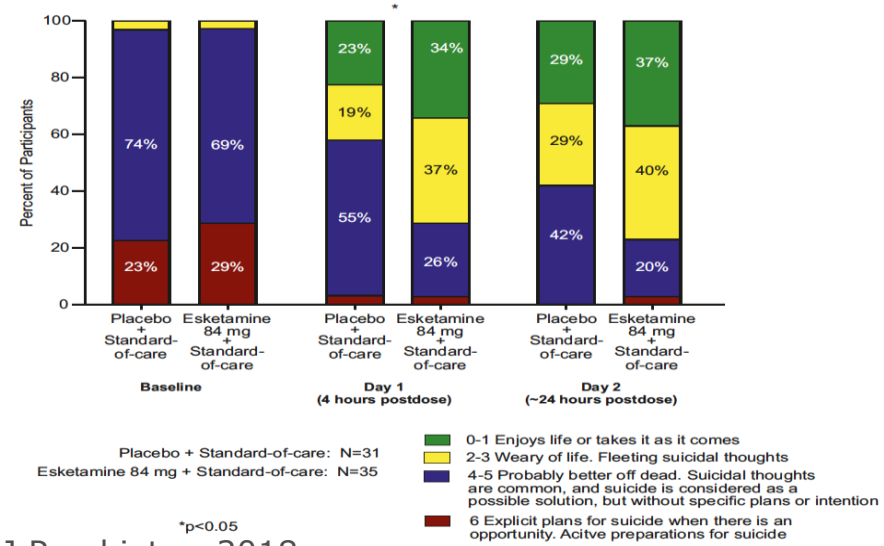


MADRS change over 25 days

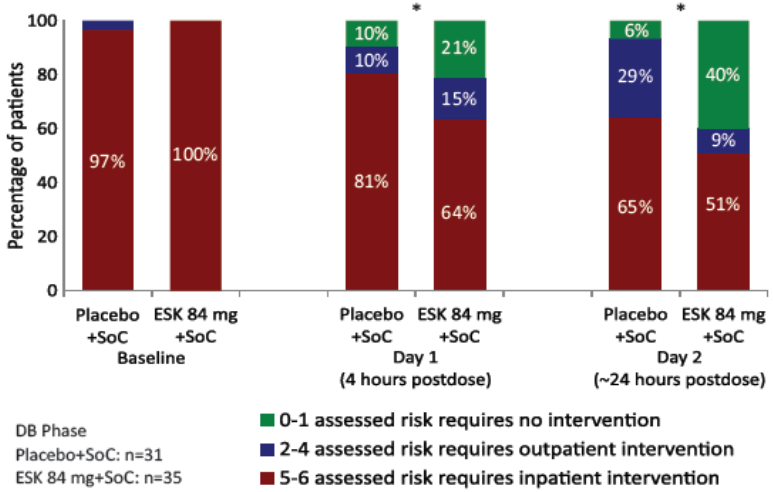


Number of Participants												
Placebo + SoC	31	31	31	31	31	31	31	31	31	31	31	31
sketamine 84 mg + SoC	35	35	35	35	35	35	35	35	35	35	35	35

MADRS: Item 10 at Baseline, day 1 (4Hr) and 24Hr: ITT



SIBAT: Frequency Distribution of Clinical Global Judgment of Suicide Risk at Baseline, day 1 (4Hr) and 24Hr: ITT



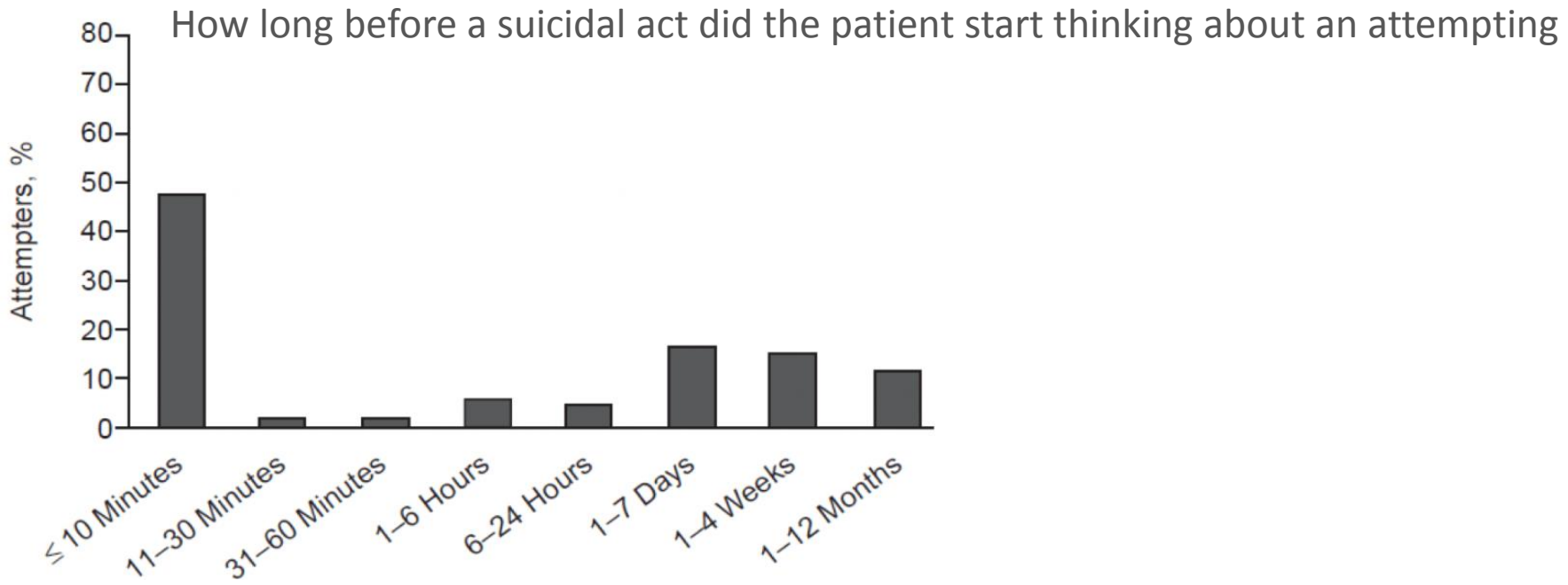
Canuso et al. Am J Psychiatry. 2018

Challenge

- **People often are motivated to deny suicidal thoughts for fear of repercussions**
  - Worrying family members
  - Involuntary or prolonged hospitalization
  - Loss of potential means

Challenge

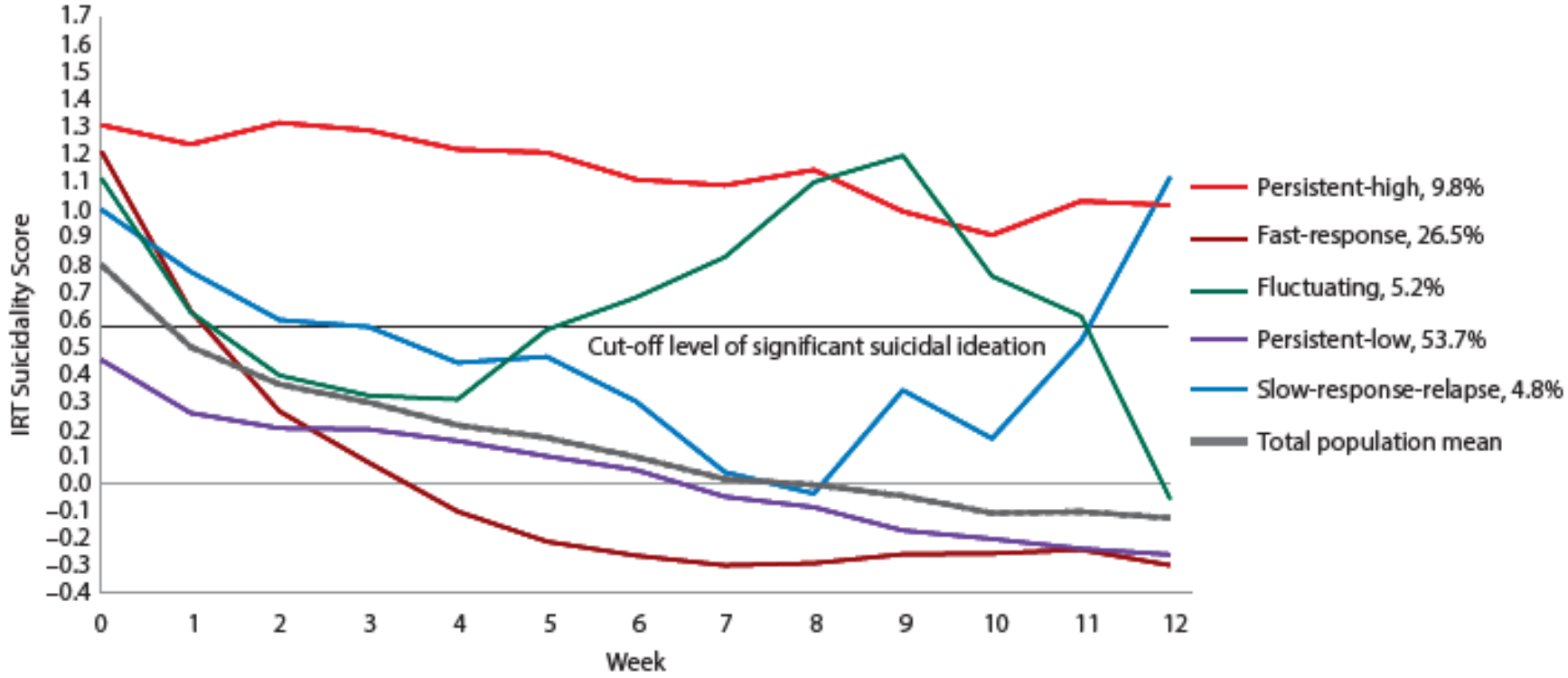
- **Suicidal thoughts can be quite transient in nature**



Deisenhammer EA, et al. J Clin Psychiatry. 2009;70(1):19-24

Trajectory of suicidal ideation response to SSRI and TCA antidepressant medications in the The GENDEP study

The Identified 5-Class GMM Trajectory Model Displaying the Status of Suicidal Ideation Among 811 Patients With MDD Throughout 12 Weeks of Antidepressant Treatment (IRT score > 0.575 represents significant suicidal ideation)[a]

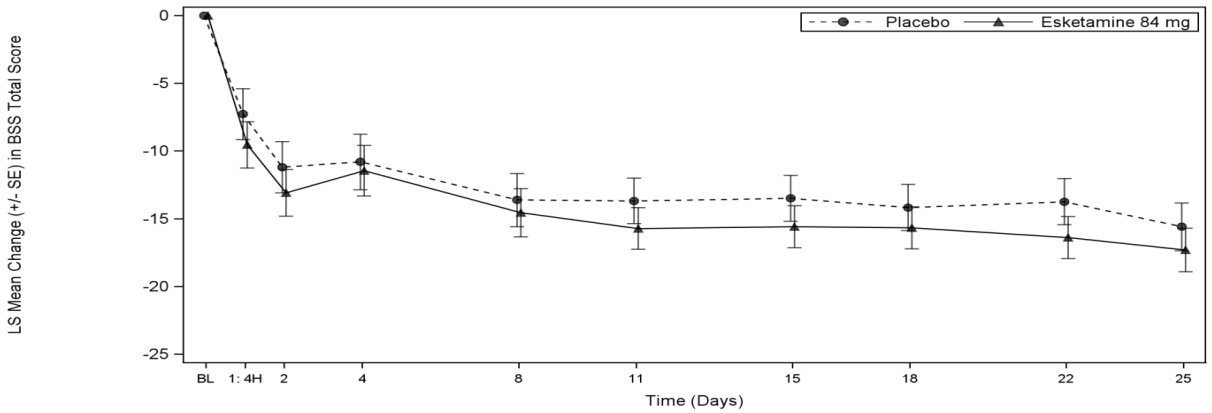


[a]The IRT suicidality score was based on the suicidal ideation items from 3 rating scales (see Supplementary Table 1). The percentage in the legend represents mean percent of the score.
Abbreviations: GMM = growth mixture modeling, IRT = item response theory, MDD = major depressive disorder.

Madsen T et al. J Clin Psychiatry 80:4, July/August 2019

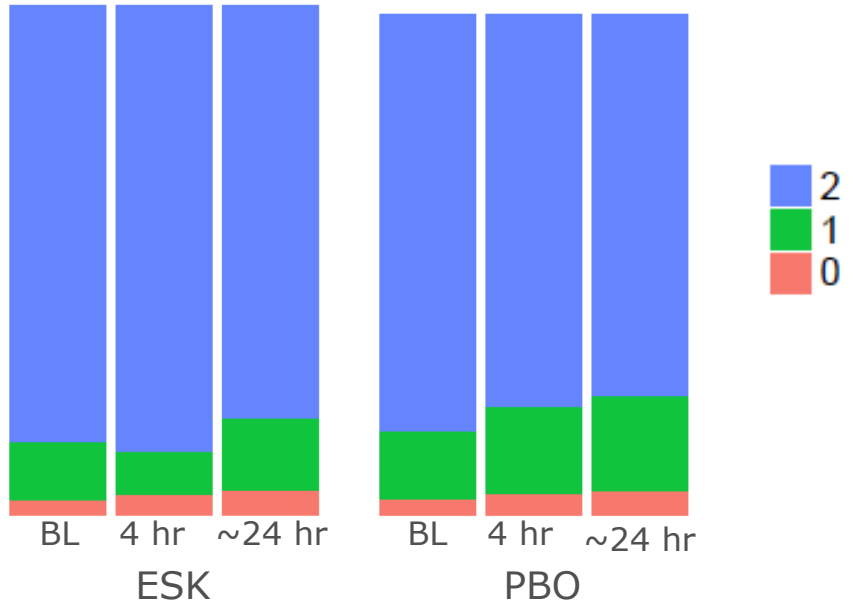
Suicidality Endpoint Must Have Sensitivity to Detect Rapid Change and Distinguish Treatment Effect

BSS LS Mean Change (LOCF)



Many BSS items insensitive to rapid change

11. Reasons for wanting to commit suicide



Janssen data on file

Challenge

- **The questions being asked are not always considered in context**

Suicidality Endpoint Must Consider the Context in which the Question is Asked

MINI suicidality module

Question B3 [Think (even momentarily) about harming or of hurting or of injuring yourself: with at least some intent or awareness that you might die as a result; or think about suicide (ie, about killing yourself)?]

- *"Not while I am here in the hospital with everyone trying to help me, I am not sure what I would do if I were home"*

Question B10 [Intend to act on thoughts of killing yourself?] obtained from the MINI

- *"Considering you took my shoe laces and belt, and are watching me around the clock, I don't really have any way of doing anything. So, I really haven't thought about acting on it, since coming into the hospital."*

Challenge

- **People may lack conscious awareness of their ideation and risk.**
  - Approximately 80% of people who die by suicide while in the hospital explicitly deny suicidal thoughts or intent in their last communication before dying.[9]

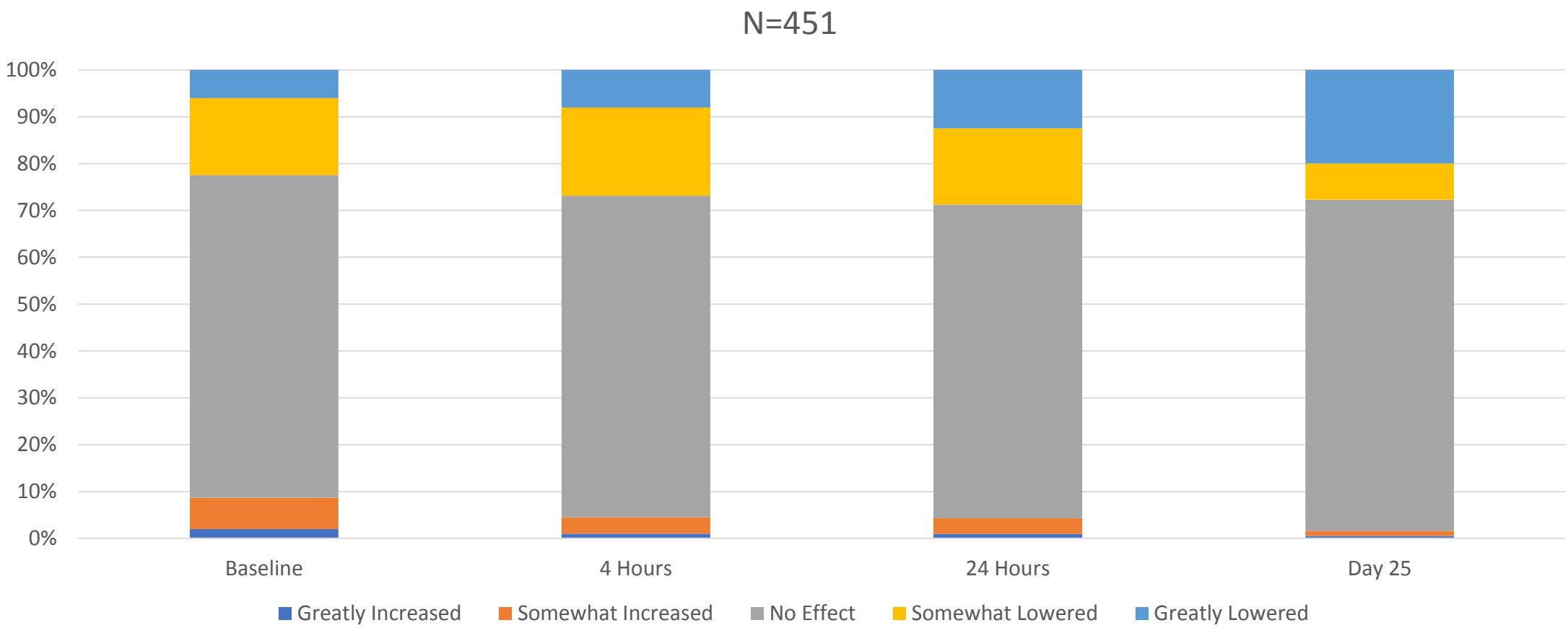
Scales

- **Attempts to use implicit measures associated with suicidal ideation**
  - Rorschach-Suicide constellation variables
  - Implicit Association Test (IAT)

Challenge

- **Administering the test could have therapeutic effects in and of itself.**

Did completing this assessment affect your desire to take your life in any way?



Janssen data on file

Recap

1. Need to clearly define what issue we are hoping to address with our studies in order develop the most relevant outcome measure
2. Need to address the timeframe we are specifically considering
3. Need to have assessment tools that consider the real-world challenges of this type of research

SIBAT Structure

Patient Modules (Modules 1 – 5)

- *Module 1:* About Me
- *Module 2:* My Risk/Protective Factors
- *Module 3:* My Current Thinking
- *Module 4:* My Actions
- *Module 5:* My Risk

Clinician Modules (Modules 6 – 8)

- *Module 6:* Clinician Interview
- *Module 7:* Clinical Global Impressions
  - Assessment of Frequency of Suicidal Thinking
  - **CGI-SS-R**
  - CGI-SR-I
  - CGI-SR-LT
- *Module 8:* Clinical Judgment of Optimal Suicide Management

Branching logic and modular structure allows for ease of use