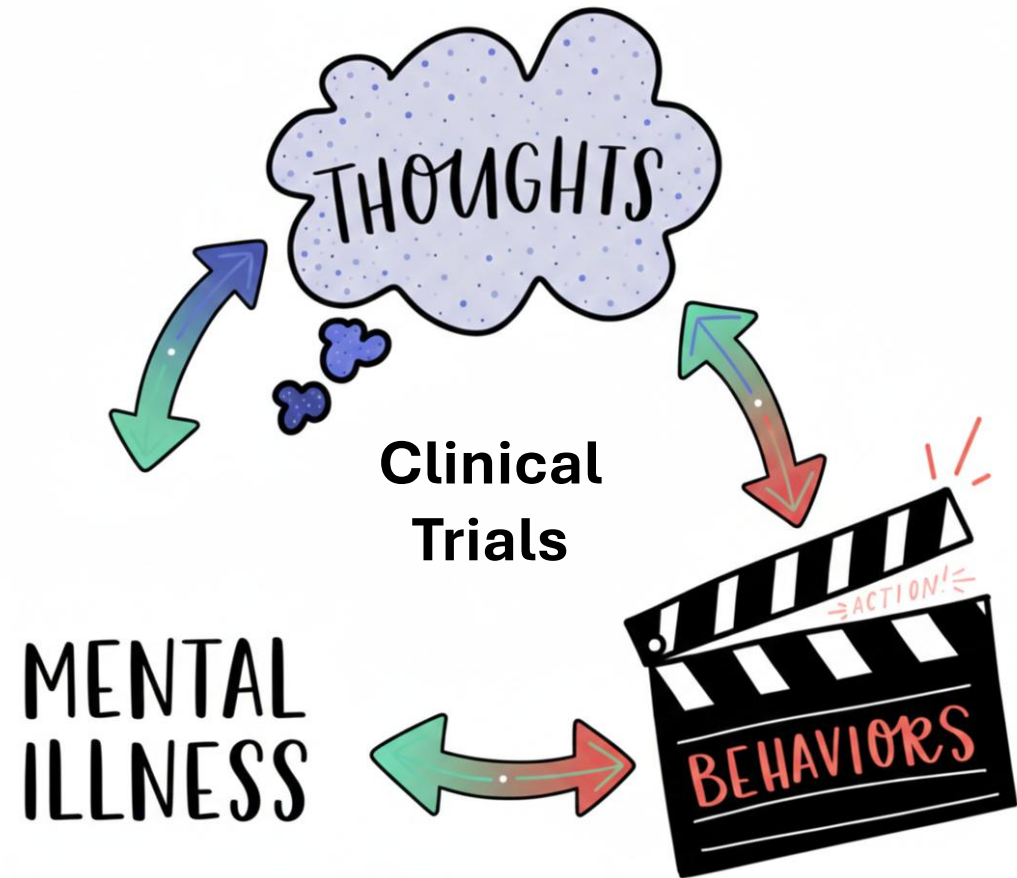


# Current Approach to Including Individuals with Suicidal Ideation and Behavior (SIB) in Clinical Trials



Steven T. Szabo, MD, PhD

# Disclosure

Employee of Neurocrine Biosciences. I am presenting in my individual capacity. The views expressed are my own and do not necessarily reflect the views of Neurocrine Biosciences, Inc.

# Current approach to suicidal ideation and behavior in clinical trials

The Columbia-Suicide Severity Rating Scale (C-SSRS) is an FDA-mandated "gold standard" for prospectively assessing suicide risk in clinical trials

<p><b>3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act</b></p> <p>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, <i>"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."</i></p> <p><i>Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?</i></p> <p>If yes, describe:</p>	<p>Yes    No</p> <p><input type="checkbox"/>    <input type="checkbox"/></p>
<p><b>4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan</b></p> <p>Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act</u> on such thoughts, as opposed to <i>"I have the thoughts but I definitely will not do anything about them."</i></p> <p><i>When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do? This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.</i></p> <p>If yes, describe:</p>	<p>Yes    No</p> <p><input type="checkbox"/>    <input type="checkbox"/></p>
<p><b>5. Active Suicidal Ideation with Specific Plan and Intent</b></p> <p>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.</p> <p><i>Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?</i></p> <p><i>What was your plan?</i></p> <p><i>When you made this plan (or worked out these details), was any part of you thinking about actually doing it?</i></p> <p>If yes, describe:</p>	<p>Yes    No</p> <p><input type="checkbox"/>    <input type="checkbox"/></p>

# Suicidal ideation and behavior (SIB) are excluded in depression trials

Depressed Patients with Suicidal Ideation



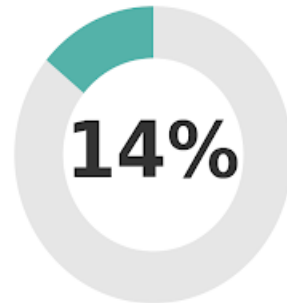
Registrational Trials Including Suicidality



Clinical Trials Mentioning Suicidality (Pre-2000)



Clinical Trials Mentioning Suicidality (Post-2000)



- **High Clinical Need:**

Up to 70% of patients with depression experience suicidal ideation.

- **Systematic Exclusion:**

Out of 64 published registrational trials (1991-2013), only 1 included subjects with suicidality.

- **Lack of Reporting:**

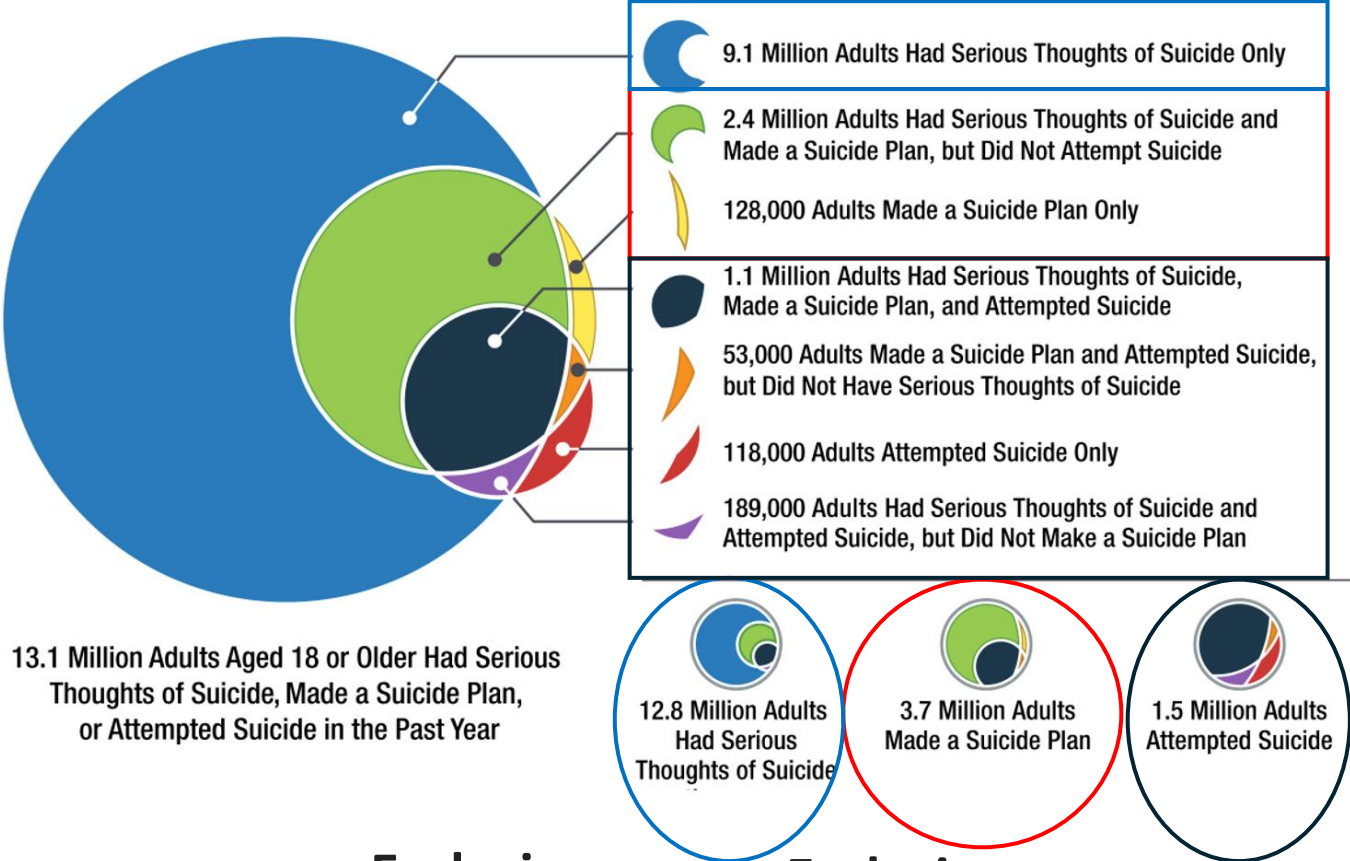
Suicidality was not mentioned in approximately 72% of clinical trials conducted before the year 2000.

- **Increased Exclusion:**

After 2000, while all trials excluded suicidal patients, mentions of suicidality in published studies dropped to only 14%.

# Application of CSSR-S exclusion criteria to adults in the United States

## Adults Aged 18 or Older Who Had Serious Thoughts of Suicide, Made a Suicide Plan, or Attempted Suicide in the Past Year; 2023



What do we know about this group and potential for clinical trials?

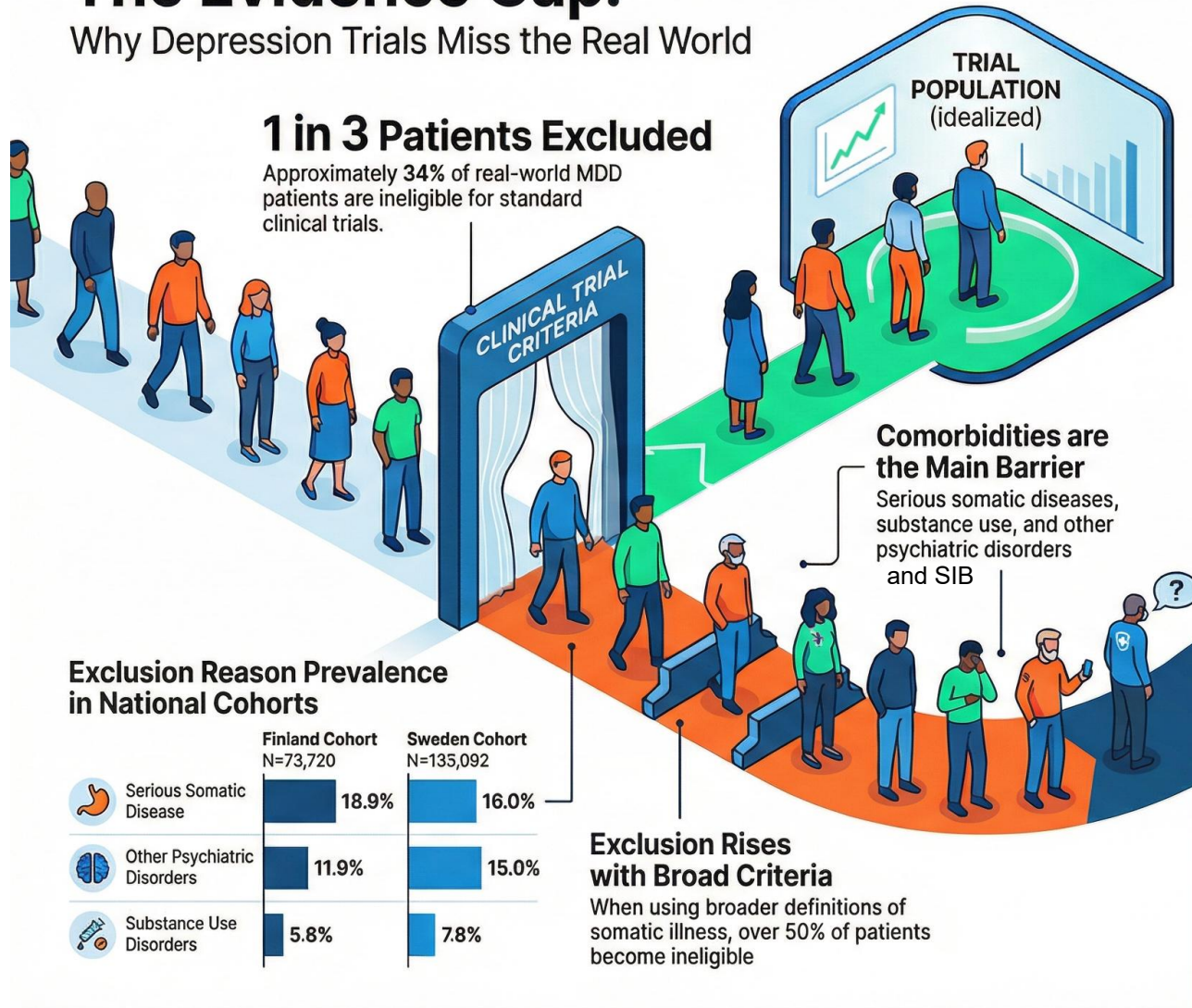
Exclusionary  
CSSR-S item 4

Exclusionary  
CSSR-S item 5

# Potential outcome if registrational trials stopped applying usual exclusion criteria

## The Evidence Gap:

Why Depression Trials Miss the Real World



*Hamina A, et., al; Representation and outcomes of individuals with major depression in routine care who are ineligible for randomized controlled trials: a nationwide register-based study. World Psychiatry. 2026*

# When in clinical development is the right time to include SIB?

## Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study

Carla M. Canuso, M.D., Jaskaran B. Singh, M.D., Maggie Fedgchin, Pharm.D., Larry Alphas, M.D., Ph.D., Rosanne Lane, M.A.S., Pilar Lim, Ph.D., Christine Pinter, M.S., David Hough, M.D., Gerard Sanacora, M.D., Ph.D., Husseini Manji, M.D., and Wayne C. Drevets, M.D.

## A Word to the Wise About Intranasal Esketamine

Alan F. Schatzberg, M.D.

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## Real-World Safety of Esketamine Nasal Spray: A Comprehensive Analysis Almost 5 Years After First Approval

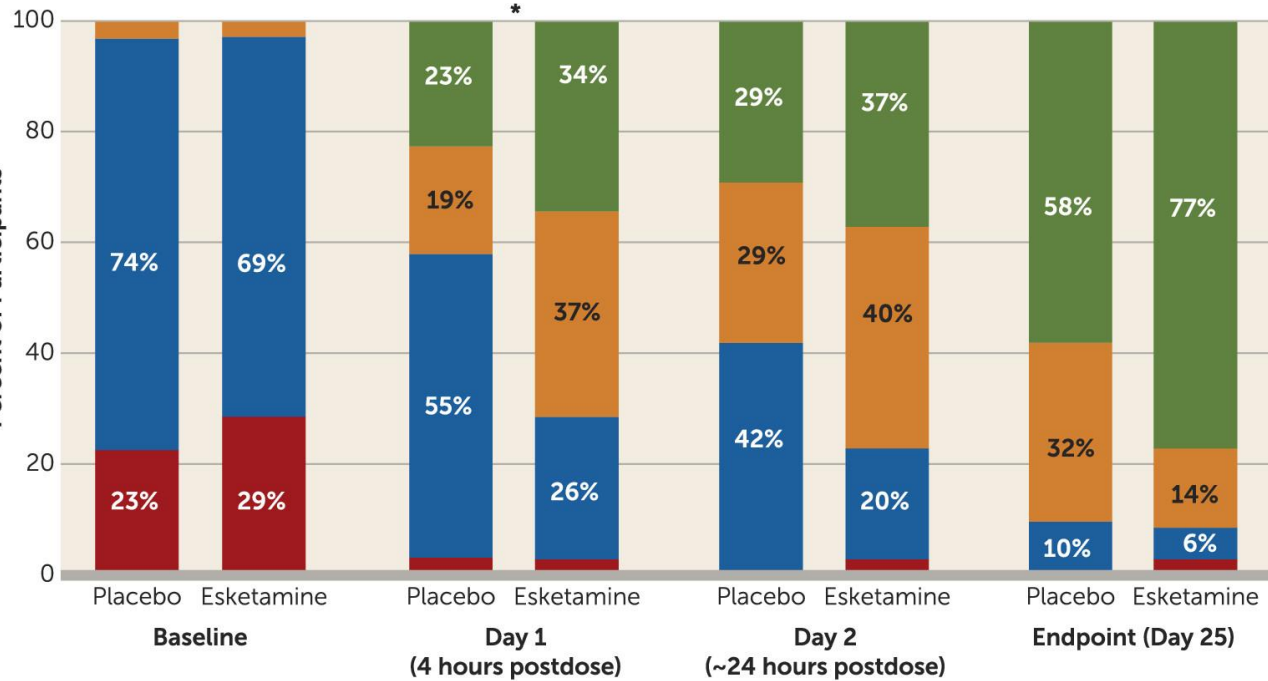
Gerard Sanacora, M.D., Ph.D.,<sup>1</sup> Muhammad Ahmed, M.D., M.P.H.,<sup>2</sup> Brianne Brown, Psy.D.,<sup>2</sup> Patricia Cabrera, M.D., M.Sc.,<sup>2</sup> Teodora Doherty, M.D.,<sup>3</sup> Mai Himedan, M.D.,<sup>2</sup> David M. Kern, Ph.D.,<sup>4</sup> Lisa Lim, Pharm.D.,<sup>2</sup> Oliver Lopena, Pharm.D.,<sup>2</sup> Ronaldo R. Naranjo, Jr., D.N.P., P.M.H.N.P.-B.C.,<sup>2</sup> Isaac Nuamah, Ph.D.,<sup>2</sup> Amir Sarayani, Pharm.D., Ph.D.,<sup>4</sup> Ibrahim Turkoz, Ph.D.,<sup>2</sup> Hannah E. Bowrey, Ph.D.<sup>5</sup>

## Esketamine 5 Years After Approval: Welcome New Data With Continuing Questions

Alan F. Schatzberg, M.D.,<sup>1</sup> Konstantinos N. Fountoulakis, M.D., Ph.D.<sup>2</sup>

# If not excluded, suicidal thoughts (Item 10) can show change

## MADRS Total Score: Endpoint with “Suicidal Thoughts”



Suicidal Ideation (item 10) can show change to antidepressant treatment [at 4 hours after first dose;  $p=0.002$ ; effect size=0.67]

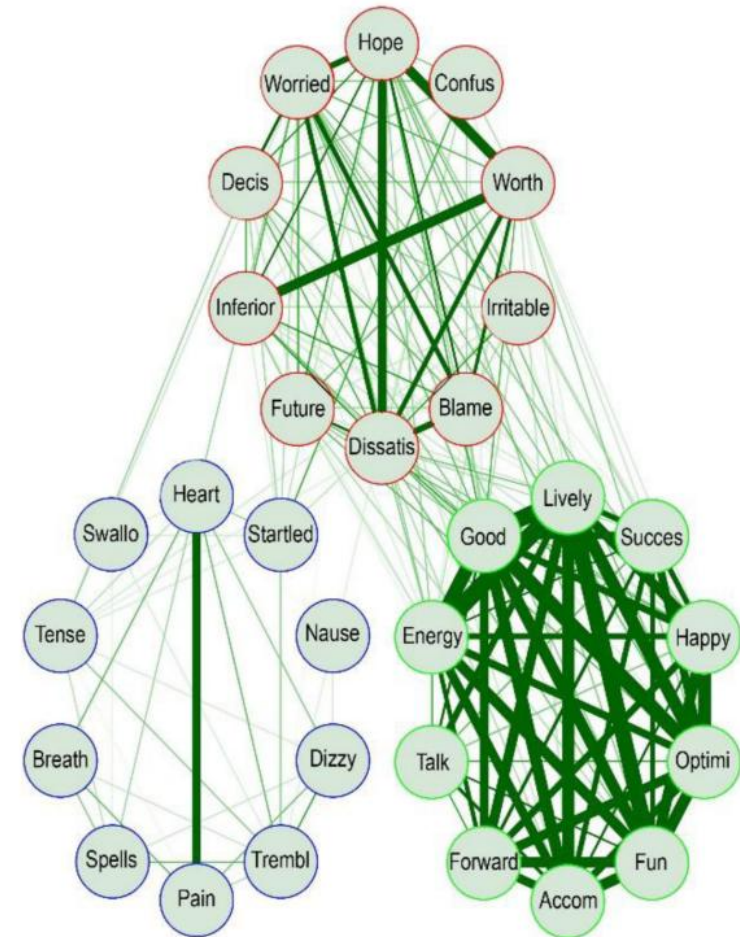
- 0-1 Enjoys life or takes it as it comes.
- 2-3 Weary of life. Fleeting suicidal thoughts.
- 4-5 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

[Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study.](#)

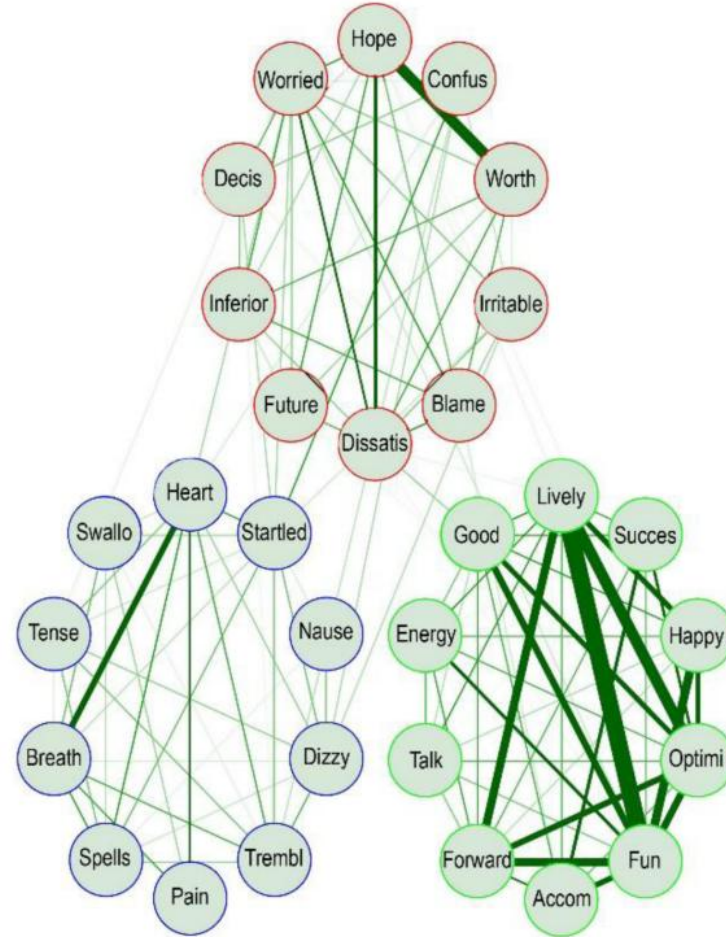
Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, Pinter C, Hough D, Sanacora G, Manji H, Drevets WC. *Am J Psychiatry*. 2018 Jul 1;175(7):620-630

# Is symptom structure of depression with SI the same as in depression?

## Depression



## Depression with SI



Mood and Anxiety Symptoms Questionnaire (MASQ-D30)

Netherlands Study of Depression and Anxiety  
Compared MDD and MDD w/SI (N = 450)

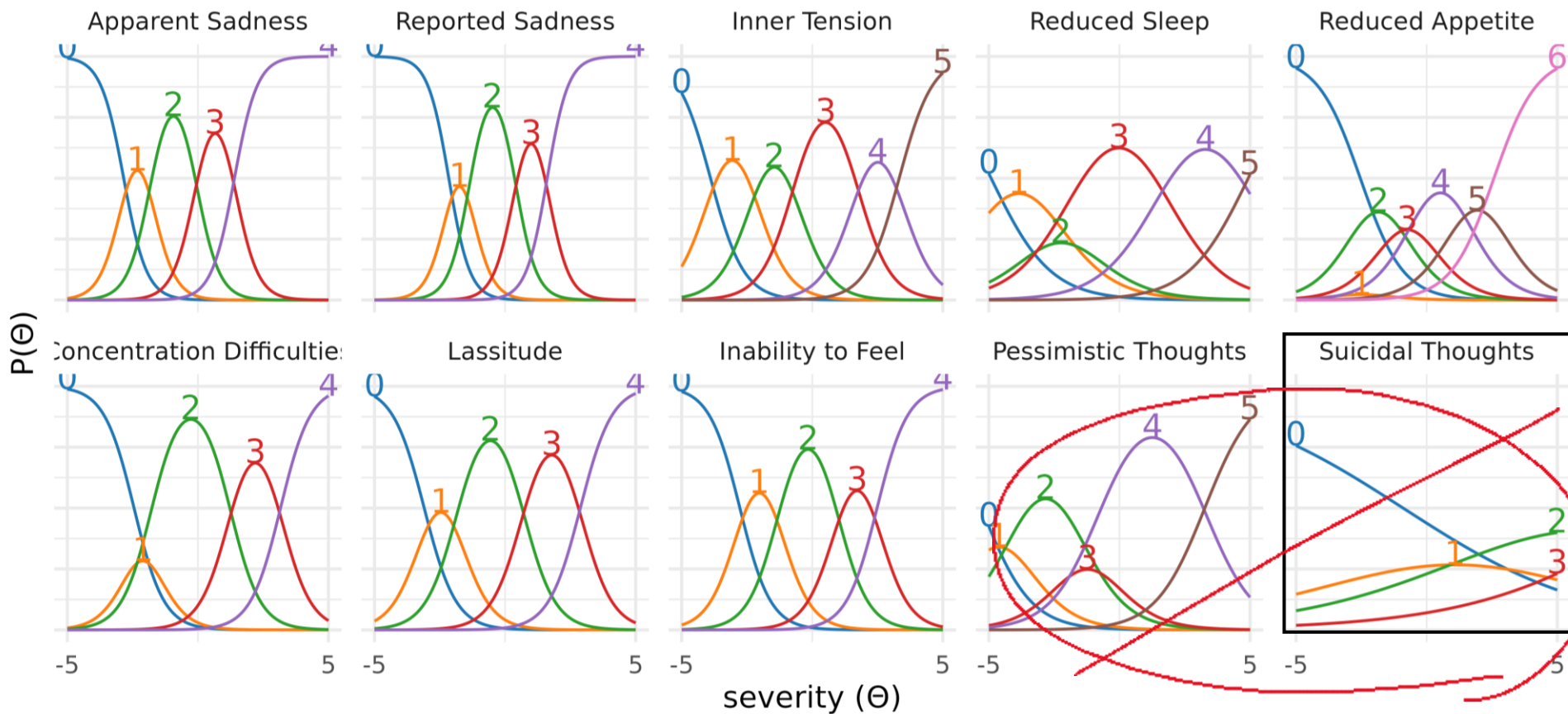
Item correlations below 0.3 are left out

Correlations of 0.5 and higher are in bold

**Suicidal depressed patients had a less good model fit compared with non-suicidal depressed patients, which could imply a difference in symptom structure.**

# Limiting SIB deteriorates psychometric properties of MADRS

(N=1500; Bipolar Depression)



Item Response Theory  
 –distinct peaks at different severity levels indicate each symptoms likelihood of being reported (y-axis) increases along defined gradations in overall depression severity (x-axis)

Sadness  
 Neurovegetative  
 Detachment  
 Negative Thoughts

Sadness  
 Neurovegetative  
 Detachment  
~~Negative Thoughts~~

Hopkins SC, Tomioka S, Szabo ST, Koblan KS. A clinical trial inclusion criteria to enrich for patients presenting with canonical symptom structure in bipolar depression. Bipolar Depression, 2024.

## **Conclusion:**

Participants with SIB have been limited in registrational trials

A staged clinical development approach for inclusion of SIB should be considered