



‘Best’ of 2025 Depressive Disorders

Prague, EPA congress
UPC woensdagseminarie

31/03/2026
06/05/2026

Prof. Em. Dr. Koen Demyttenaere

University Psychiatric Centre KU Leuven, Belgium

koen.demyttenaere@uzleuven.be

Key factors used to choose these papers

- NOT the genuine scientific value of the papers
- NOT the importance of the journal where the papers were published
- NOT the reputation of the authors producing the papers
- **Papers touching on topics with debate or controversy**
- **Papers illustrating conceptual or methodological issues**
- **Papers with clinical relevance**



ASSESSMENT OF SUICIDALITY

met dank aan Pierre Kroll

SHORT COMMUNICATION **OPEN ACCESS**

Billy Mackenzie: Sometimes Wild, Often Lonely

David Baldwin 

University Department of Psychiatry, University of Southampton, Southampton, UK

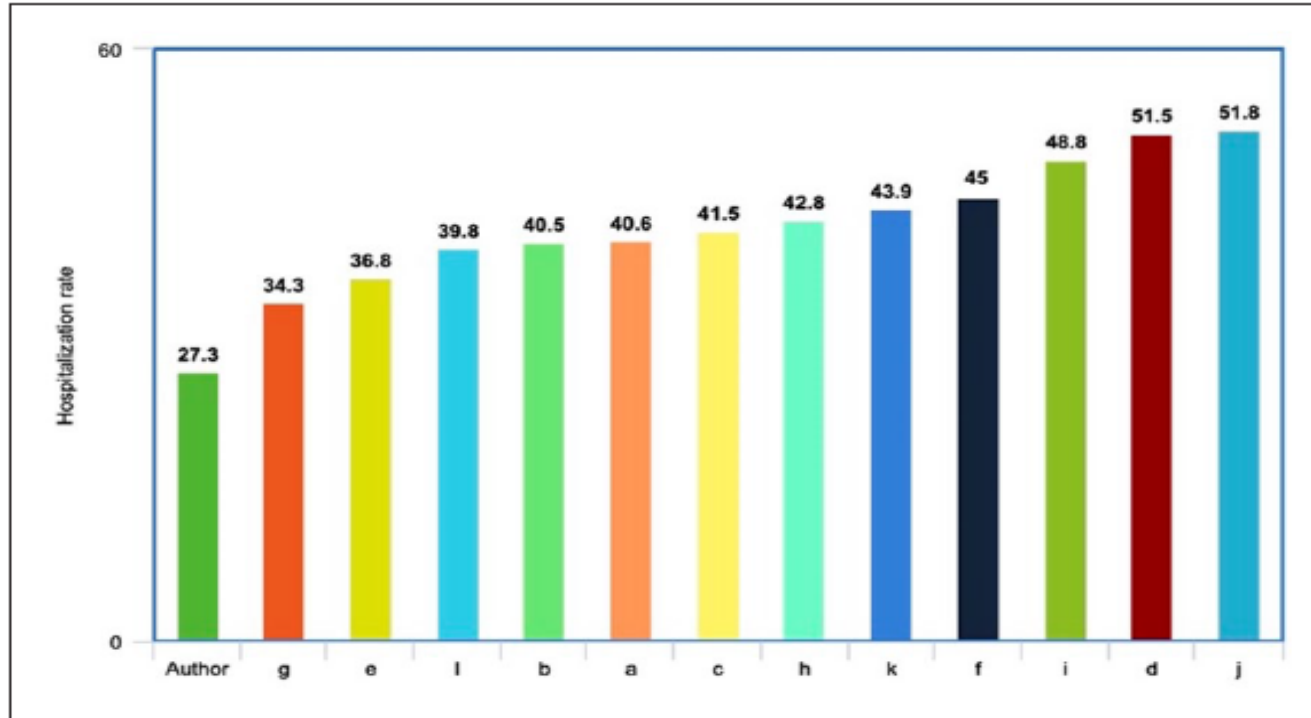
Correspondence: David Baldwin (dsb1@soton.ac.uk)

Received: 23 September 2025 | **Revised:** 23 September 2025 | **Accepted:** 25 September 2025

William MacArthur ('Billy') Mackenzie died alongside an apologetic suicide note, in a garden shed at his father's cottage in Auchterhouse, Scotland, after an overdose of amitriptyline, beta-blockers and paracetamol. He was 64 days short of his fortieth birthday. Three weeks earlier, on New Years Eve 1996, he had been admitted to Ninewells Hospital, Dundee, requiring assisted ventilation after consuming a large quantity of prescribed hypnotics. Then, his father had entreated the assessing psychiatrist to transfer his son to the hospital psychiatry ward, but Billy had maintained the overdose was an 'accident', so he was instead discharged home with a recommendation to start antidepressants.

Assessment of danger ... and the physician's expertise

Variance in hospitalization in ER explained by...



Lower hospitalization rate :

- Clinician feeling comfortable/ connected with the patient
- More experienced clinician = lower hospitalization rate

Suicide prediction, prevention, and the blame culture: A narrative review based on trends in mortality rates

European Psychiatry

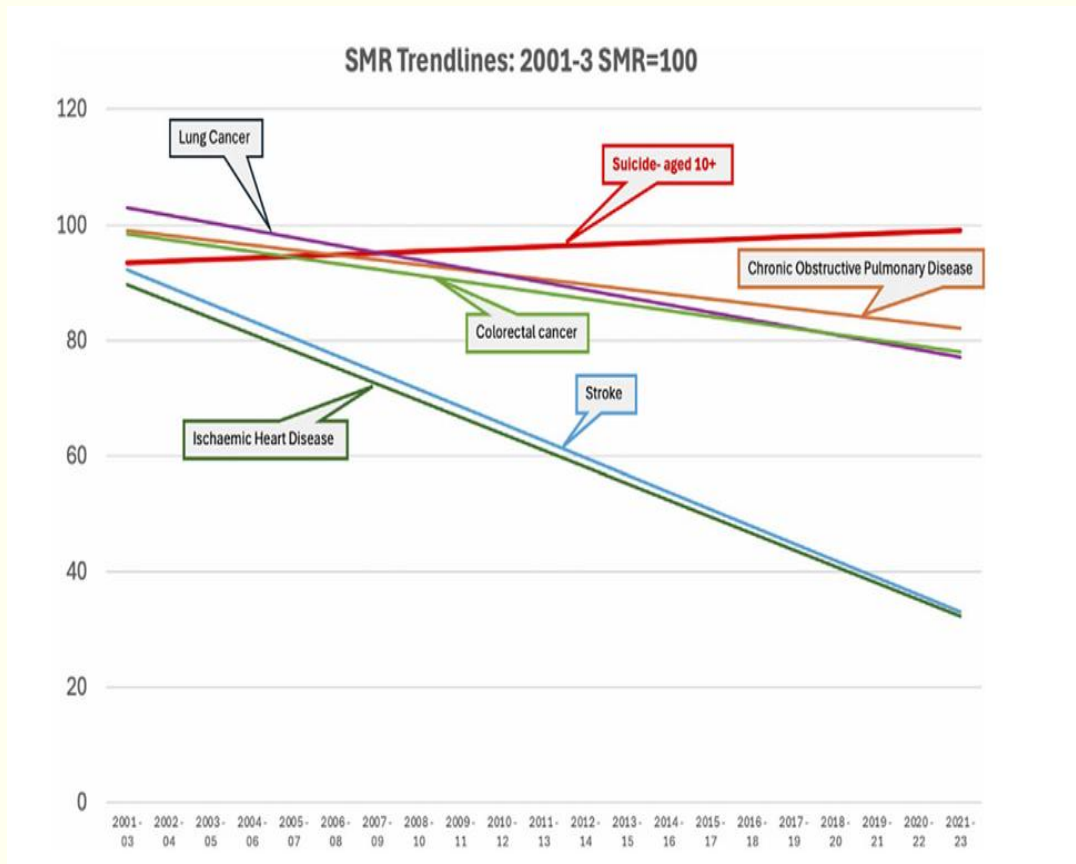
www.cambridge.org/epa

Review/Meta-analysis

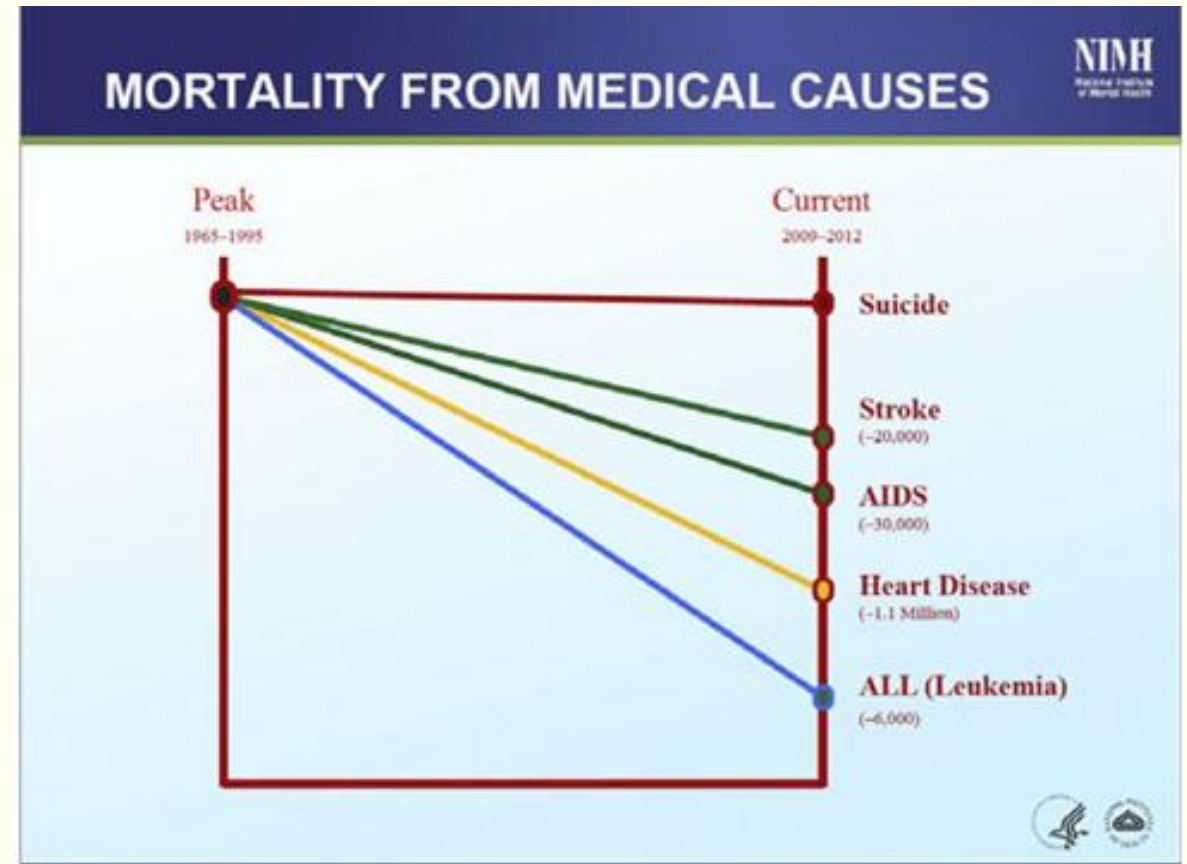
Cite this article: Beezhold J, Porter T, Pinto da Costa M, Wise J, Seker A, Rojnic-Kuzman M, de Picker L, Selwyn V, Buwalda V, Eraslan D, Hanon C, Winter R, Briggs M, Heales S, Whitelock T, Collins D (2025). Suicide prediction, prevention, and the blame culture: A narrative review based on trends in mortality rates. *European Psychiatry*, **68**(1), e172, 1–8
<https://doi.org/10.1192/j.eurpsy.2025.10139>

Conclusions. The challenge for psychiatry is that SMR data suggest that we have been unable to significantly reduce suicide SMR unlike that for physical disorders. This needs to be fully

A mental disorder and subsequent suicide are not necessarily cause and effect in the same way as in other medical conditions (e.g. leukemia and subsequent death)



UK



USA

Posner, Brent, Lucas, Gould, Stanley, Brown, Fisher, Zelazny, Burke, Oquendo, & Mann
© 2008 The Research Foundation for Mental Hygiene, Inc.

full version 2008

Instructions: Check all risk and protective factors that apply. To be completed following the patient interview, review of medical record(s) and/or consultation with family members and/or other professionals.			
Suicidal and Self-Injury Behavior (Past week)		Clinical Status (Recent)	
☐	Actual suicide attempt	☐	Lifetime
☐	Interrupted attempt	☐	Lifetime
☐	Aborted attempt	☐	Lifetime
☐	Other preparatory acts to kill self	☐	Lifetime
☐	Self-injury behavior w/o suicide intent	☐	Lifetime
Suicide Ideation (Most Severe in Past Week)		☐	Hopelessness
☐	Wish to be dead	☐	Helplessness*
☐	Suicidal thoughts	☐	Feeling Trapped*
☐	Suicidal thoughts with method (but without specific plan or intent to act)	☐	Major depressive episode
☐	Suicidal intent (without specific plan)	☐	Mixed affective episode
☐	Suicidal intent with specific plan	☐	Command hallucinations to hurt self
Activating Events (Recent)		☐	Highly impulsive behavior
☐	Recent loss or other significant negative event	☐	Substance abuse or dependence
	Describe:	☐	Agitation or severe anxiety
		☐	Perceived burden on family or others
☐	Pending incarceration or homelessness	☐	Chronic physical pain or other acute medical problem (AIDS, COPD, cancer, etc.)
☐	Current or pending isolation or feeling alone	☐	Homicidal ideation
Treatment History		☐	Aggressive behavior towards others
☐	Previous psychiatric diagnoses and treatments	☐	Method for suicide available (gun, pills, etc.)
☐	Hopeless or dissatisfied with treatment	☐	Refuses or feels unable to agree to safety plan
☐	Noncompliant with treatment	☐	Sexual abuse (lifetime)
☐	Not receiving treatment	☐	Family history of suicide (lifetime)
Other Risk Factors		Protective Factors (Recent)	
☐		☐	Identifies reasons for living
		☐	Responsibility to family or others; living with family
		☐	Supportive social network or family
		☐	Fear of death or dying due to pain and suffering
		☐	Belief that suicide is immoral, high spirituality
		☐	Engaged in work or school
		☐	Engaged with Phone Worker *
		Other Protective Factors	
		☐	
Describe any suicidal, self-injury or aggressive behavior (include dates):			

SUICIDAL IDEATION		Lifetime: Time He/She Felt Most Suicidal	Past 1 month
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.			
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. <i>Have you wished you were dead or wished you could go to sleep and not wake up?</i>		Yes No ☐ ☐	Yes No ☐ ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., "I've thought about killing myself") without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. <i>Have you actually had any thoughts of killing yourself?</i>		Yes No ☐ ☐	Yes No ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act 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 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>Have you been thinking about how you might do this?</i>		Yes No ☐ ☐	Yes No ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts but I definitely will not do anything about them." <i>Have you had these thoughts and had some intention of acting on them?</i>		Yes No ☐ ☐	Yes No ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. <i>Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</i>		Yes No ☐ ☐	Yes No ☐ ☐
INTENSITY OF IDEATION The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.			
Lifetime - Most Severe Ideation:		Most Severe	Most Severe
Type # (1-5) _____ Description of Ideation _____			
Recent - Most Severe Ideation:			
Type # (1-5) _____ Description of Ideation _____			
Frequency <i>How many times have you had these thoughts?</i> (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day _____			
Duration <i>When you have the thoughts how long do they last?</i> (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time _____			
Controllability <i>Could/can you stop thinking about killing yourself or wanting to die if you want to?</i> (1) Easily to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts _____			
Deterrents <i>Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?</i> (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply _____			
Reasons for Ideation <i>What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?</i> (1) Completely to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (2) Mostly to get attention, revenge or a reaction from others (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (0) Does not apply _____			

SUICIDAL BEHAVIOR
(Check all that apply, so long as these are separate events; must ask about all types)

	Lifetime		Past 3 months	
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, as a result of act. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is any intent/desire to die associated with the act, then it can be considered an actual suicide attempt. There does not have to be any injury or harm. Just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. Have you made a suicide attempt? Have you done anything to harm yourself? Have you done anything dangerous where you could have died? What did you do? Did you _____ as a way to end your life? Did you want to die (even a little) when you _____? Were you trying to end your life when you _____? Or did you think it was possible you could have died from _____? Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? Self-Injurious Behavior without suicidal intent(s) If yes, describe:	Yes ☐	No ☐	Yes ☐	Past 3 months ☐
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐	No ☐	Yes ☐	No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (if not for that, actual attempt would have occurred). Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-injurious behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by someone else. Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
Acts or Preparations or Behavior: Preparatory actions toward imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:	Yes ☐	No ☐	Yes ☐	No ☐
	Total # of preparatory acts		Total # of preparatory acts	
	_____		_____	
	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:	
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lacerative speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; medical hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; medical/hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	Enter Code	Enter Code	Enter Code	
Potential Lethality: Only Answer if Actual Lethality=0 Highly lethal if actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).	Enter Code	Enter Code	Enter Code	
0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	_____	_____	_____	

In the United Kingdom, the National Institute of Health and Care Excellence has acknowledged the reality that suicide risk assessment tools are not clinically useful

The challenge for suicide prevention is that, despite all efforts, no tool or method has been found to identify those who will go on to die by suicide with clinically useful accuracy. The presence of suicide risk factors cannot tell us whether or when an individual may attempt suicide

National Institute for Health and Care Excellence. Self-harm: assessment, management and preventing recurrence. 2022.

Available: <https://www.nice.org.uk/guidance/ng225>



England

About us

Our work

Commissioning

Get involved

Date published: 4 April, 2025

Date last updated: 11 June, 2025

[Mental health](#)

Staying safe from suicide

Best practice guidance for safety assessment, formulation and management

Every day, 17 people die by suicide in the UK. Of those, five are in contact with mental health services, and **four of those five (80%) are assessed as 'low' or 'no' risk at their last contact.**

Suicide prediction tools, scales, and stratification (for example, into low, medium, or high risk) are flawed because **suicidal impulses are highly changeable and can shift in minutes.**

The use of static risk stratification, often based on simplistic questions, is still widespread, but it is unacceptable.

Clinical guidelines on self-harm and suicide prevention: taking uncertainty into account in the evidence base

Aida Seyedsalehi ,¹ Seena Fazel ^{1,2}

¹Department of Psychiatry,
University of Oxford, Oxford, UK
²Oxford Health NHS Foundation
Trust, Oxford, UK

Correspondence to
Professor Seena Fazel; seena.
fazel@psych.ox.ac.uk

Received 11 December 2025
Accepted 17 January 2026

We propose that there is an urgent need for more rigorous primary research assessing model impact, feasibility and acceptability, as well as empirical work addressing concerns about potential harms and misuse of tools, notably the denial of care.

While prediction models should not be prematurely implemented in clinical practice without adequate validation and impact assessment, well-developed and validated tools in this area have the potential to improve clinical care for individuals who self-harm.

Original Investigation | Psychiatry

Cognitive Behavior Therapy With and Without Narrative Assessment and Suicide Attempts A Systematic Review and Meta-Analysis

Wilco C. Janssen, MSc; Saskia Y. M. Mérelle, PhD; Wouter van Ballegooijen, PhD; Renske Gilissen, PhD; Claudi L. H. Bockting, PhD

JAMA Network Open. 2025;8(11):e2544632. doi:10.1001/jamanetworkopen.2025.44632

Invited Commentary | Psychiatry

A Narrative Approach to Assess Suicide—Tell Me Your Story

Justin C. Baker, PhD, ABPP

JAMA Network Open. 2025;8(11):e2544639. doi:10.1001/jamanetworkopen.2025.44639

Key Points

Question Are cognitive behavioral interventions that include a narrative assessment associated with a greater reduction in the risk of suicide attempts than those without?

Findings In this meta-analysis of 23 randomized clinical trials with 3262 participants, interventions incorporating a narrative assessment were associated with reduced suicide attempts, while those without were not.

Meaning These findings suggest that including a narrative assessment may enhance the effectiveness of interventions in preventing suicide attempts.

moving away from **syndromal approach**

(warning signs and symptoms, risk factors, protective factors
...resulting in a designated level of suicide risk)

towards a **narrative (Aeschi) approach**

(**functional contextualism approach** : idiographic data
unique to the individual patient's experience of suicidality,
including factors promoting and sustaining suicidality)
...close to **chain analysis** (DBT)

Activation of a suicidal state is often rapid and unpredictable
as the suicidal mode follows a nonlinear time course :

Narrative assessment allows the patient to reflect
on what transpired during this distressing time and
there is a dialogue with the clinician's nonjudgmental reflections

Suicide is an action taking the place of feeling...
the role of professionals is to help the patients 'put the feelings into words to encourage expression of pain', aiming to 'reduce the risk of action' (Gibbons R, 2024)

BJPsych

The British Journal of Psychiatry (2025)
1–5. doi: 10.1192/bjp.2025.10458

A clinician's guide to probabilistic suicide risk
prediction tools: cautions and pitfalls

Alastair Cockburn and Matthew Large

- * More time spent with completing tools than with patients ?
- * Do we become risk managers (risk aversion, defensive psychiatry)?
- * Prioritizing perceived suicide risk over other debilitating experiences ?
- * Tool could de-prioritize 'lower risk' patients ?
- * Gender and age bias : risk of older men versus suffering of young women ?
- * Suicide is as much a cultural phenomenon as a medical one :
are tools universally valid ?
- * Can good clinicians outperform tools ?
- * *False induction of predictability can induce guilt in caregiver*

From Static to Dynamic Prediction of Suicide Risk

Josh Nguyen, MS; Dominic B. Dwyer, PhD; Barnaby Nelson, PhD; Lianne Schmaal, PhD

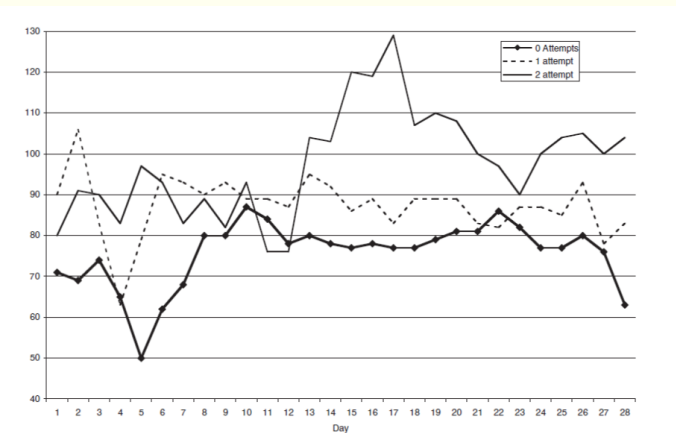
jamapsychiatry.com

JAMA Psychiatry November 2025 Volume 82, Number 11 1

© 2025 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Suicide risk is highly fluctuating over time

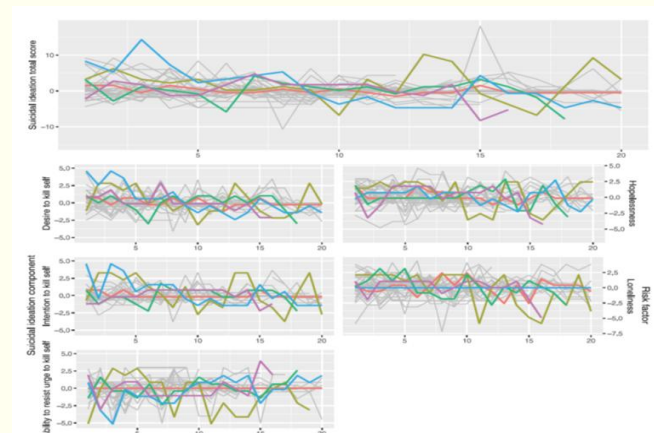
- Most risk prediction models rely on static information collected at a single time point
- Most models reduce the rich complexity of a person's suicide risk high vs low risk of attempt
- What is high risk ? 5%, 10%, 20%,



Level of daily fluctuation in suicidal ideation

- No attempts : 6.12
- 1 attempt : 9.21
- ≥ 1 attempt : 10.69

Witte TK et al., 2006

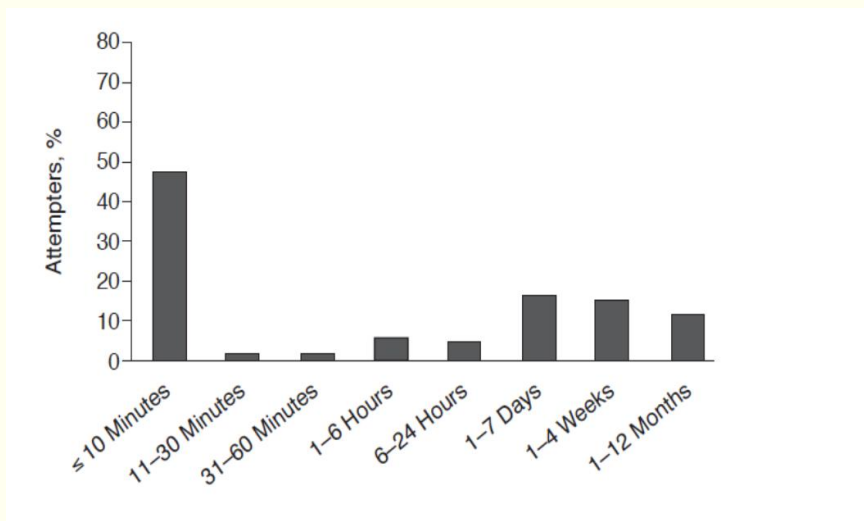


28%/29% of all ratings of SI are at least one SD above or below the previous response

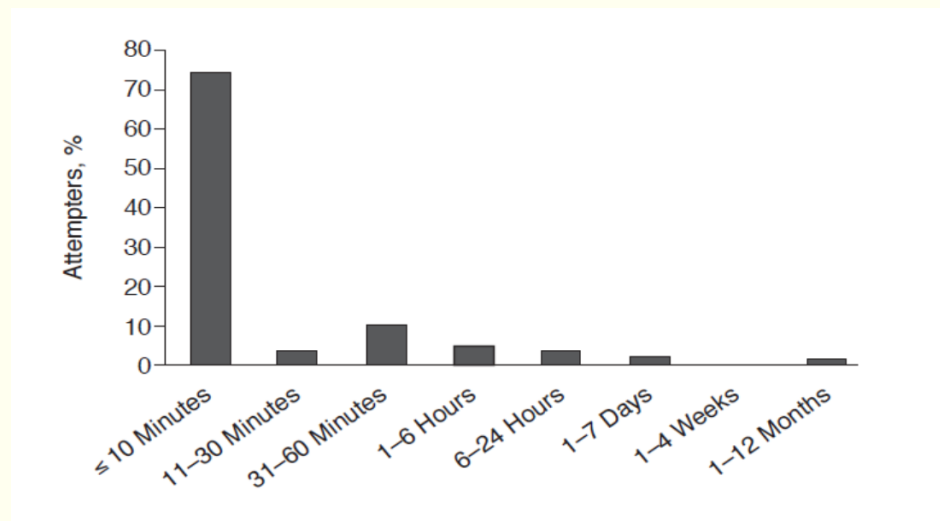
Kleiman EM et al., 2017

There is evidence that many people acting on suicidal or self-harm impulses may have no plans or intentions to do so even minutes beforehand.

Time between first occurrence of a thought of suicide and suicide attempt



Time between decision to commit suicide act and attempt



Deisenhammer EA et al., 2009



TREATMENT

-vagal nerve stimulation-

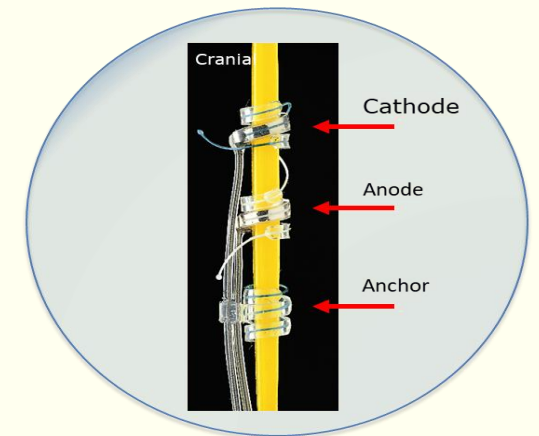
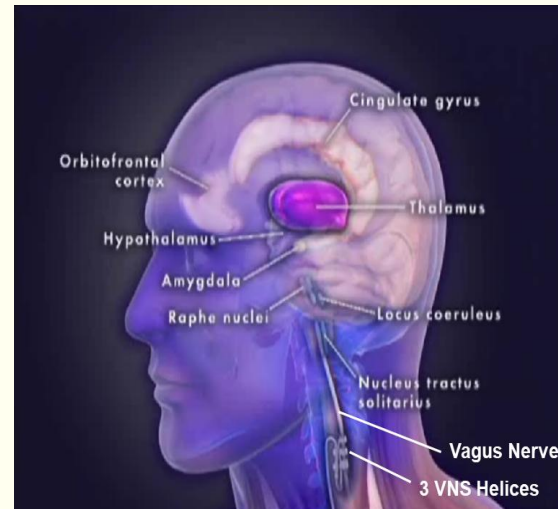
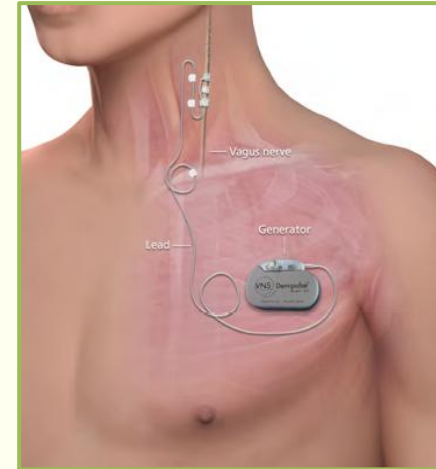
RECOVER study (US):

Blinded 12 month active VNS versus sham stimulation
in very severely treatment resistant depression

Approved Indications for VNS Therapy®

Approved in the EU in **1994** for use as an **adjunctive** therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by **partial** seizures (with or without secondary generalization) or **generalized seizures**, which are **refractory** to antiepileptic medications

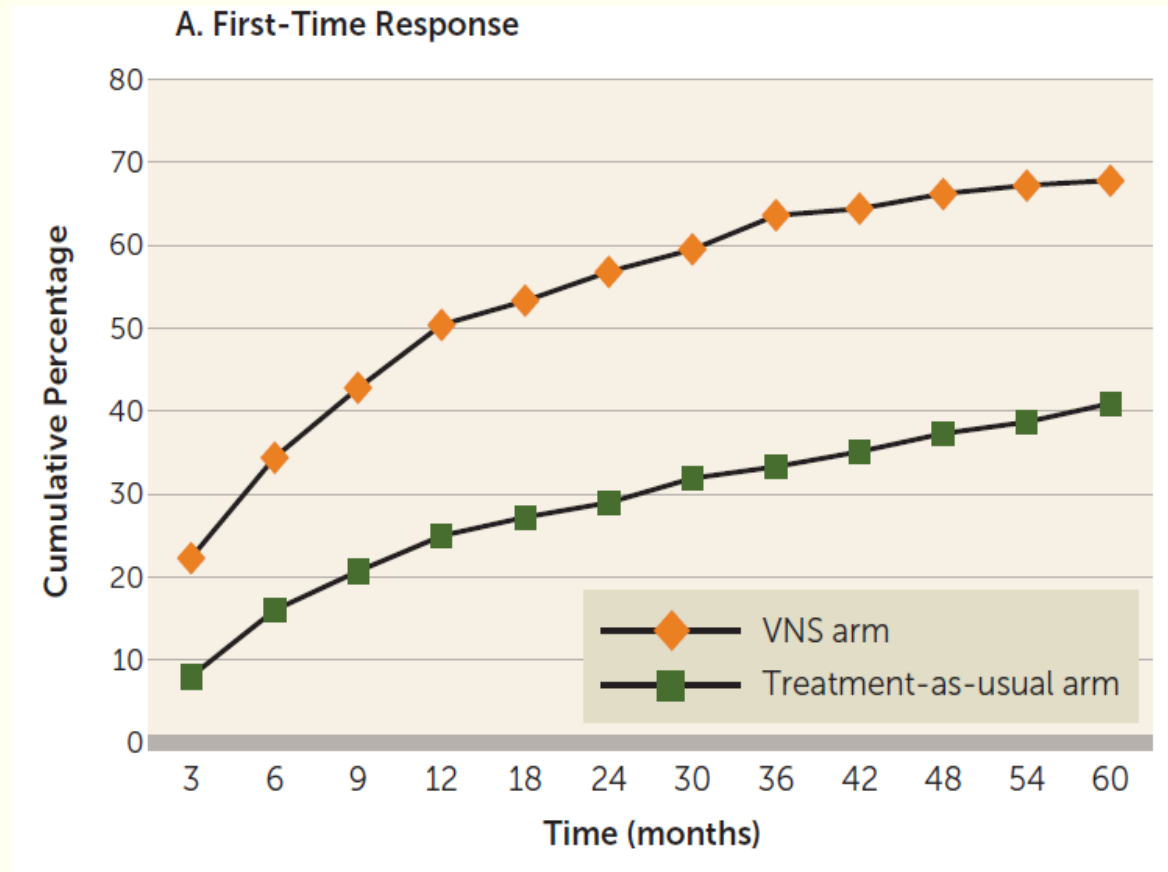
Approved in the EU in **2003** for the treatment of **chronic or recurrent depression** in patients that are in a **treatment-resistant** or **treatment-intolerant** major depressive episode.



Background : Aaronson ST et al., AJP 2017

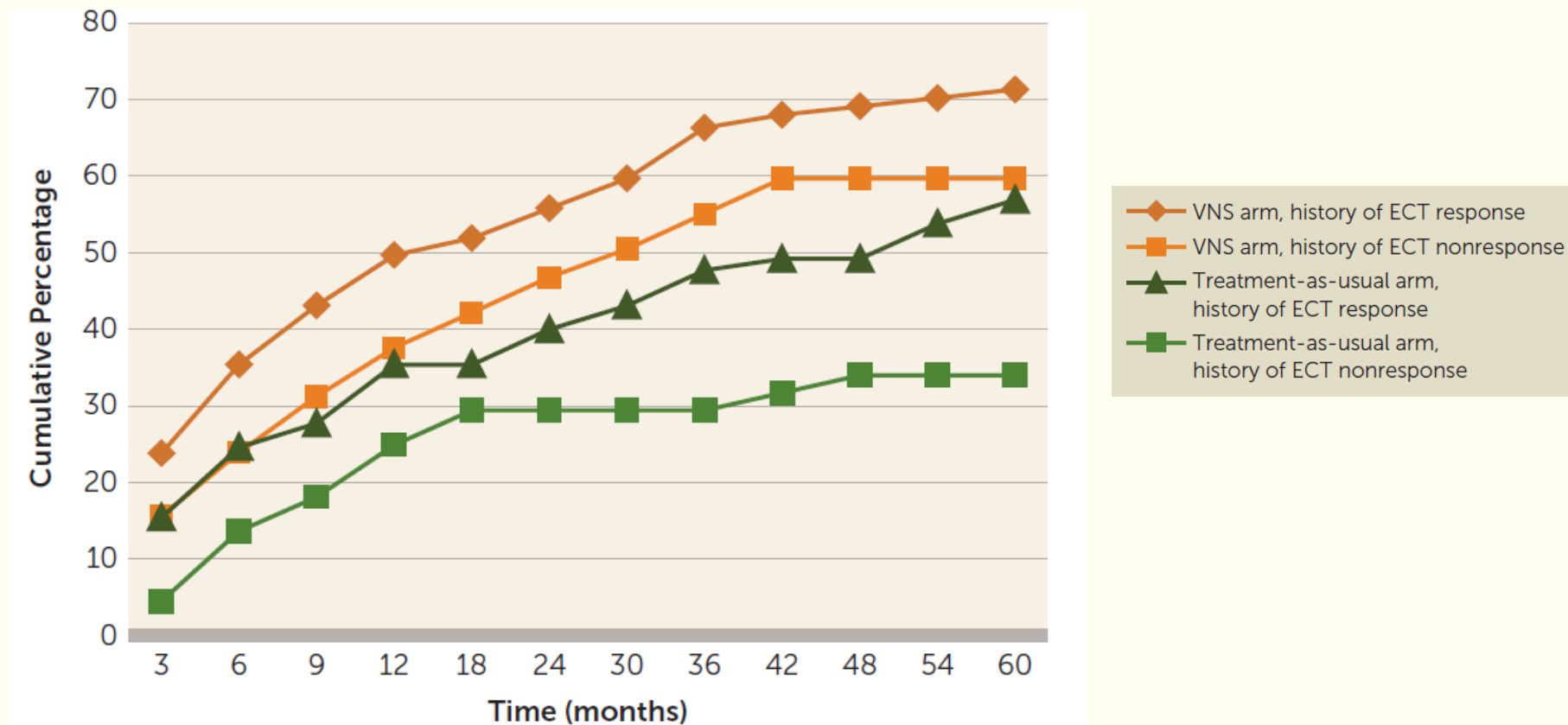
- 5 year observational study :
 - VNS versus TAU
- N = 795
 - ≥ 2 year duration
 - ≥ 3 previous episodes
 - ≥ 4 failed treatments
- **Primary endpoint : response MADRS**

Response rates : 67.6% versus 40.9%



Response :

patients with a history of response or nonresponse to ECT



Suicidality and Mortality

Measure	VNS Group (N=494)	Treatment-as-Usual Group (N=301)
Number of deaths during study participation	7	8
Exposure (patient-years)	1,985.08	926.49
All-cause mortality per 1,000 person-years	3.53	8.63
Number of suicides during study participation	2	2
Suicides per 1,000 person- years	1.01	2.20

RECOVER study (US):

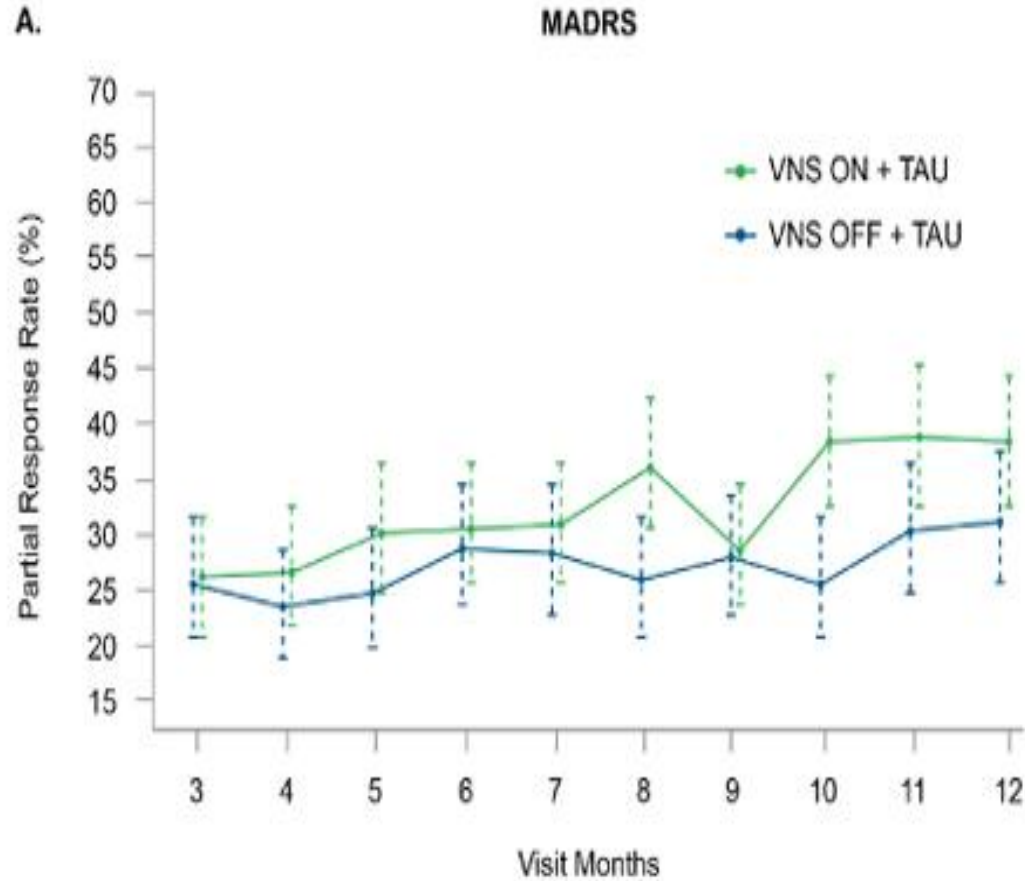
Blinded 12 month active VNS versus sham stimulation
in very severely treatment resistant depression

	RESTORE-LIFE MDD only, excluding BL MADRS score <22 (N=100)	RECOVER (N=493) ¹	
		Active	Sham
Age, years	48.7 (12.3)	56.0 (14.4)	54.9 (14.0)
Gender			
Female	54.0%	69.9%	61.9%
Male	46.0%	30.1%	38.1%
Employed, %	21.0%	26.1%	23.8%
Primary diagnosis, %			
MDD, recurrent	82.0%	56.6%	52.5%
MDD, single-episode	18.0%	43.4%	47.5%
Bipolar	—	—	—
Age at onset of first symptoms of depression, years	27.5 (13.9)	21.2 (12.0)	21.1 (12.4)
Age at diagnosis of any major mood disorder, years	32.1 (13.1)	27.7 (12.7)	27.3 (12.0)
Duration of current MDE, years	7.5 (7.1)	17.3 (15.7)	18.3 (15.6)
Number of prior hospital admissions for mood disorder in lifetime	8.5 (8.4)	2.2 (4.0)	1.9 (3.7)
Number of suicide attempts in lifetime	0.9 (1.5)	0.8 (1.4)	0.9 (2.0)

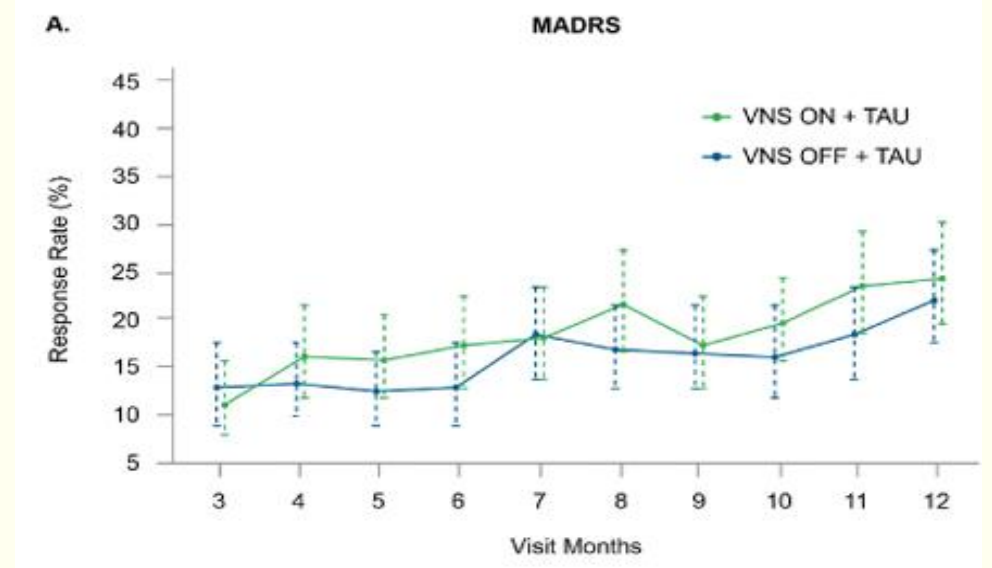
	RESTORE-LIFE MDD only, excluding BL MADRS score <22 (N=100)	RECOVER (N=493) ¹	
		Active	Sham
Number of failed antidepressant treatments*	14.8 (8.4)	13.5 (9.3)	13.0 (7.4)
Number of failed antidepressant medications	11.4 (6.5)	11.5 (8.6)	10.8 (5.7)
Number of patients with prior ECT	88.0%	45.3%	46.7%
MADRS total score (range, 0–60)	32.3 (6.1)	34.2 (4.9)	34.4 (4.8)
QIDS-SR total score (range, 0–27)	18.2 (3.9)	17.4 (3.7)	17.7 (3.4)

partial response and response rates

(Conway CR et al., Brain Stimulation 2025)



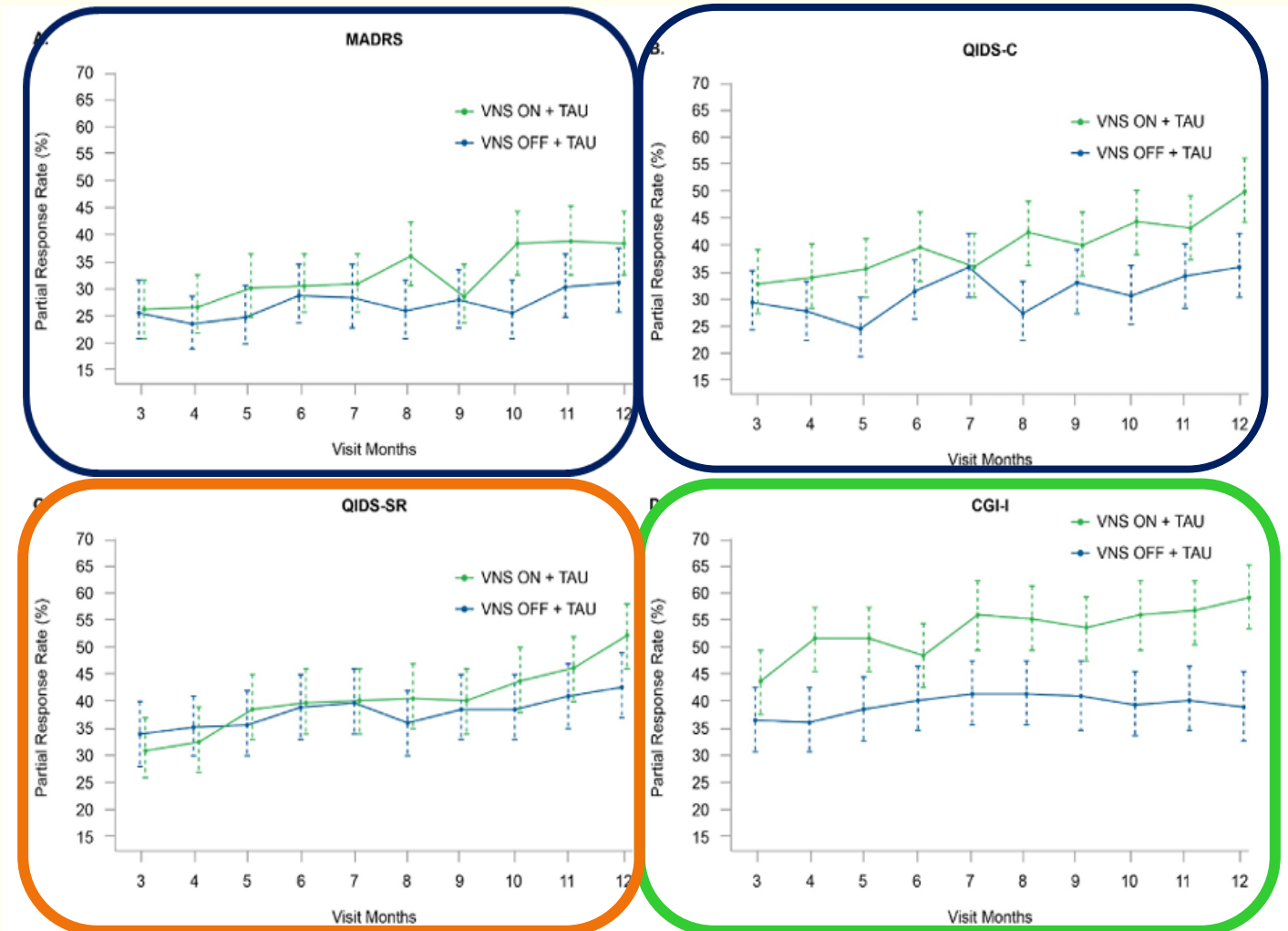
% MADRS partial responders %



% MADRS responders

partial response = minimum clinically important difference

(Conway CR et al., Brain Stimulation 2025)



MADRS : blinded central rating
QIDS-C : blinded central rating

- **MADRS** : blinded central rating
- **QIDS-C** : blinded central rating
- **QIDS-SR** : patient rated
- **CGI-I** : clinician rated

QIDS-SR : patient rated

CGI-I : clinician rated

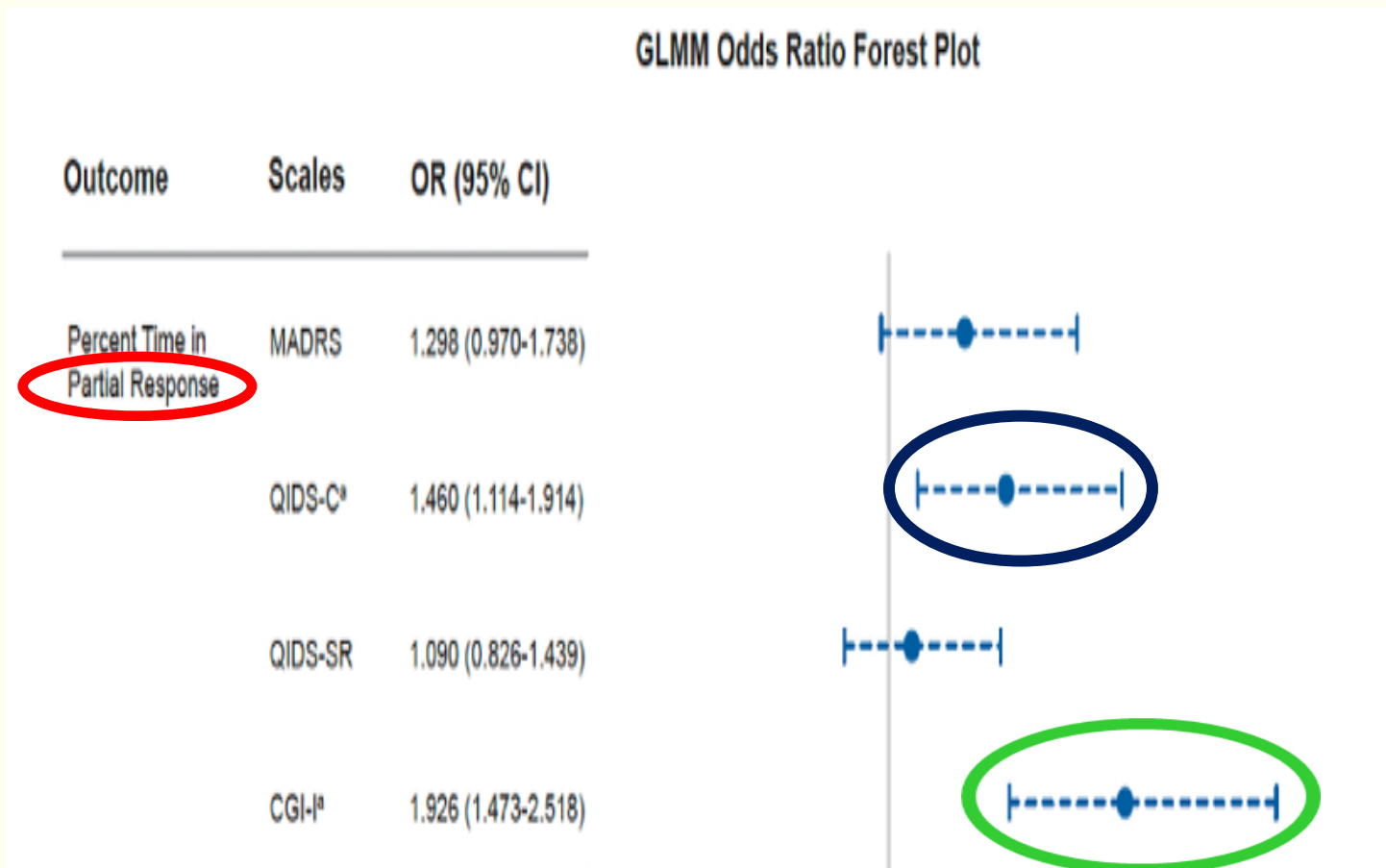
67.5% of patients guessed Rx arm (ON)

53.3% of patients guessed Rx arm (OFF)

integrative metrics : % time in ...

(Conway CR et al., Brain Stimulation 2025)

Primary endpoint : % time in MADRS response : not significant



MADRS : blinded central rating

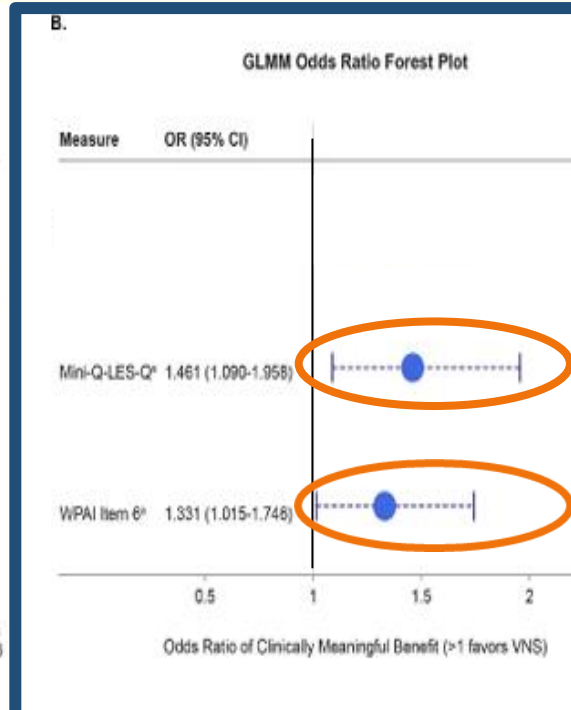
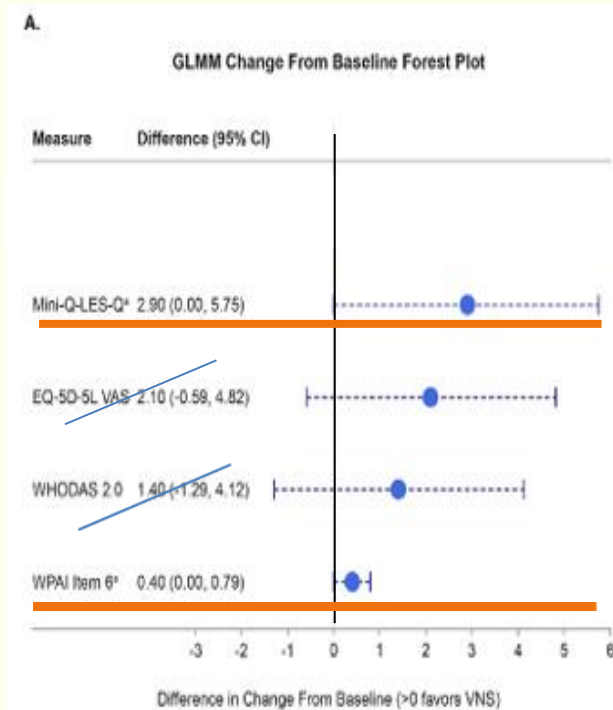
QIDS-C : blinded central rating

QIDS-SR : patient rated

CGI-I : clinician rated

Life Enjoyment and Satisfaction *and* Functioning

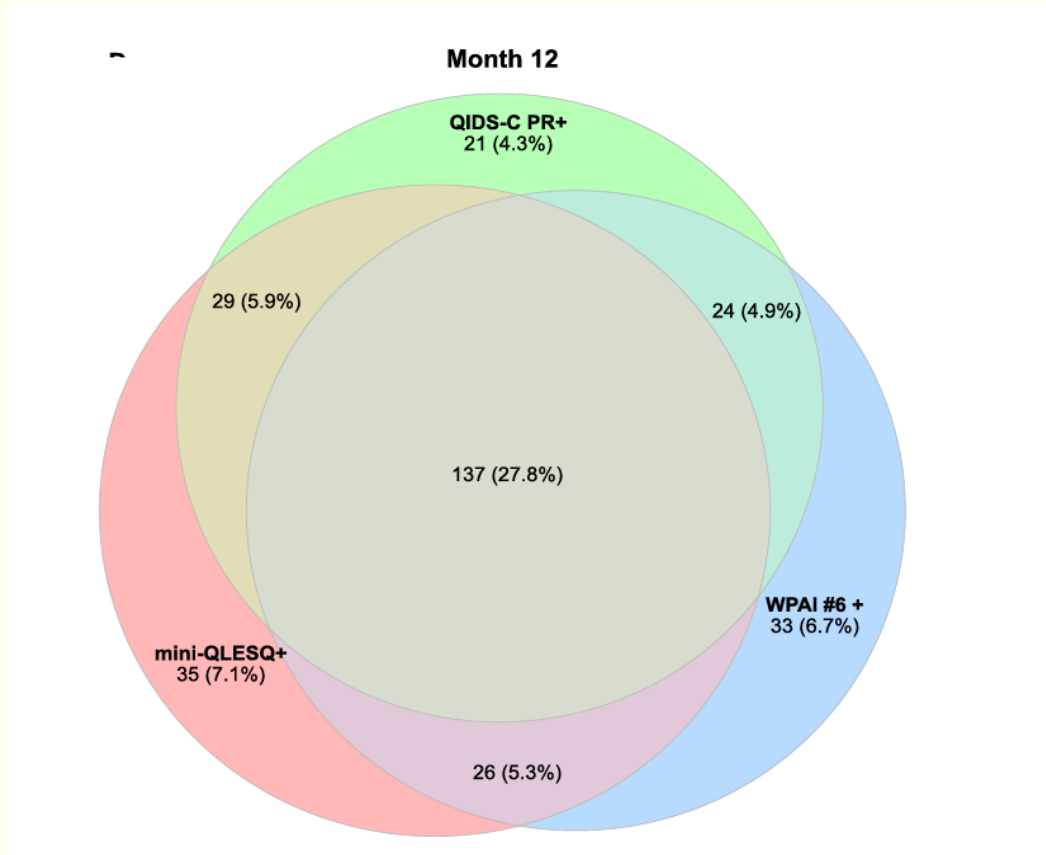
(Rush AJ et al., Brain Stimulation 2025)



- **MCID** : minimal clinically important difference
 - (mini) Q-LES-Q : $\geq 11.89\%$ increase
(how satisfied are you with....?)
 - WPAI item 6 : 2 points increase
(how much did your *PROBLEM* affect your ability to do your regular daily activities, other than work at a job?)
By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc.)

tripartite metric

(symptoms, life enjoyment and satisfaction, daily activities)



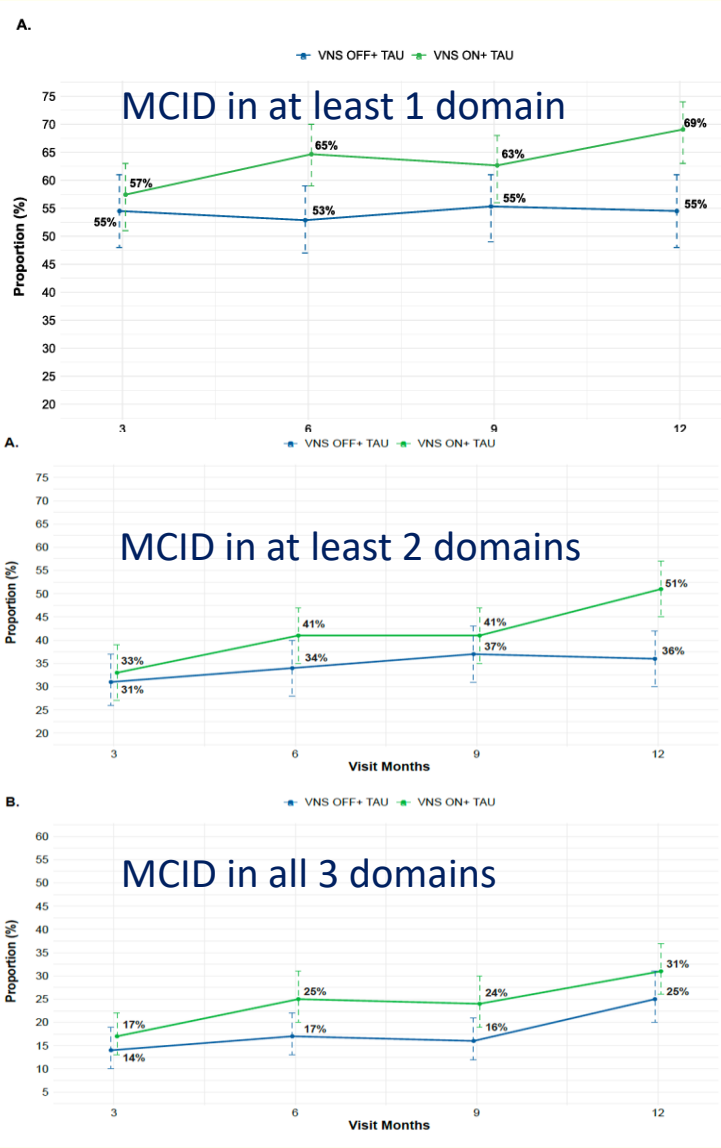
MCID : minimal clinically important difference

Within subgroup with QIDS-C partial response at 12 months (as symptomatic MCID) (N=211)

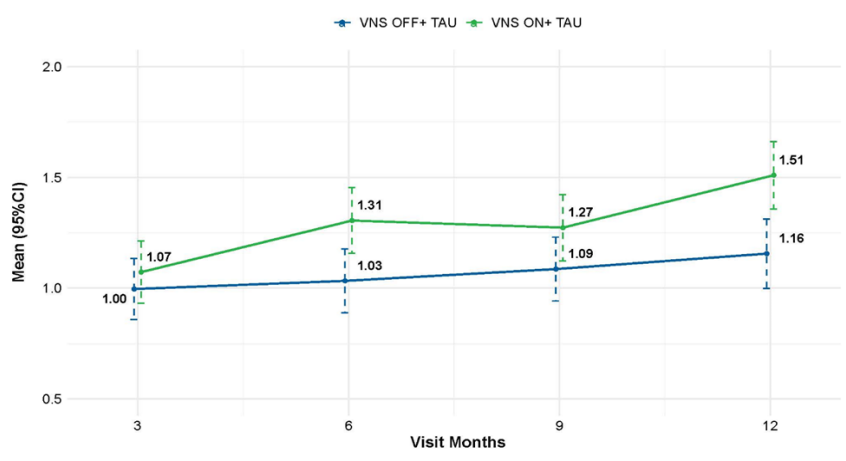
- 65% MCID in 3 domains
- 25% MCID in 2 domains
- 10.0% MCID in 1 domain (symptomatic)

**at 12 months,
62% of all patients had an MCID in at least 1 domain**

tripartite metric (QIDS-C, mini-Q-LES-Q, WPAI item 6)



tripartite metric (0-3) : n domains with MCID



tripartite metric (0-12) : n domains with MCID (sum of 4 time points)

partial response	VNS on	VNS off	P-value
MADRS PR+	4.8	4.1	0.04
QIDS-C PR+	5.2	4.3	0.009
QIDS-SR PR+	5.2	4.5	0.06

comments



- **Integrative metric**
 - Closer to clinical reality
- **Tripartite metric (multidomain)**
 - Closer to patient expectations



- **Primary negative...**
secondary exploratory, not confirmatory
- **Cut-offs for MCID somewhat arbitrary**
- **Multiple testing (risk of type I error/false positives)**
 - 3 symptomatic outcome measures (MADRS, QIDS-C, QIDS-SR) (and not WHODAS/EQ-5D-5L)
 - Binary metrics (reaching 1, 2, 3 domains)
 - 1 domain reaches MCID (0-4 as sum of 4 assessments)
 - 1,2 or 3 domains reach MCID (0-12 as sum of 4 assessments)



Magic Cece

(MedChemExpress LLC)

TREATMENT

-aticaprant-

Johnson & Johnson (J&J) is dropping its Phase III major depressive disorder (MDD) programme for aticaprant due to 'insufficient efficacy in the target population'. The VENTURA programme, evaluating the experimental drug as an adjunctive treatment for MDD, included five Phase III trials.

There had been a lot of hope for aticaprant, with GlobalData previously touting it as the most promising pipeline product for MDD due to its novel MOA and focus on anhedonia, a hard-to-treat symptom.



European Archives of Psychiatry and Clinical Neuroscience (2025) 275:1593–1597
<https://doi.org/10.1007/s00406-024-01851-7>

INVITED REVIEW

Aticaprant, a kappa opioid receptor antagonist, and the recovered 'interest and pleasure' in the concept of major depressive disorder

Koen Demyttenaere¹ 



The 'promise' of biomarker proof of mechanism (POM) in the Fast Fail (FAST-MAS) approach:

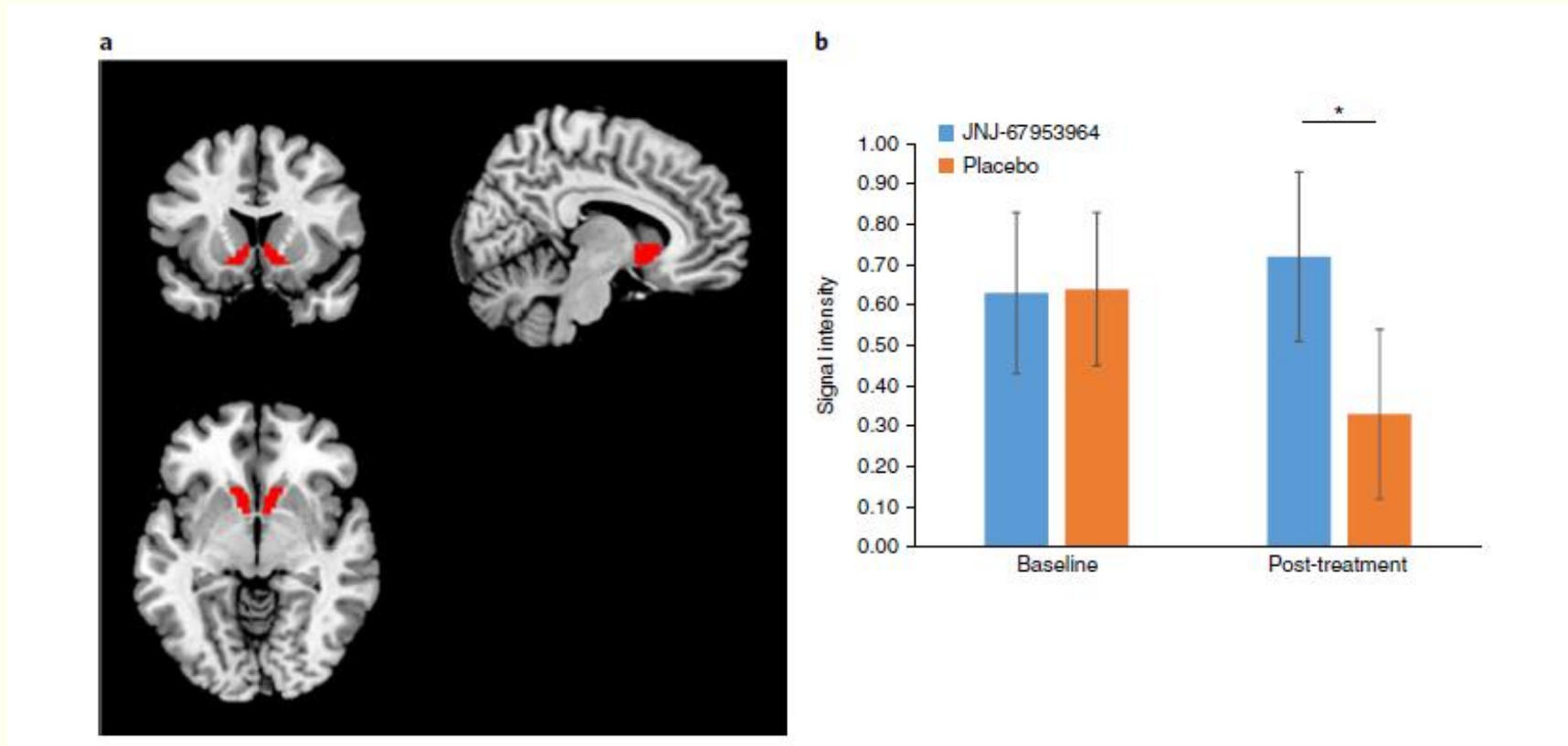
....impacting the brain circuitry hypothesized to mediate clinical effects....

- NIMH : too many compounds based on targets that should correct a dysfunction contributing to the illness fail to show benefits in the later stages of clinical trials
- **FAST Program aims to evaluate brain target in early phases of drug development**
 - Does the compound engage a target in the brain ?
 - Does the compound measurably change a feature of brain function ?
- First successful example :
 - FAST-MAS (Fast Fail Trials – Mood and Anxiety Spectrum) showed that blocking the kappa opioid receptor antagonist (**aticaprant = JNJ-67953964**, previously CERC-501 and LY2456302) had a significant effect on brain circuits involved in reward and pleasure

The *'promise'* of biomarker proof of mechanism (POM) in the Fast Fail (FAST-MAS)

:

....impacting the brain circuitry hypothesized to mediate clinical effects....



Mean fMRI ventral striatum activation in anticipation of rewards in the monetary incentive delay task

The ‘promise’ of biomarker proof of mechanism (POM) in the Fast Fail (FAST-MAS) :

....impacting the brain circuitry hypothesized to mediate clinical effects....

Variable	JNJ-67953964	Placebo	n	P	Effect size (Hedges' g)
Primary outcome measure					
Mean fMRI ventral striatal activation in MID task in anticipation of gain contrasted with no-incentive trials	0.72 (0.67)	0.33 (0.68)	88	0.0095	0.58
Secondary outcome measures					
Mean SHAPS	30.8 (3.7)	32.4 (3.6)	88	0.0345	0.44
PRT change in response bias from block 1 to block 2	0.059 (0.15)	0.066 (0.15)	76	>0.10	0.10
Exploratory outcome measures					
Maximum fMRI ventral striatal activation in MID task in anticipation of gain contrasted with no-incentive trials	2.84 (0.86)	2.36 (0.86)	88	0.012	0.55
Mean fMRI ventral striatal activation in MID task in anticipation of loss contrasted with no-incentive trials	0.73 (0.6)	0.07 (0.6)	88	<0.001	1.12
Maximum fMRI ventral striatal activation in MID task in anticipation of loss contrasted with no-incentive trials	2.73 (0.8)	2.18 (0.8)	88	0.0035	0.66
Mean PRT response bias	0.153 (0.013)	0.070 (0.018)	76	0.030	0.49
TEPS anticipatory subscale	32.8 (5.5)	32.6 (5.4)	88	>0.10	0.03
TEPS consummatory subscale	29.3 (4.2)	27.1 (4.2)	88	0.017	0.51
EEfRT	0.41 (0.11)	0.41 (0.11)	83	>0.10	0.00
VAS anhedonia	4.2 (1.5)	4.6 (1.5)	88	>0.10	0.30
Resting-state EEG delta current density in rostral anterior cingulate	62.0 (77.9)	81.2 (81.1)	81	>0.10	0.24
HAM-D	10.8 (4.0)	11.1 (3.9)	89	>0.10	0.09
HAM-A	11.0 (4.2)	10.6 (4.4)	89	>0.10	0.09
CGI-I	3.27 (0.7)	3.20 (0.6)	89	>0.10	0.08
CGI-S	3.28 (0.5)	3.32 (0.5)	89	>0.10	0.08
CPFQ	21.1 (4.2)	21.1 (4.2)	88	>0.10	0.00

Means are baseline-corrected values derived from mixed-effects models. CGI-I, Clinical Global Impression of Improvement.

Aticaprant in a 8-wk, double-blind, placebo-controlled trial in patients with anhedonia and a mood or anxiety disorder :

- Aticaprant **significantly increased BOLD activation in the ventral striatum activation (during reward anticipation) (Monetary Incentive Delay tasks)** compared with placebo
- Aticaprant resulted in **higher ability to learn from reward feedback and in a more sustained preference toward the more frequently rewarded stimulus (PRT : Probabilistic Reward Task)** while resulting in an **unaltered EEfRT (Effort Expenditure for Reward tasks)**
- While there was **also superiority on the SHAPS and the TEPS consummatory subscale, no significant differences were found neither for other anhedonia measures nor for clinical (symptomatic or functional) measures**

Hesitations on the ‘neurobiological promise’ : divergence between neurobiological/behavioral and subjective measures

Do we believe our eyes, our computer screens or what patients share with us ?

Bivariate correlation matrix of reward variables at baseline.

	VS	PRT	EEfRT	SHAPS	TEPS-A	TEPS-C	VASA
VS	-	0.08	0.11	-0.01	-0.03	-0.08	0.07
PRT	-	-	-0.10	-0.07	-0.20	-0.10	0.05
EEfRT	-	-	-	0.24*	0.22*	0.20	0.10
SHAPS	-	-	-	-	0.68**	0.70**	0.65**
TEPS-A	-	-	-	-	-	0.69**	0.63**
TEPS-C	-	-	-	-	-	-	0.51**
VASA	-	-	-	-	-	-	-



Imaging
or
Cognitive neuroscience
or
Phenomenologically based questionnaires



The Tower of Babel story from Genesis 11 describes humanity, united with one language, attempting to build a city and a tower reaching heaven to make a name for themselves.

God confounded their speech, creating different languages and scattering them across the earth, halting the construction.

This event explains the origin of diverse languages and serves as a lesson against human pride

Diagnostic tools / Assessment tools



- **Brain imaging**
- **Scales / Questionnaires**
 - Self-rating, Computer Adaptive Testing (CAT, e.g. NIH toolbox)
- **Behavioral computer tests : ‘reward deficits’**
 - Primary instinctual reward (e.g. food, sex) *versus* secondary non-instinctual reward (e.g. money)
 - e.g. Monetary Incentive Delay task (MID), Effort Expenditure for Reward (EEfR)

...do we still have trust in what patients entrust us ?

...are we giving up interpersonal communication for computerized communication ?

Talking about Anhedonia : a Tower of Babel ?

Questionnaires versus Computer tests



- **Clinical/Phenomenological Language** : *interest and pleasure*
 - Anticipatory and consummatory hedonic tone / sensory (physical) and social hedonic tone /positive affect
 - **Scales** : SHAPS : (?) golden standard : ‘i would enjoy...’ interest/pastimes, social interaction, sensory experiences, food/drinks’
TEPS, MAP-SR, SLIPS, ACIPS, LAPS, VAS-(an)hedonia, EPDS anhedonia subscale
- **Cognitive Neuroscience / Neurobiological Language** (*in line with RDoC*)
 - Stimulus, readiness for reward, activating reward association, feedback integration, energy expenditure to attain reward, compute effort/action plan, updating reward presence and value, expectation, motivation, anticipation, interest, pleasure/liking
 - **Computer tests** : Probabilistic Reward Task (PRT), Monetary Incentive Delay task (MID), Effort-Expenditure for Rewards Task (EEfRT)
- **(Hybrid) Language**
 - **Scale** : Dimensional Anhedonia Rating Scale (DARS) :
Combining SHAPS language with reward language :
subject has to choose 2 activities within the 4 SHAPS domains (interest/pastimes, social interaction, sensory experiences, food/drinks) with reward language (reward motivation, reward responsiveness, expected fun, drive)

Assessing anhedonia : Leuven Affect and Pleasure Scale (LAPS) ?



- **Sensory anhedonia :**

- Having interest in or looking forward to... a good meal or a drink, touching and being touched, a warm and sunny day, smelling the forest or the sea, listening to music, walking on the beach, looking at something beautiful...
- Taking pleasure from or enjoying ... a good meal or a drink, touching and being touched, a warm and sunny day, smelling the forest or the sea, listening to music, walking on the beach, looking at something beautiful.....

- **Social anhedonia :**

- Having interest in or looking forward to contacts with people important to me
- Taking pleasure from or enjoying to contacts with people important to me



Assessment tools for positive affect / anhedonia



- **Scales for measuring positive affect/anhedonia**
 - **PANAS** : positive and negative affect, no affiliative positive affect
 - **SHAPS** : so called gold standard...but 'i would enjoy....' ????
 - **TEPS** : only physical anhedonia
 - **ACIPS/MAP-SR/SLIPS** : only social anhedonia
 - **NIH toolbox** : scales on positive affect, life satisfaction, meaning and purpose, positive social development, companionship, social support
 - **DARS** : Dimensional Anhedonia Rating Scale : interest, motivation, effort, enjoyment for 4 domains (hobbies, social activities, food/drinks, sensory experiences)
 - **LAPS anhedonia subscale** : physical and social anhedonia / anticipatory and consummatory
 - **LAPS positive affect subscale** : activated/deactivated pos. affect, affiliative pos. affect (caring, loving, secure, safe)
 - **EPDS anhedonia subscale** : 2 items (EPDS has 3 subscales : anhedonia, anxiety, depression)

When psychiatrists try to build a city and a tower reaching heaven in Shinar (Babylon)



- The so-called **MADRS anhedonia subscale** :
 - 5 items (apparent sadness, reported sadness, concentration difficulties, lassitude, inability to feel)



When psychiatrists try to build a city and a tower reaching heaven in Shinar (Babylon)



- The so-called MADRS anhedonia subscale :
 - 5 items (~~apparent sadness, reported sadness, concentration difficulties~~, lassitude, inability to feel)

Effectiveness of repeated Esketamine nasal spray administration on anhedonic symptoms in treatment-resistant bipolar and unipolar depression: A secondary analysis from the REAL-ESK study group.

d'Andrea G, Cavallotto C, Pettorruso M, Lorenzo GD, Carullo R, De Berardis D, Rosso G, Barlati S, Martiadis V, Tamagnini G, Raffone F, Mammarella G, d'Attilio A, Vannucchi T, Nicola MD, De Filippis S, Andriola I, Zanardi R, De Giorgi A, Petralia A, Pigato G, Serafini G, Dell'Oso BM, Clerici M, Vita A; REAL-ESK Study Group; Sensi SL, McIntyre RS, Martinotti G. Psychiatry Res. 2025 Oct;352:116655. doi: 10.1016/j.psychres.2025.116655. Epub 2025 Jul 26.

Cao, B., Park, C., Subramaniapillai, M., Lee, Y., Iacobucci, M., Mansur, R.B., Zuckerman, H., Phan, L., McIntyre, R.S., 2019. The Efficacy of Vortioxetine on Anhedonia in Patients With Major Depressive Disorder. Front. Psychol. 10, 17. <https://doi.org/10.3389/fpsy.2019.00017>.

Comparative effectiveness of repeated ketamine infusions in treating **anhedonia** in bipolar and unipolar depression.

Zheng W, Gu LM, Sun CH, Zhou YL, Wang CY, Lan XF, Zhang B, Ning YP.

J Affect Disord. 2022 Mar 1;300:109-113. doi: 10.1016/j.jad.2021.12.105. Epub 2021 Dec 26.

The effect of adjunctive cariprazine on symptoms of **anhedonia** in patients with major depressive disorder.

McIntyre RS, Maletic V, Masand P, Wilson AC, Yu J, Adams JL, Kerolous M.

J Affect Disord. 2025 Sep 15;385:119366. doi: 10.1016/j.jad.2025.05.026. Epub 2025 May 6.

Effect of venlafaxine on **anhedonia** and amotivation in patients with major depressive disorder.

McIntyre RS, Agid O, Biesheuvel E, Purushottamahanti P.

CNS Spectr. 2024 Jun;29(3):206-214. doi: 10.1017/S1092852924000245. Epub 2024 Apr 30.

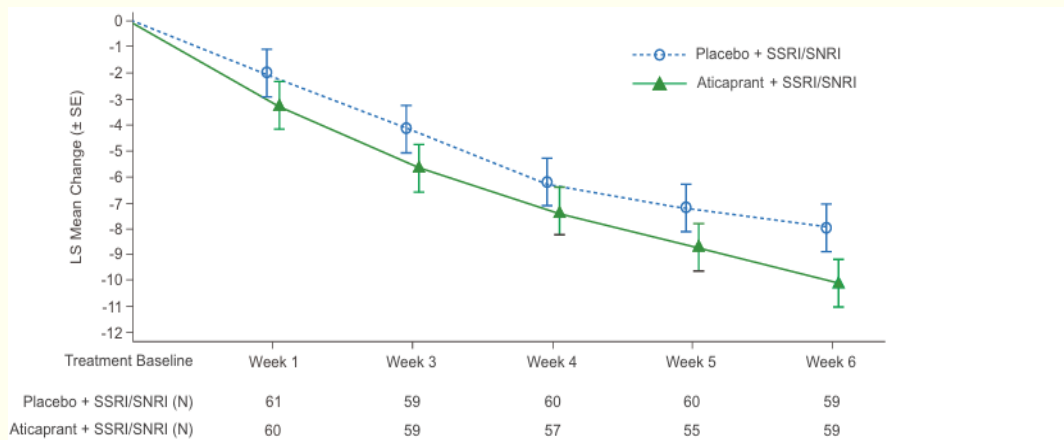
Efficacy of Vortioxetine on **Anhedonia**: Results from a Pooled Analysis of Short-Term Studies in Patients with Major Depressive Disorder.

McIntyre RS, Loft H, Christensen MC.

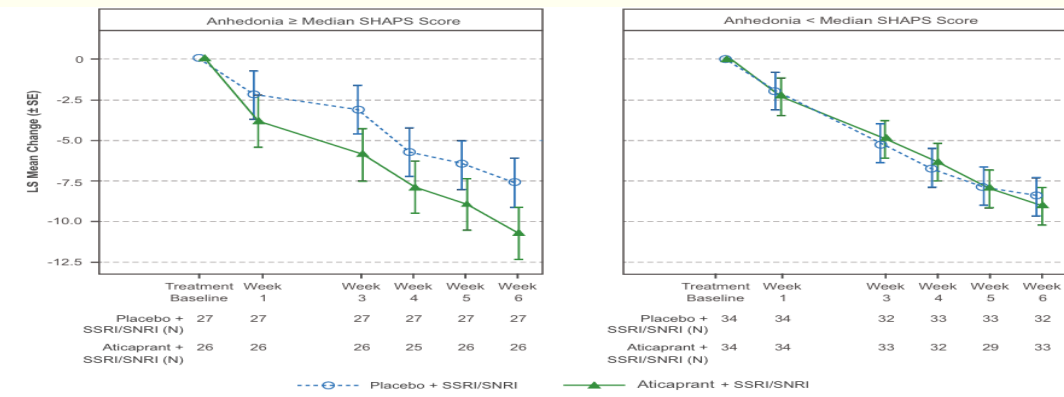
Neuropsychiatr Dis Treat. 2021 Feb 22;17:575-585. doi: 10.2147/NDT.S296451. eCollection 2021.

Aticaprant versus Placebo

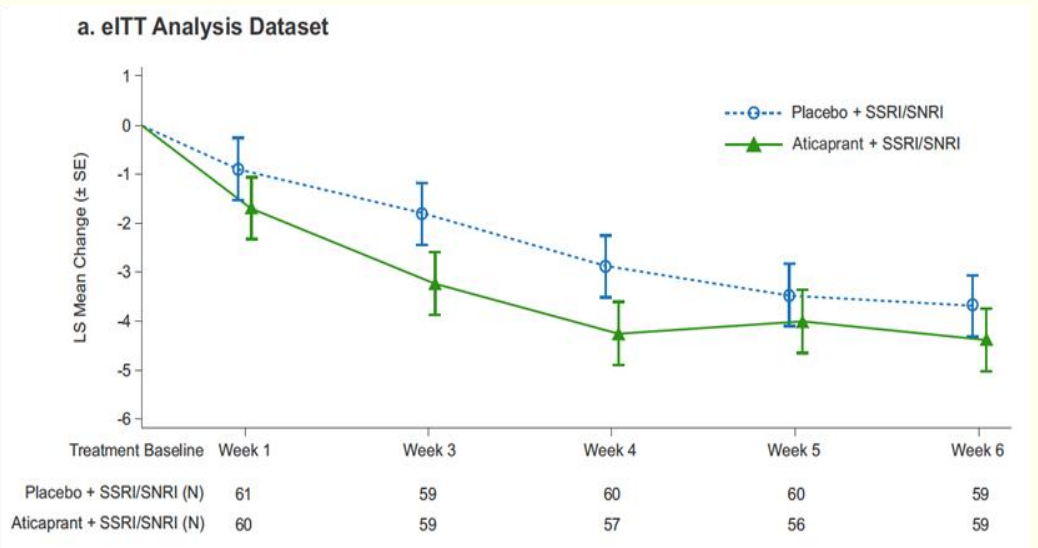
Neuropsychopharmacology (2024) 49:1437–1447; <https://doi.org/10.1038/s41386-024-01862-x>



Decrease in MADRS : P= 0.04; ES 0.23



Decrease in MADRS in higher versus lower baseline anhedonia
Higher : P= 0.07; ES 0.36 Lower : P= 0.35; ES 0.07



Anhedonia (SHAPS) improvement : P= 0.42; ES 0.07

Differentiation aticaprant-placebo on individual MADRS items

MADRS symptoms

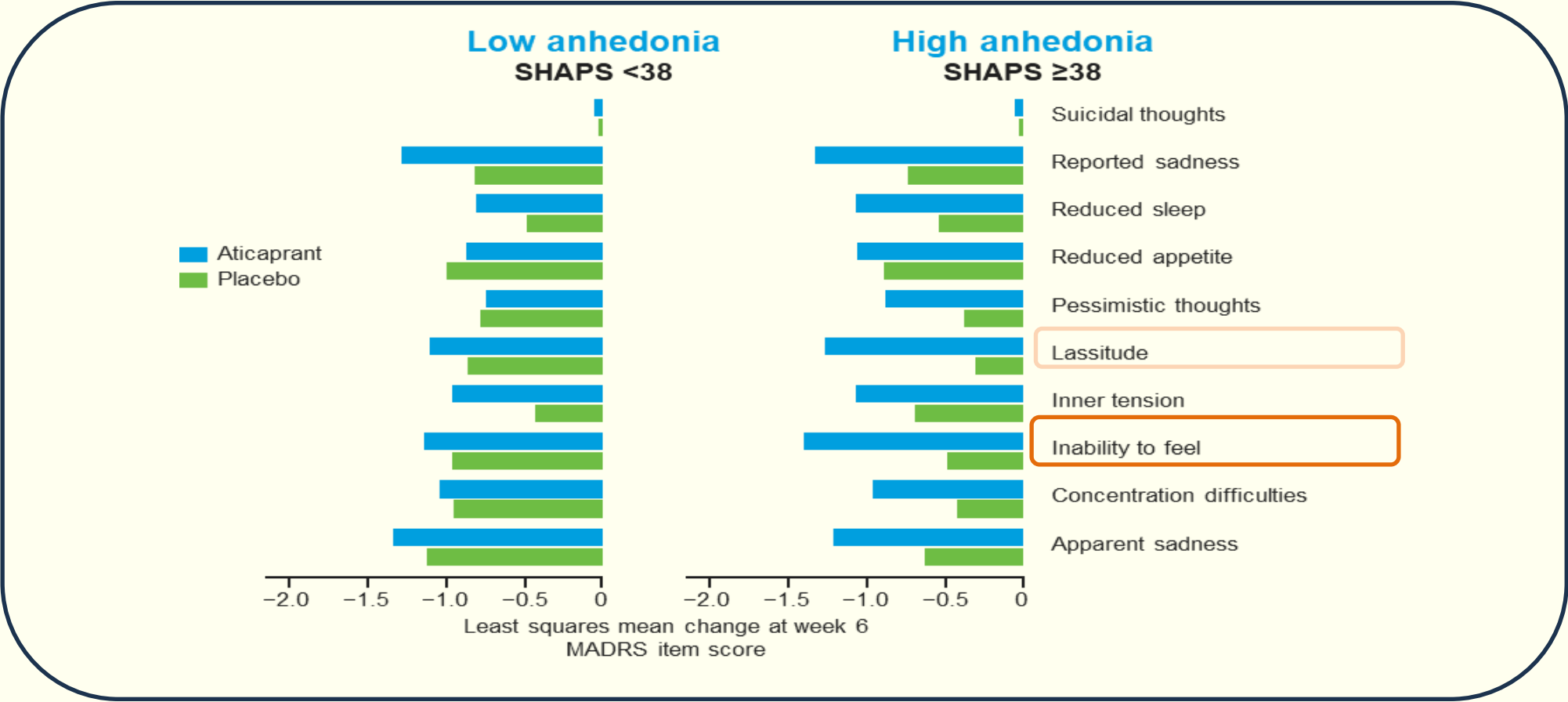
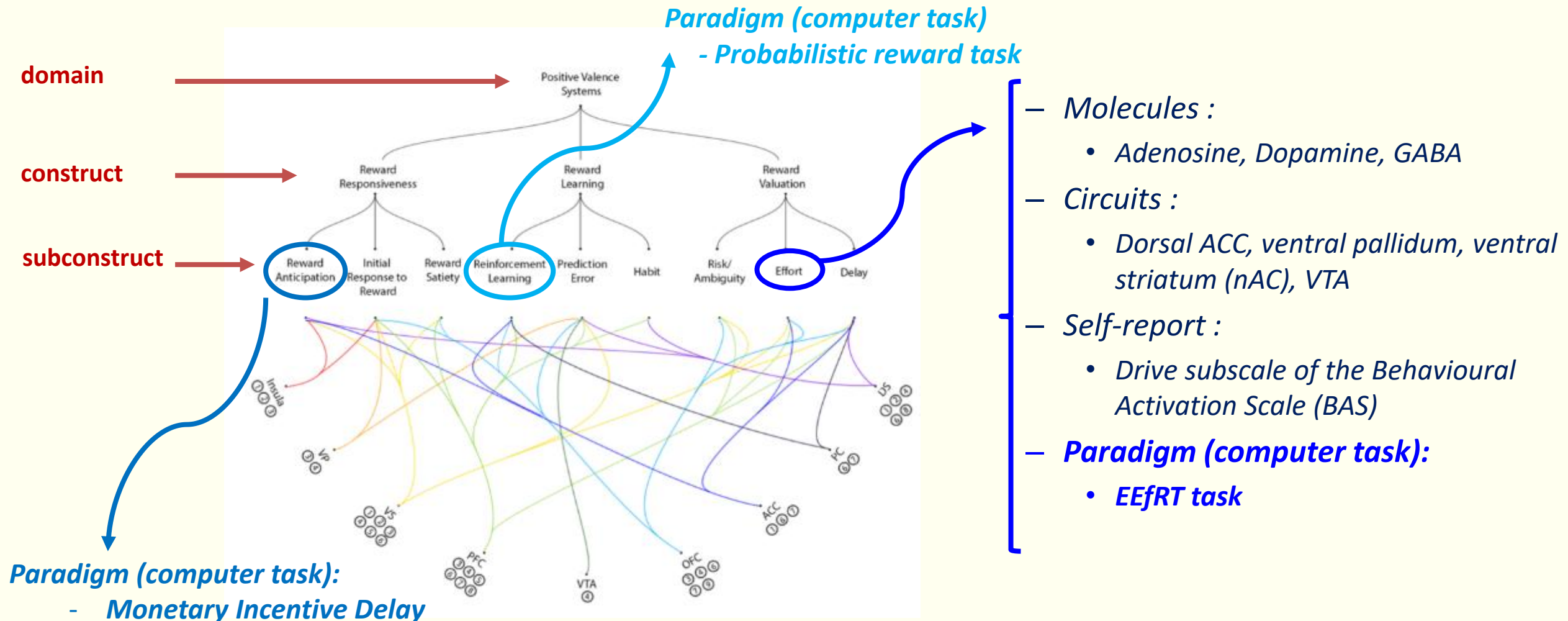


Figure adapted from Schmidt ME, et al. Poster presented at: 61st Annual Meeting of American College of Neuropsychopharmacology; December 4–7, 2022; Phoenix, AZ, US.

Positive Valence Systems Domain is one of the constructs in NIMH Research Domain Criteria (RDoC) project



For each subconstruct : molecules, circuits, genes, self-report, paradigm

From NIMH FAST-FAIL to NIMH RDoC : a bridge too far (???)

Paris J and Kirmayer LR, 2016



this failure is also a blow to the domain-based model

1. It uses models from neuroscience that are insufficiently developed
2. It is based on the premise that mental phenomena and mental disorders can be reduced to neural activity, with consideration of cognition but without consideration of experience and social interaction
3. It downplays psychosocial and relational factors in psychopathology and treatment

**The recent trial failures are “not the nail in the coffin” for more focused psychiatric drug development,...
“They just tell you how much we still have to learn.” (Bill Potter)**

THANK YOU

