TSPP 70th Annual Convention and Scientific Program

November 7, 2026

Innovations in Pharmacotherapy for Difficult-to-Treat Mood Disorders

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Faculty Disclosures

***consultant/advisor*:** AtaiBeckley, Autobahn Therapeutics, Aytu Biopharma, Bristol-Myers Squibb, Boehringer-Ingelheim, Definium Therapeutics, Douglas Pharmaceuticals, Engrail Therapeutics, Motif Neurotech, Neumora, Newleos, Sensorium Biosciences, Seaport, Supernus, Xenon Pharmaceuticals

***Research contracts*:** Abbott, Engrail Therapeutics, Neumora Therapeutics

***Off label use*:** Racemic ketamine is off-label for psychiatric conditions in the U.S.

In March 2026 the French drug regulatory agency approved intravenous racemic ketamine for the treatment of adult severe suicidal crisis

Learning Objectives

1. **Summarize** several major recent studies evaluating glutamate modulators for treatment-resistant depression and major depressive disorder

2. **Evaluate** the scientific rationale for several novel pharmacotherapy approaches for mood disorders

3. **Identify** future directions for clinical and translational research for experimental therapeutics

Outline of Talk

- Targeting Glutamate Signaling in Mood Disorders
  - Ketamine/esketamine
  - Do mechanistic insights offer rationale for new targets (e.g., AMPA receptor, mTOR, mu-opioid receptor)?
- Beyond Glutamate -- Novel mechanisms in late-stage development
  - Kv7 potassium channel opener
- Psychedelics

Global Economic Cost of Major Depression

- MDD affects approximately 300 million people worldwide
- Profound impact of depression on labor force participation, educational attainment and work experience
- Global burden of depression will be **$12 trillion** between 2025 and 2050, representing 0.460% of annual global GDP
- Highest economic burdens are in US and China

WHO, 2017; Cao et al Nature Medicine 2026

Unmet Needs in Depression Therapeutics

At least 31 approved antidepressant meds

Numerous monoamine-based antidepressants (SSRIs, SNRIs, atypical antipsychotics, TCAs, MAOIs, etc); however:

- Modest effect sizes vs placebo
- Adverse events
- Relatively slow onset of action
- Uncertain efficacy for suicidal ideation and behavior

FDA-Approved Therapies for Difficult-to-Treat Depression

- **Device/neuromodulation**
  - Electroconvulsive therapy (ECT)
  - Repetitive transcranial magnetic stimulation
  - Vagus nerve stimulation
  - Transcranial direct current stimulation (tDCS)

Pivotal trial of deep brain stimulation of subgenual cingulate cortex underway

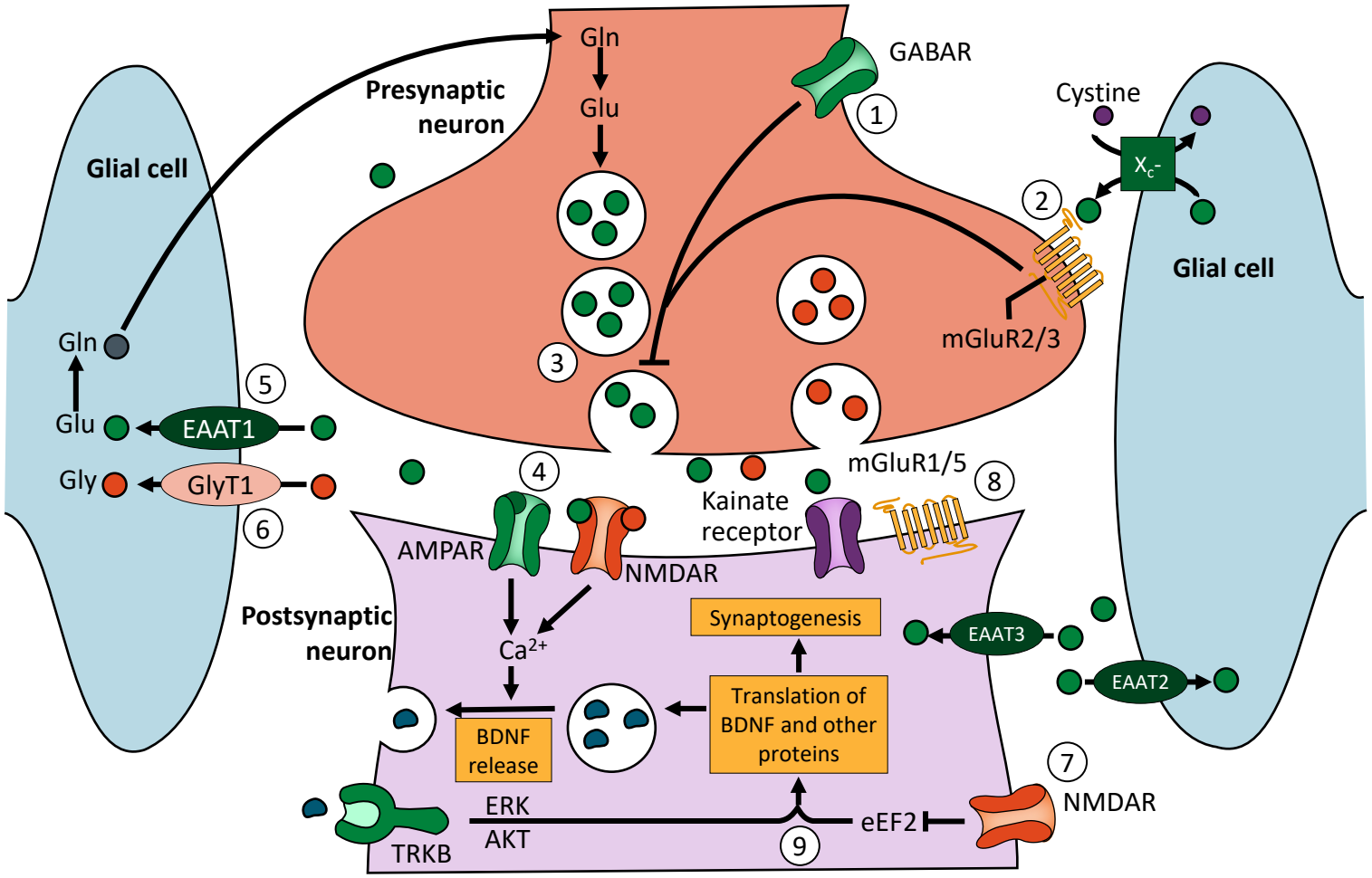
- **Olanzapine/fluoxetine combination**: Treatment-resistant depression (TRD) indication

- **Adjunctive atypical antipsychotics**
  - Aripiprazole
  - Quetiapine XR
  - Brexpiprazole
  - Cariprazine
  - lumateperone
- **Adjunctive esketamine nasal spray**: TRD indication

Multiple glutamate modulating and novel mechanism drugs in development

Jha MK and Mathew SJ, *AJP* 2023

Targeting Glutamate Signaling in Depression

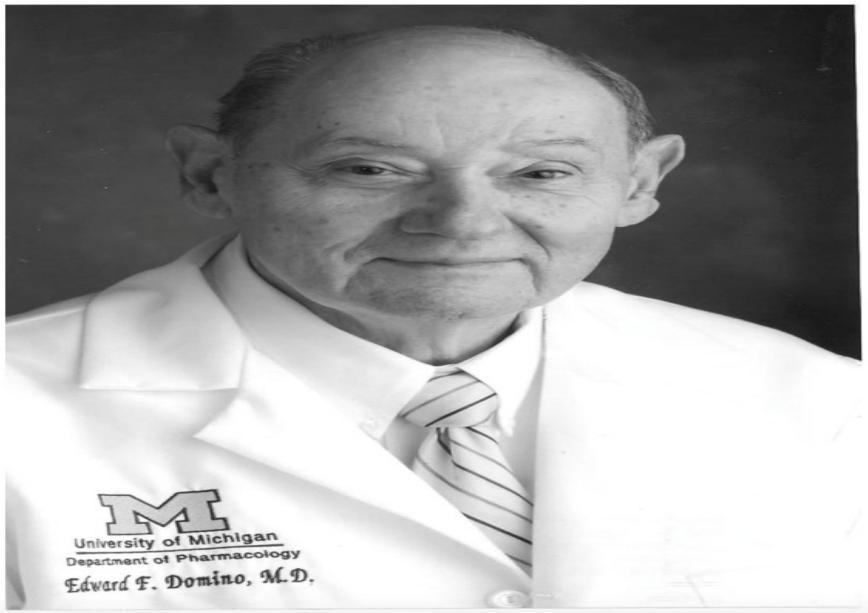


- Multiple targets within the glutamate system for novel drug discovery
  - NMDA and AMPA receptors
  - Metabotropic glutamate receptors
  - Key regulatory proteins: glycine transporter 1 and excitatory amino acid transporters.
- Multiple glutamate-based compounds have entered clinical testing over the past decade-plus

Murrough, Abdallah, Mathew. Nat Rev Drug Discovery. 2017;16:472.

Ketamine: A Dissociative Anesthetic

- Derivative of phencyclidine (PCP)
- FDA approved anesthetic since 1970 (**Schedule III**)
- Studied extensively as a model of psychosis
- Substance of abuse (eg, “Special K”)

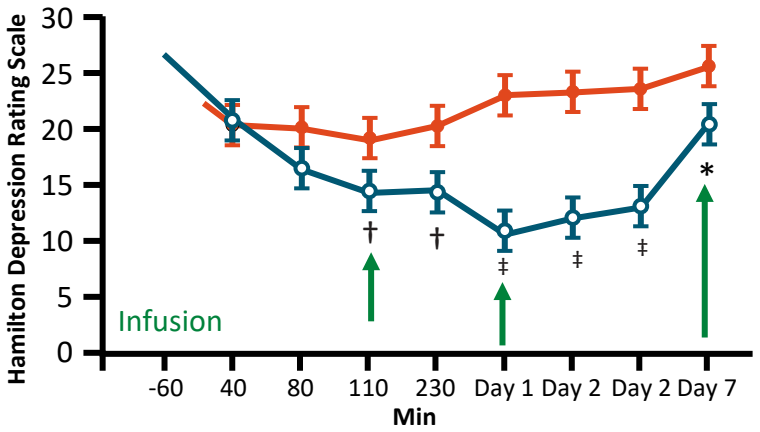


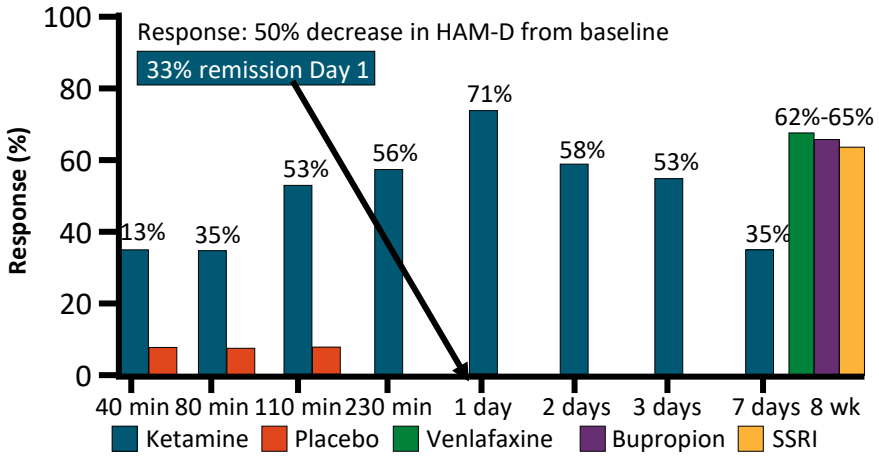


Domino EF. *Anesthesiology*. 2010

Single Subanesthetic Dose Ketamine Infusion Trials in Treatment Resistant Depression

Ketamine (0.5 mg/kg over 40 min) Rapidly Effective vs Saline Placebo: Replication Study (N = 17)



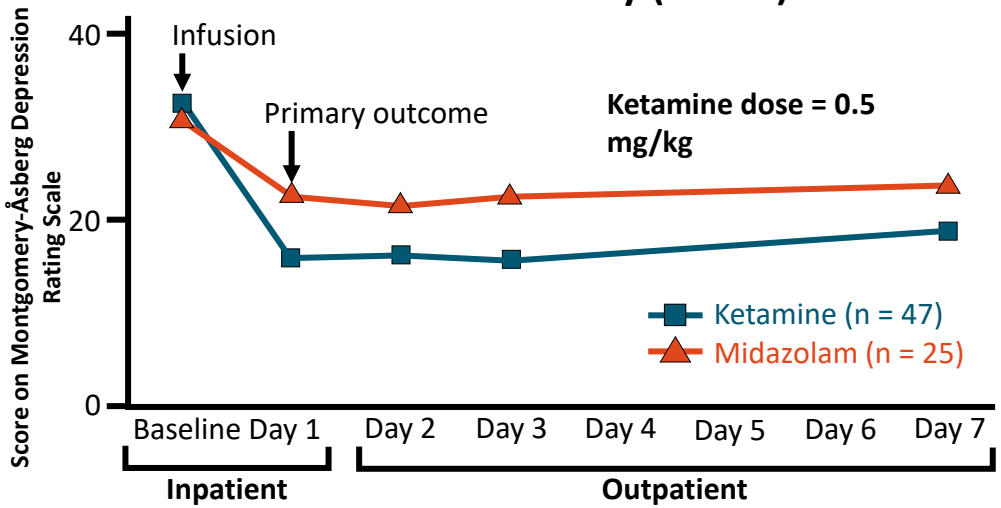


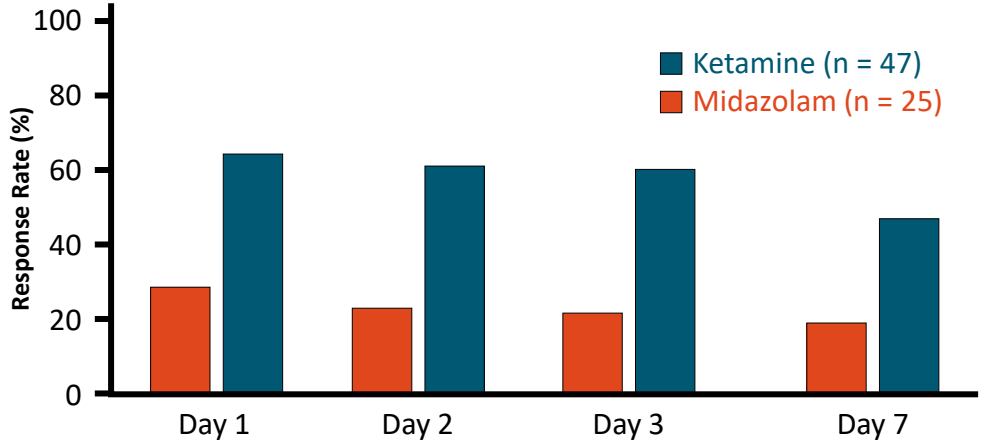
*P <.05; †P <.01; ‡P <.001.

Zarate et al. Arch Gen Psychiatry. 2006.

Ketamine Superior to Psychoactive Control: Baylor/Mt Sinai NIMH-Funded Study (N = 72)



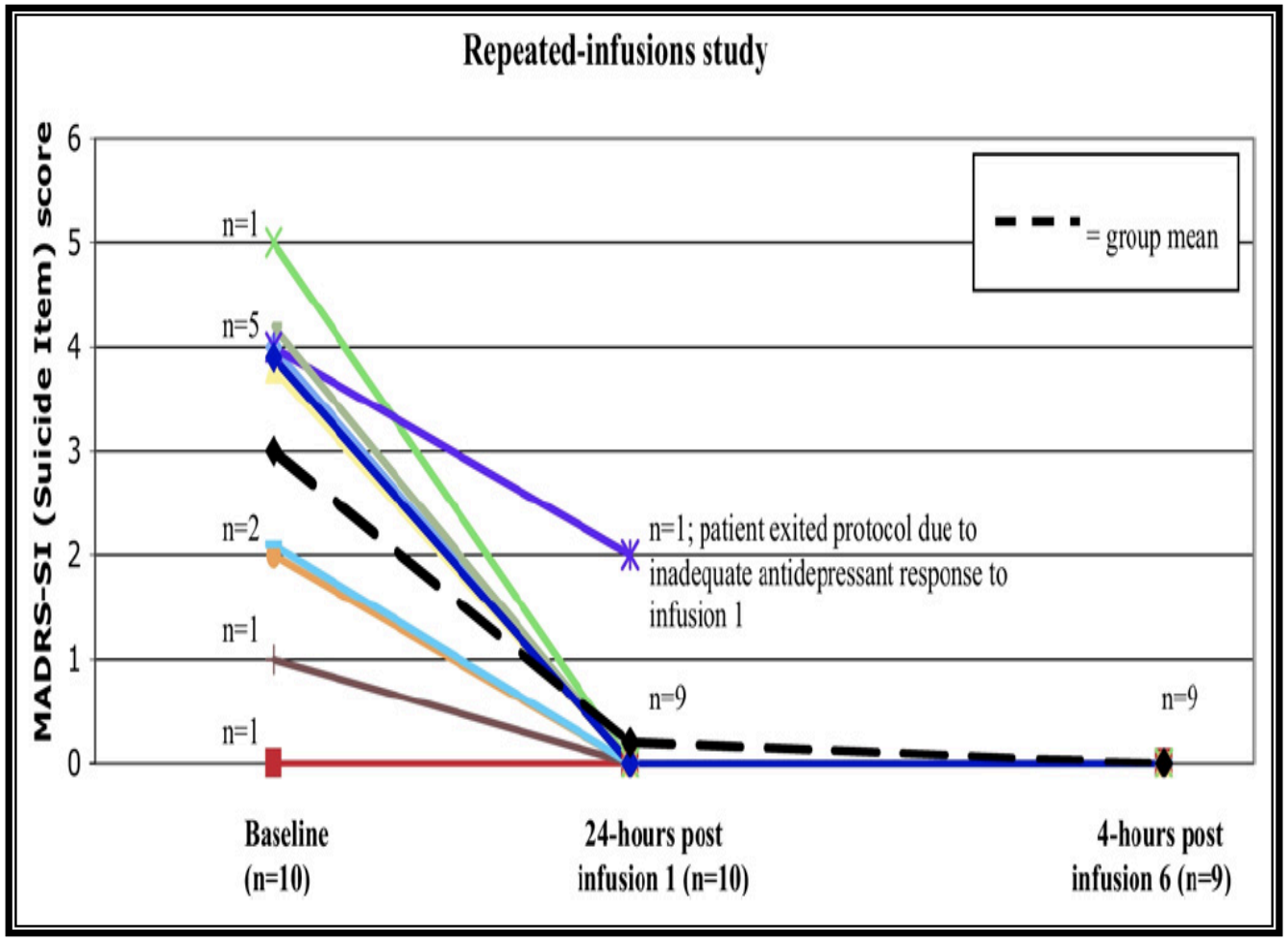




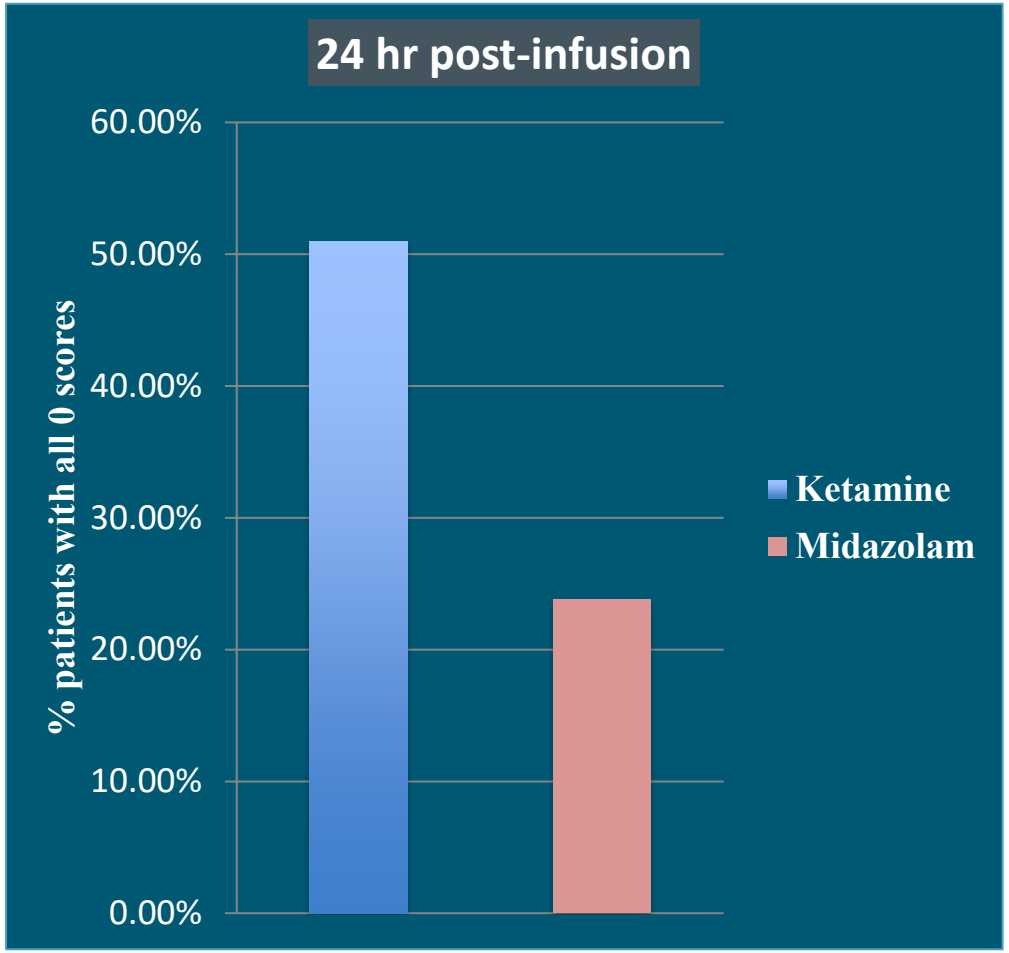
Murrough et al. Am J Psychiatry 2013.



Initial reports of ketamine's impact on suicidal ideation



Price RB et al Bio*l Psychiatry* 2009



Price RB et al *Dep Anxiety* 2014

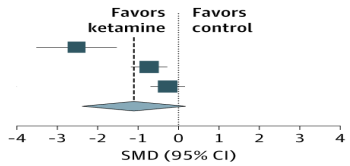
Ketamine Infusions and Rapid Reduction of Suicidal and Depressive Symptoms in Major Depressive Episode: A Systematic Review and Meta-Analysis (26 RCTs, n=1166)

Suicidal symptoms

A Suicidal symptoms at 4 h after a single ketamine infusion

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Hu et al,[38] 2016	13	14	−2.521 (−3.515 to −1.527)
Grunebaum et al,[42] 2018	40	40	−0.729 (−1.177 to −0.280)
Lin et al,[56] 2024	42	42	−0.268 (−0.694 to 0.158)
Total			−1.104 (−2.383 to 0.176)

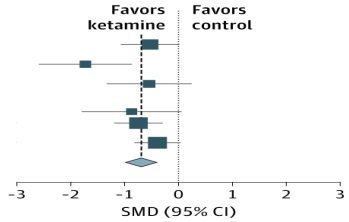
Heterogeneity: $\tau^2 = 1.1662$; $\chi^2 = 16.81$; $df = 2$; $P < .001$; $I^2 = 88.1\%$



B Suicidal symptoms at 24 h after a single ketamine infusion

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Price et al,[37] 2014	36	21	−0.528 (−1.068 to 0.011)
Hu et al,[38] 2016	13	14	−1.729 (−2.594 to −0.863)
Murrough et al,[39] 2015	12	12	−0.545 (−1.333 to 0.243)
Grunebaum et al,[40] 2017	9	9	−0.871 (−1.796 to 0.054)
Grunebaum et al,[42] 2018	40	40	−0.743 (−1.192 to −0.294)
Lin et al,[56] 2024	42	42	−0.391 (−0.819 to 0.037)
Total			−0.691 (−0.983 to −0.400)

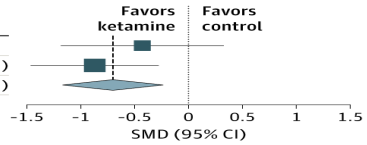
Heterogeneity: $\tau^2 = 0.0366$; $\chi^2 = 8.02$; $df = 5$; $P = .16$; $I^2 = 37.7\%$



C Suicidal symptoms at 1 mo after a single ketamine infusion

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Hu et al,[38] 2016	12	14	−0.429 (−1.185 to 0.327)
Feeney et al,[46] 2021	40	16	−0.871 (−1.465 to −0.277)
Total			−0.702 (−1.169 to −0.235)

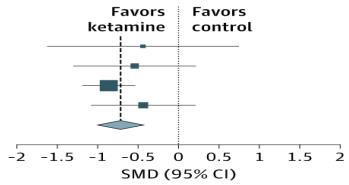
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.81$; $df = 1$; $P = .37$; $I^2 = 0\%$



D Suicidal symptoms at the end of treatment after repeated ketamine infusions

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Sinyor et al,[48] 2018	5	4	−0.440 (−1.626 to 0.746)
Ionescu et al,[49] 2019	13	13	−0.543 (−1.302 to 0.216)
Abbar et al,[50] 2022	73	83	−0.863 (−1.191 to −0.536)
Ahmed et al,[51] 2023	18	18	−0.436 (−1.083 to 0.211)
Total			−0.717 (−1.002 to −0.431)

Heterogeneity: $\tau^2 = 0.0062$; $\chi^2 = 1.89$; $df = 3$; $P = .59$; $I^2 = 0\%$

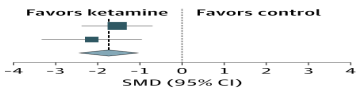


Depressive symptoms

A Depressive symptoms at 4 h after a single ketamine infusion

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Hu et al,[38] 2016	13	14	−1.539 (−2.379 to −0.700)
Chen et al,[41] 2018	8	8	−2.142 (−3.330 to −0.955)
Total			−1.740 (−2.426 to −1.055)

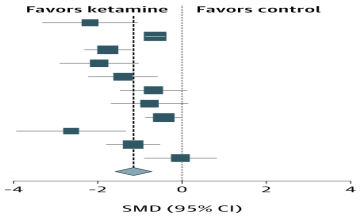
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.66$; $df = 1$; $P = .42$; $I^2 = 0\%$



B Depressive symptoms at 24 h after a single ketamine infusion

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Zarate et al,[32] 2006	9	9	−2.182 (−3.315 to −1.050)
Diazgranados et al,[33] 2010	9	9	−0.638 (−0.871 to −0.405)
Murrough et al,[35] 2013	47	25	−1.763 (−2.323 to −1.203)
Sos et al,[36] 2013	9	18	−1.966 (−2.902 to −1.029)
Hu et al,[38] 2016	13	14	−1.403 (−2.225 to −0.581)
Murrough et al,[39] 2015	12	12	−0.679 (−1.475 to 0.117)
Grunebaum et al,[40] 2017	9	9	−0.773 (−1.689 to 0.142)
Grunebaum et al,[42] 2018	40	40	−0.435 (−0.874 to 0.004)
Chen et al,[41] 2018	8	8	−2.632 (−3.932 to −1.332)
Phillips et al,[43] 2019	22	21	−1.161 (−1.797 to −0.525)
Pattanaseri et al,[53] 2024	10	9	−0.041 (−0.901 to 0.819)
Total			−1.150 (−1.584 to −0.717)

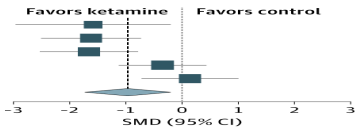
Heterogeneity: $\tau^2 = 0.3800$; $\chi^2 = 41.05$; $df = 10$; $P < .001$; $I^2 = 75.6\%$



C Depressive symptoms at 3 d after a single ketamine infusion

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Berman et al,[31] 2000	4	5	−1.582 (−2.961 to −0.204)
Sos et al,[36] 2013	9	18	−1.621 (−2.509 to −0.733)
Hu et al,[38] 2016	12	14	−1.656 (−2.528 to −0.784)
Murrough et al,[39] 2015	12	12	−0.346 (−1.125 to 0.432)
Pattanaseri et al,[53] 2024	10	9	0.141 (−0.721 to 1.002)
Total			−0.967 (−1.733 to −0.202)

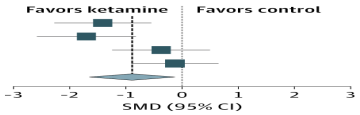
Heterogeneity: $\tau^2 = 0.5289$; $\chi^2 = 13.91$; $df = 4$; $P = .008$; $I^2 = 71.2\%$



D Depressive symptoms at 1 wk after a single ketamine infusion

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Sos et al,[36] 2013	9	18	−1.411 (−2.273 to −0.548)
Hu et al,[38] 2016	12	14	−1.703 (−2.582 to −0.825)
Pattanaseri et al,[53] 2024	10	9	−0.372 (−1.241 to 0.496)
Murrough et al,[39] 2015	12	12	−0.126 (−0.900 to 0.647)
Total			−0.889 (−1.648 to −0.129)

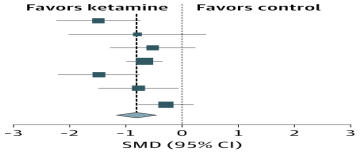
Heterogeneity: $\tau^2 = 0.4141$; $\chi^2 = 9.77$; $df = 3$; $P = .02$; $I^2 = 69.3\%$



E Depressive symptoms at the end of treatment after repeated ketamine infusions

Source	No. Ketamine	No. Control	SMD, IV, random (95% CI)
Singh et al,[47] 2016	18	16	−1.489 (−2.236 to −0.742)
Sinyor et al,[48] 2018	5	4	−0.795 (−2.020 to 0.430)
Ionescu et al,[49] 2019	13	13	−0.523 (−1.280 to 0.235)
Abbar et al,[50] 2022	73	83	−0.667 (−0.989 to −0.346)
Ahmed et al,[51] 2023	18	18	−1.480 (−2.204 to −0.755)
Ohtani et al,[52] 2024	15	16	−0.775 (−1.487 to −0.062)
Jelovac et al,[54] 2025	32	30	−0.286 (−0.781 to 0.208)
Total			−0.811 (−1.162 to −0.460)

Heterogeneity: $\tau^2 = 0.1089$; $\chi^2 = 11.63$; $df = 6$; $P = .07$; $I^2 = 48.4\%$



Shim et al JAMA Psychiatry. 2026;83(7):714-731



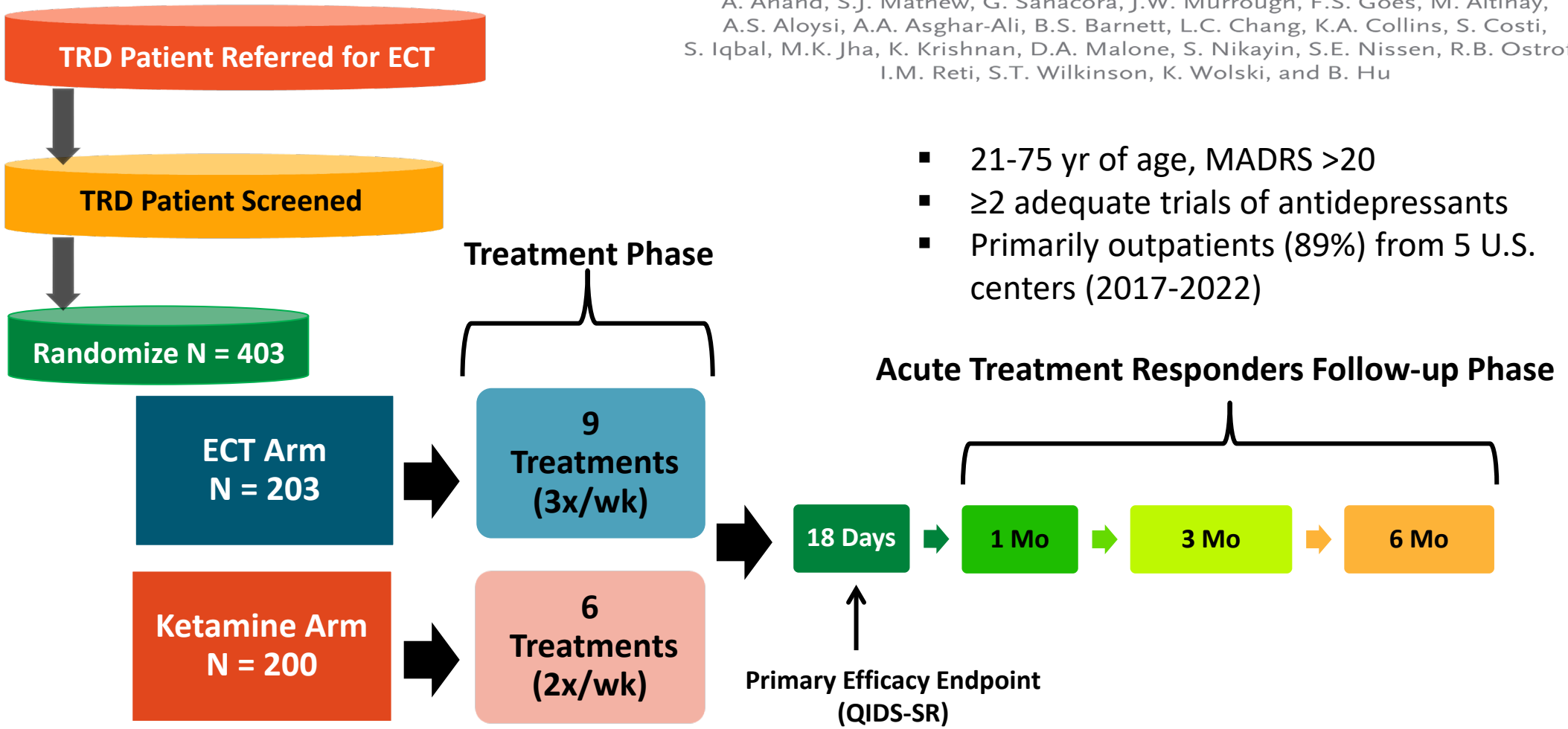
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

A. Anand, S.J. Mathew, G. Sanacora, J.W. Murrough, F.S. Goes, M. Altinay, A.S. Aloysi, A.A. Asghar-Ali, B.S. Barnett, L.C. Chang, K.A. Collins, S. Costi, S. Iqbal, M.K. Jha, K. Krishnan, D.A. Malone, S. Nikayin, S.E. Nissen, R.B. Ostroff, I.M. Reti, S.T. Wilkinson, K. Wolski, and B. Hu

- 21-75 yr of age, MADRS >20
- ≥2 adequate trials of antidepressants
- Primarily outpatients (89%) from 5 U.S. centers (2017-2022)

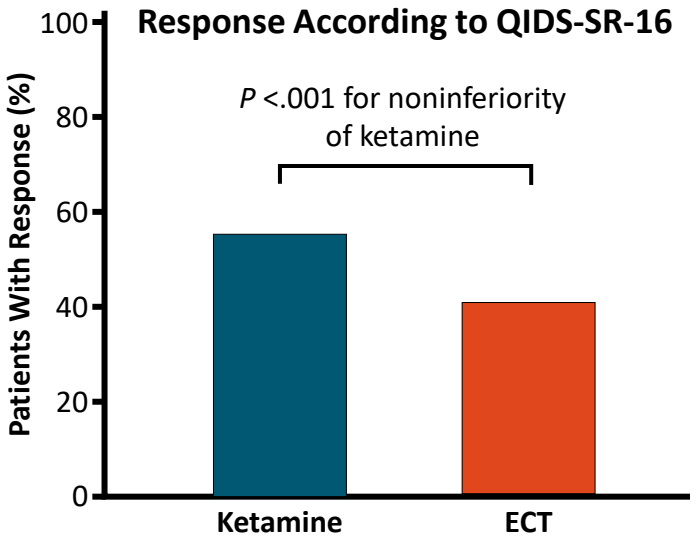


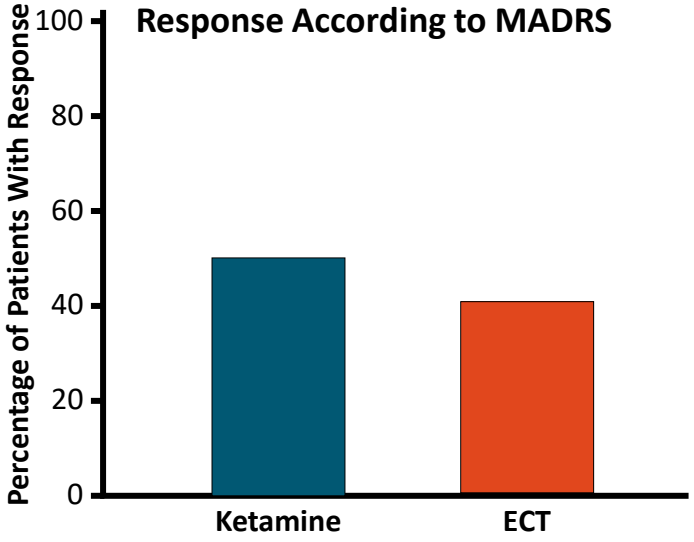
NCT03113968. Mathew et al. Contemp Clin Trials. 2019;77:19; Anand A, Mathew SJ, et al NEJM 2023.

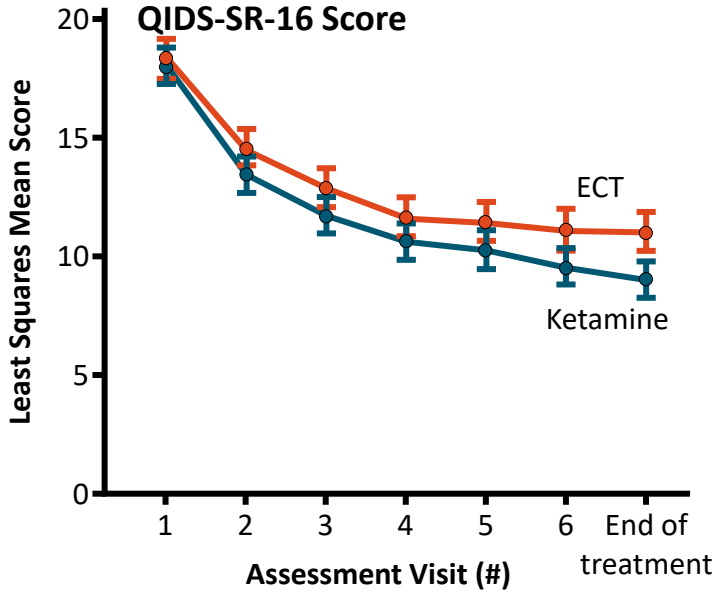
ELEKT-D Results

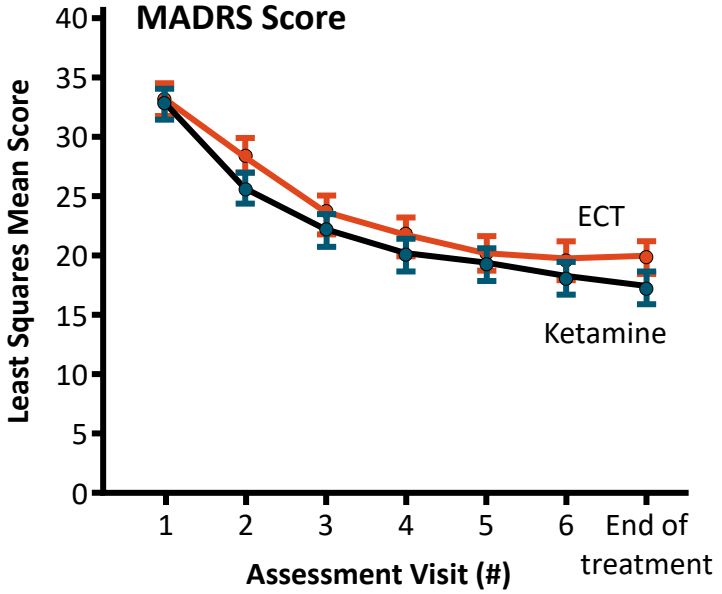
- Participants received IV ketamine (0.5 mg/kg body weight BIW) or acute course of ECT (TIW) over 3-5 wk
- Primary endpoint: decrease of ≥50% from baseline on QIDS-SR-16
- **IV ketamine was noninferior to ECT at the primary endpoint**
- Unusually low ECT remission rate = 20% (contrast to KetECT trial (63%) after 12 treatments)

Anand A, Mathew SJ, Sanacora G et al. NEJM. 2023



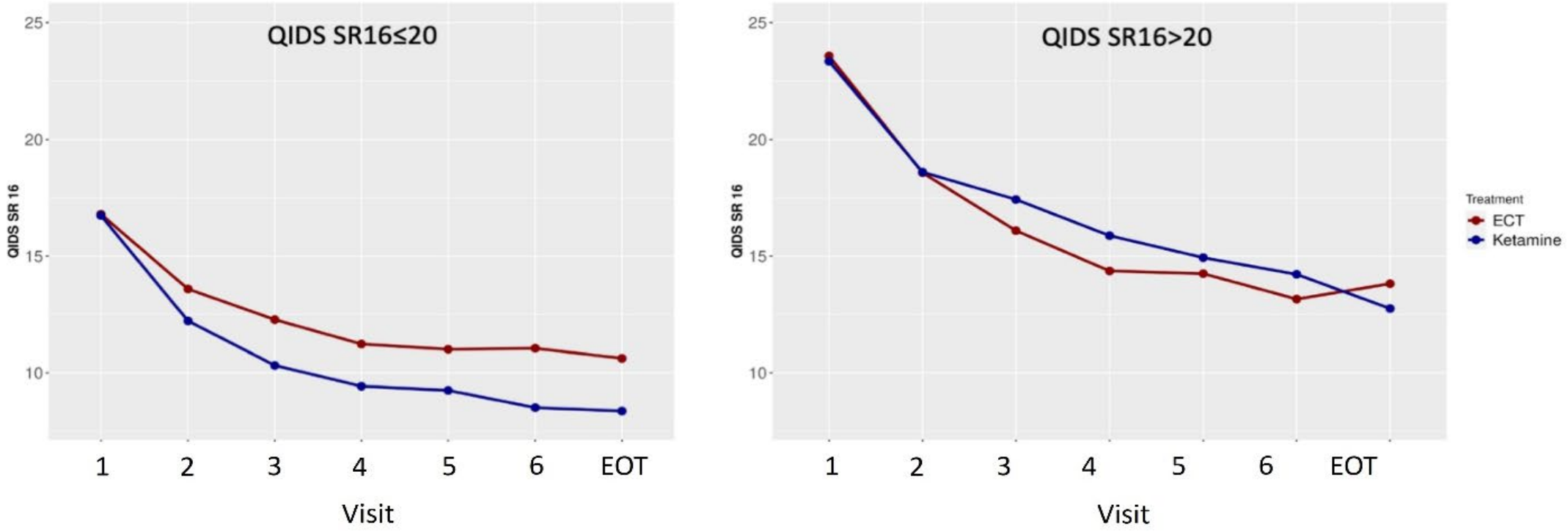








ELEKT-D Trial: Effect of baseline depressive severity



- Baseline QIDS-SR16 ≤20 ➔ greater reduction with ketamine vs ECT.
- Baseline QIDS-SR16 >20) ➔ greater reduction with ECT vs ketamine earlier during treatment (i.e., by week-2).

Jha MK et al. *JAMA Network Open*.2024

Serial IV ketamine as adjunctive therapy to inpatient care for depression: The KARMA-Dep 2 Randomized Controlled Trial

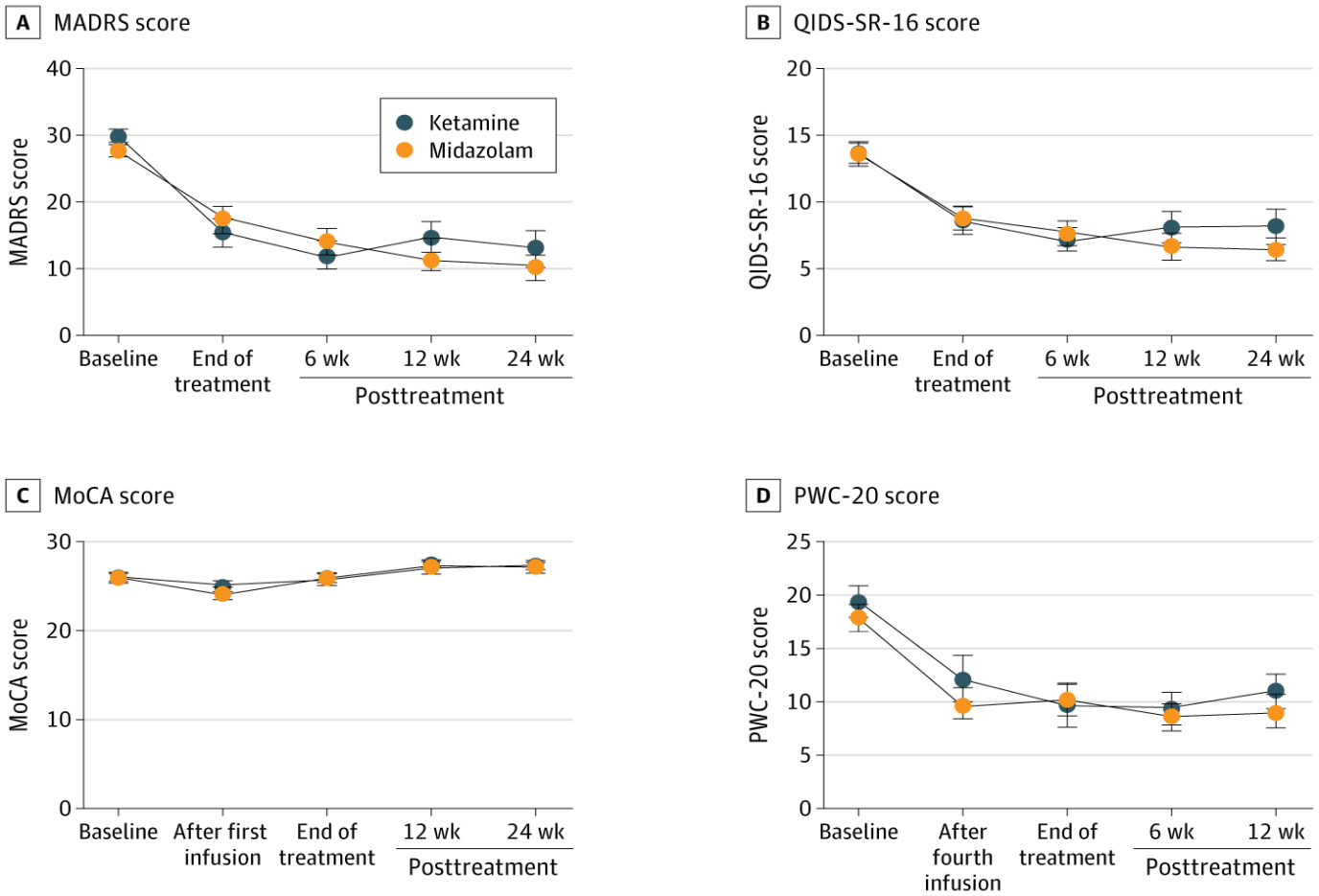


Table 2. Treatment-Emergent Adverse Events Occurring in ≥10% of Participants

Adverse event	No. (%)	
	Ketamine group (n = 32)	Midazolam group (n = 30)
Participants with ≥1 adverse event	29 (90.6)	28 (93.3)
Fatigue	12 (37.5)	13 (43.3)
Sleep disturbance	8 (25.0)	14 (46.7)
Abnormal liver function test	9 (28.1)	10 (33.3)
Dizziness	7 (21.9)	6 (20.0)
Headache	8 (25.0)	5 (16.7)
Bradycardia	3 (9.4)	7 (23.3)
Hypertension	7 (21.9)	3 (10.0)
Other arrhythmias	3 (9.4)	5 (16.7)
Hypotension	2 (6.2)	5 (16.7)
Nausea	6 (18.8)	0 (0.0)
Anxiety or panic attack	2 (6.2)	3 (10.0)

Jelovac et al *JAMA Psychiatry* 2025

FDA Approved Indications for Esketamine Nasal Spray

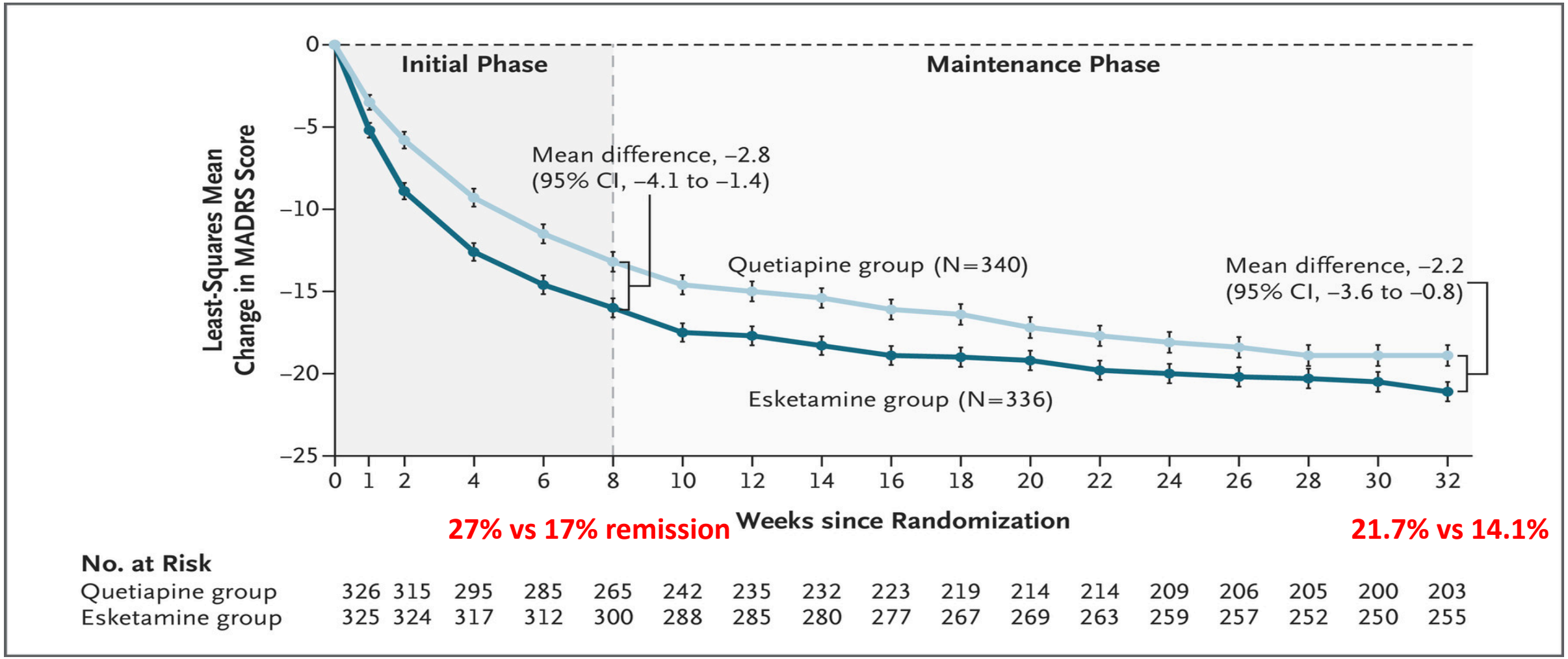
- March 2019: FDA approved esketamine nasal spray in conjunction with an oral antidepressant for TRD in adults (*Jan 2025*- supplemental approval as **monotherapy**)
- July 2020: FDA approved indication of depressive symptoms in adults with MDD with acute suicidal ideation or behavior

Requires REMS Program

- Administered under direct supervision of healthcare professional
- Monitored for ≥2 hr after administration
- Not dispensed for home use
- Data registry
- Driving restrictions

Esketamine PI.

ESCAPE-TRD: open-label, single-blind, randomized, comparative trial (n=676)



Reif A, et al *NEJM* 2023

Dropout due to safety/tolerability: 4.2% (ESK) vs 11% (QTP)

Six years after approval of esketamine nasal spray: Many unanswered questions

Six Years After Approval of Esketamine Nasal Spray for Serious Depression: Clinical Conundrums and Unanswered Questions

Sanjay J. Mathew, M.D., Nicholas Murphy, Ph.D.

Ketamine was approved in 1970 as an intravenous anesthetic agent, and over the past 10–15 years has been increasingly repurposed for "off-label" use in major depressive disorder (MDD) and several other psychiatric conditions. In March 2019, the U.S. Food and Drug Administration (FDA) approved the first ketamine-derived medication for a psychiatric indication—esketamine nasal spray—specifically for adjunctive therapy in adults with treatment-resistant depression (with an additional approval in 2020 for depressive symptoms in MDD with acute suicidal ideation or behavior). The development of esketamine, the (*S*)-enantiomer of racemic ketamine, was guided by the view that the increased potency of this enantiomer would permit lower dosing and mitigate racemic ketamine's well-known immediate side effects (i.e., dissociation, sedation). However, given the continued presence of these adverse effects as well as ketamine's abuse liability and Schedule III classification, the clinical implementation of esketamine has been subject to a Risk Evaluation and Mitigation Strategy (REMS), which mandates in-clinic drug self-administration, a postdosing monitoring period of at least 2 hours, driving restrictions, and other procedural safeguards (1). Six years after its approval, many questions remain about esketamine's role in clinical practice amid an increasingly complex mental health treatment landscape.

The broader psychiatric treatment landscape in the United States has evolved considerably since the COVID-19 pandemic, with an increasing proportion of visits conducted via telemedicine. For a drug with potential abuse liability

Given these developments, the report by Fountoulakis et al. (6) in this issue of the *Journal* is particularly timely and offers a cautionary view. The authors conducted a systematic review and meta-analysis of esketamine, with a primary focus on short-term (up to 4 weeks) depressive and suicidality outcomes. The included studies examined the adjunctive use of esketamine added to an ongoing or newly initiated treatment with an oral antidepressant, administered twice per week for 4 consecutive weeks. The review followed best-practice PRISMA guidelines and included 87 reports (11 of which were randomized placebo-controlled trials for the two indications). A key strength of the report is its comprehensiveness in including the entirety of the published literature through March 2024.

The review highlights several major limitations of the esketamine clinical trials data to date, including marginal effect sizes after the first week, the lack of controlled long-term efficacy data, and negligible evidence for efficacy against suicidality. As noted by the authors, a challenge in interpreting the effect sizes for the phase 3 trials was the requirement of a change in the background oral antidepressant, an unusual study design

The review highlights several major limitations of the esketamine clinical trials data to date, including marginal effect sizes after the first week, the lack of controlled long-term efficacy data, and negligible evidence for efficacy against suicidality.

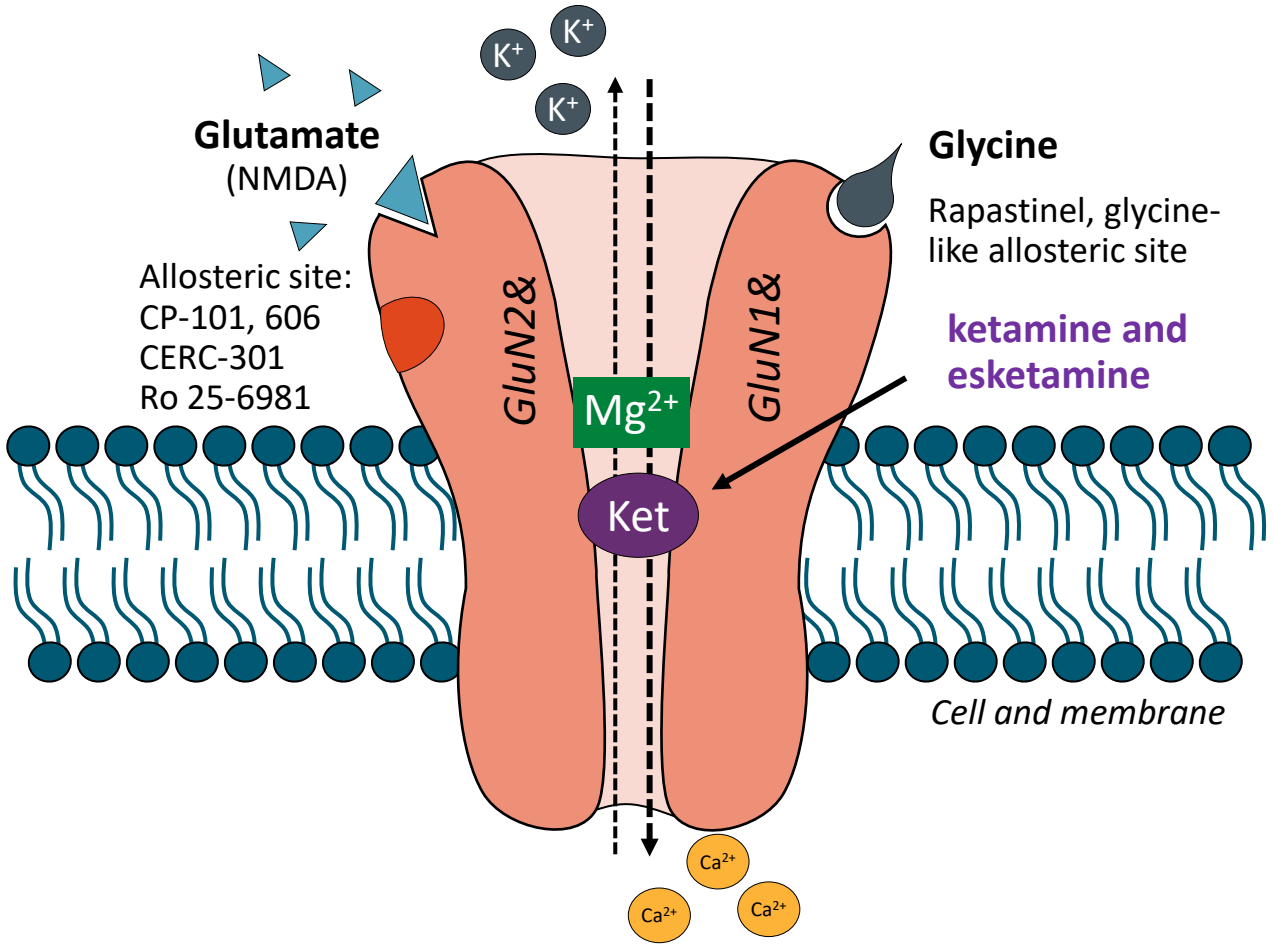
- Meta-analysis of 87 reports (11 RCTs): marginal effect sizes after first week
- Only 1 of 3 short-term TRD studies met primary endpoint
- No evidence of protection vs suicide or suicide attempts

Mathew SJ & Murphy N, *Am J Psychiatry* 2025

Mechanistic Insights:
Can understanding mechanisms of actions of ketamine help identify new therapeutic targets?

"Ketamine without the trip"

Ketamine's Conventionally Understood Pharmacology: NMDA Receptor Channel Blocker



- Binds to PCP site deep within ionotropic channel pore
- Non-competitive antagonist (does not compete with endogenous Glu or Gly ligands)
- At rest, Mg is bound to inner channel.
- Membrane depolarization relieves Mg^{2+} block, and with co-agonist binding, Ca^{2+} and Na^{+} enter cell

Duman. F1000Res. 2018;7:F1000 Faculty Rev-659. Mothet. J Neurochem. 2015;135:210.

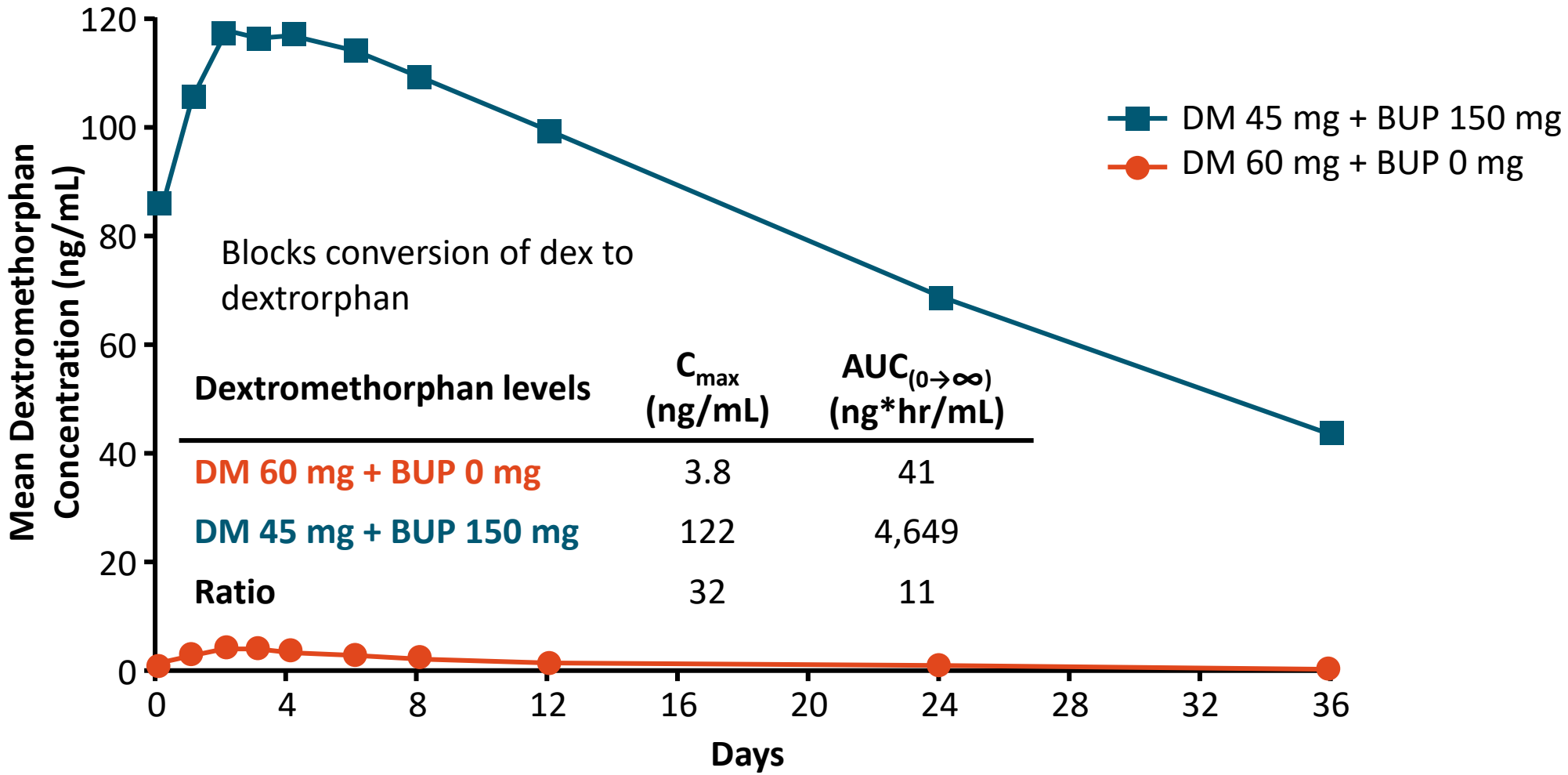
However: Numerous NMDA receptor modulators have failed in major depression/TRD over the past decade

Problem Attempting to Address for Racemic Ketamine	Drugs	Development Phase (Halted)
High "Trapping" within NMDA receptor channel leads to dissociation and toxicity	Lanicemine Memantine	Phase 2b
Lack of NMDAR subtype selectivity	***NR2B antagonists/NAMs*** MIJ821 CP-101,606 MK-0657/CERC-301 (rislemdaz) BI1569912 NBI-107077 ***NR2D antagonist***: Esmethadone	Phase 2 Phase 3
S-isomer is the wrong enantiomer	Arketamine	Phase 2
Need for Glycine Allosteric Site Modulation	Rapastinel AV-101(4-chlorokynurenine)	Phase 3 Phase 2b/3

Zarate CA et al. 2006; Smith EG et al. 2013; Sanacora G et al. 2017; Preskorn SH et al. 2008; press releases: Novartis, Perception; VistaGen, Allergan, Neurocrine

Dextromethorphan/Bupropion

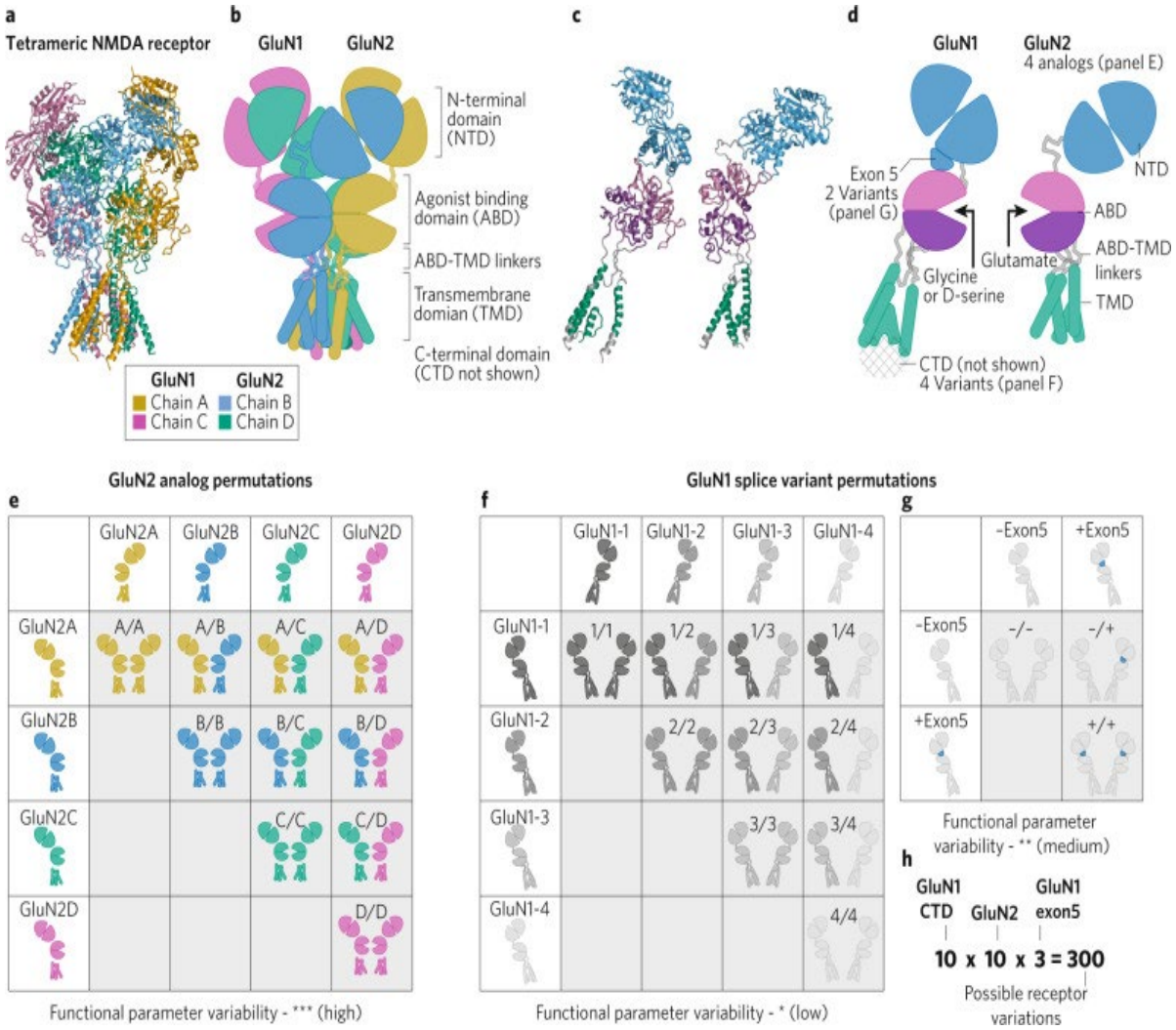
CYP2D6 Inhibition Substantially Increases Dextromethorphan C_{max} and AUC



Dextromethorphan levels	C_{max} (ng/mL)	$AUC_{(0\rightarrow\infty)}$ (ng*hr/mL)
DM 60 mg + BUP 0 mg	3.8	41
DM 45 mg + BUP 150 mg	122	4,649
Ratio	32	11

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/215430Orig1s000MultidisciplineR.pdf

NMDAR diversity arising from assembly of different subunits and splice variants: " *dizzying number of different NMDARs*"



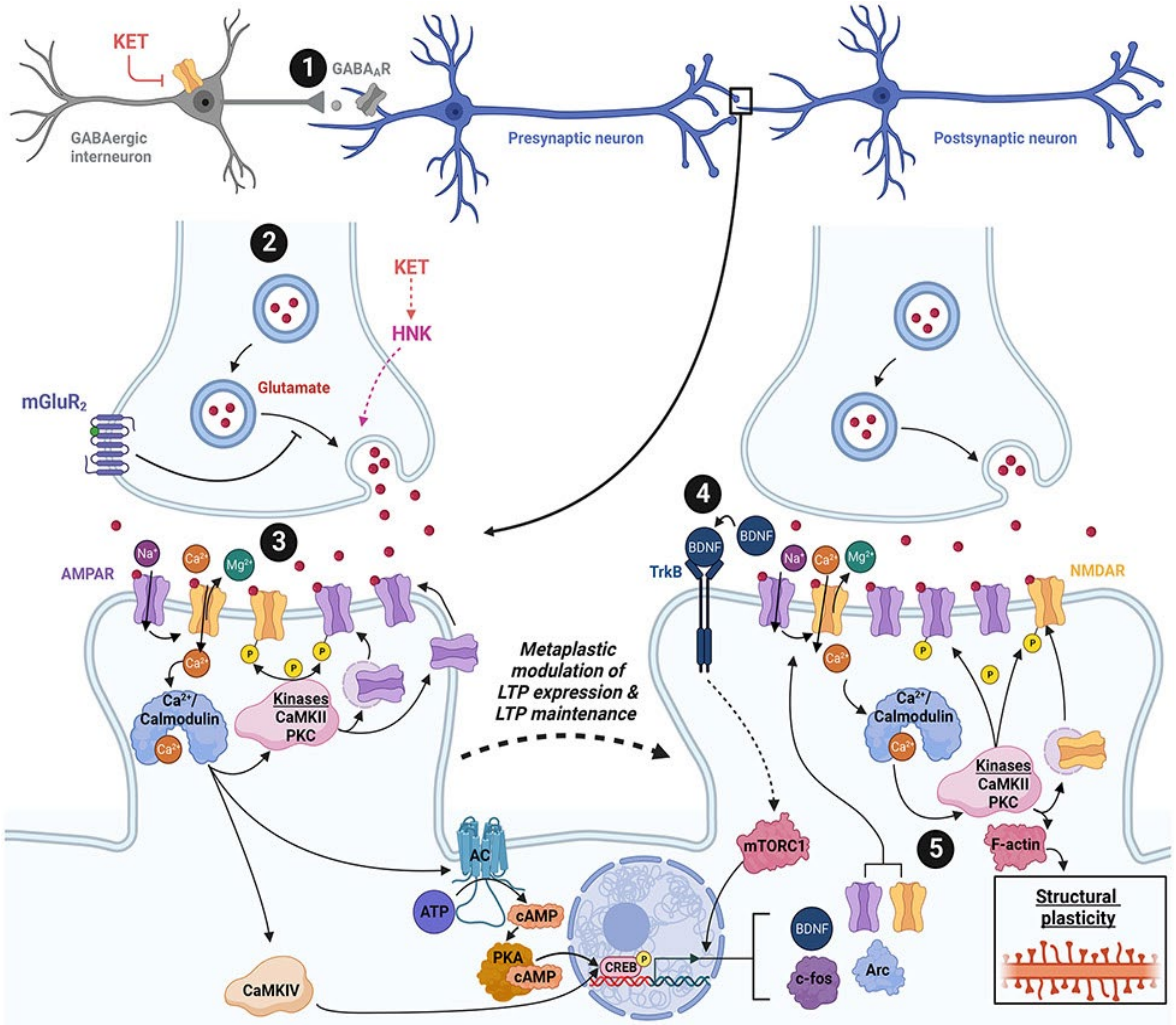
- Different GluN2 subunits confer different biophysical properties
  - Sensitivity to Mg^{2+} block
  - Sensitivity to allosteric modulators
  - Deactivation time course
  - Single channel conductance
  - Channel open probability for an agonist-bound receptor
  - Agonist potency
- GluN1 splice variants
  - Differences in glu and glycine potency
  - Regulation by Zn^{2+} and protons

Hanson JE et al NPP 2024

What is unique about ketamine's mechanism of action?

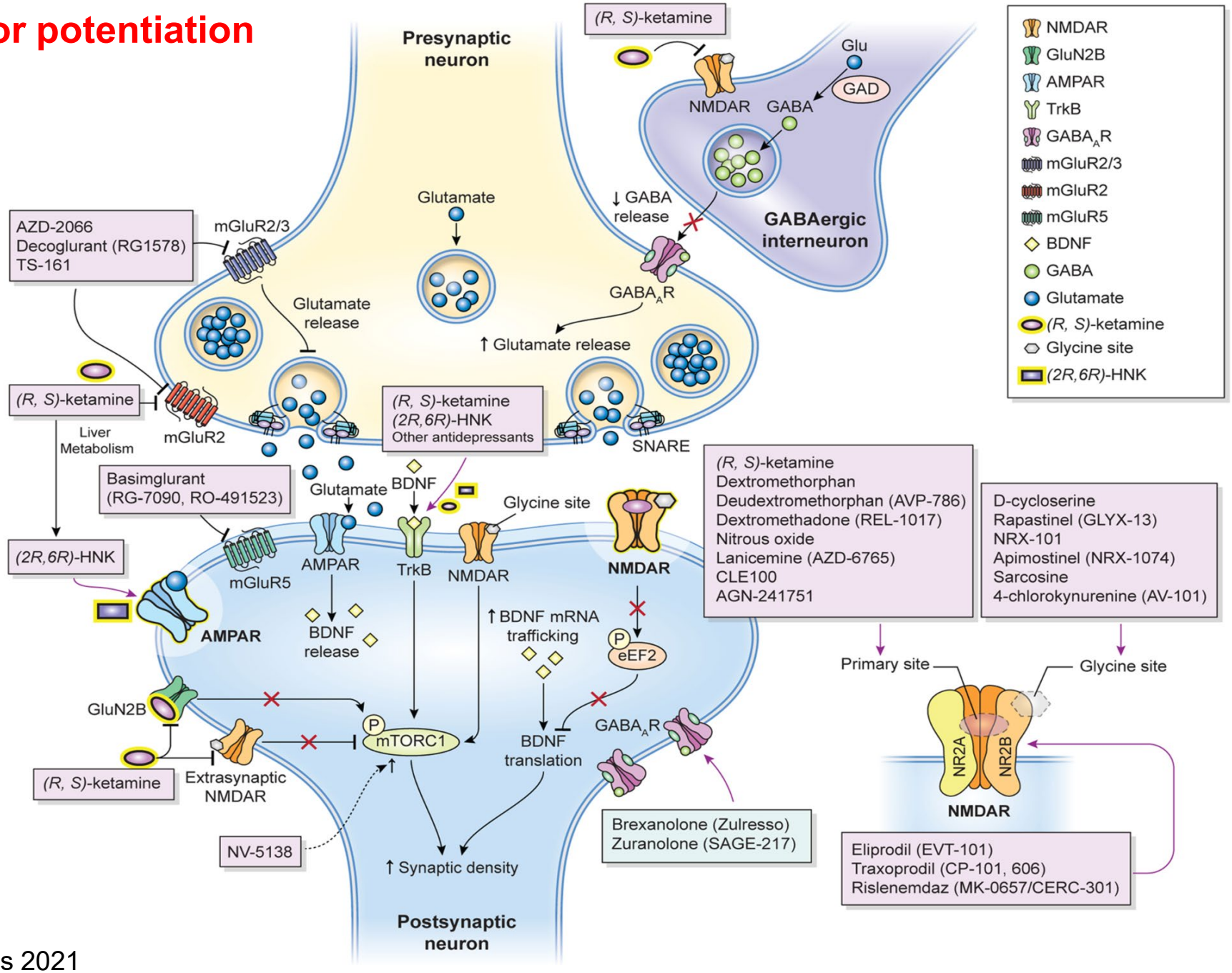
- Impact on parvalbumin interneurons: ketamine *reduces PV-interneuron activity* and results in excitatory neuron disinhibition
  - Manifests as increased gamma frequency
  - PV neurons are insensitive to GluN2B NAMs

- Action of ketamine metabolites (HNK) on non-NMDA receptor targets (e.g. **AMPA receptor potentiation**)



Brown KA & Gould TD, 2024

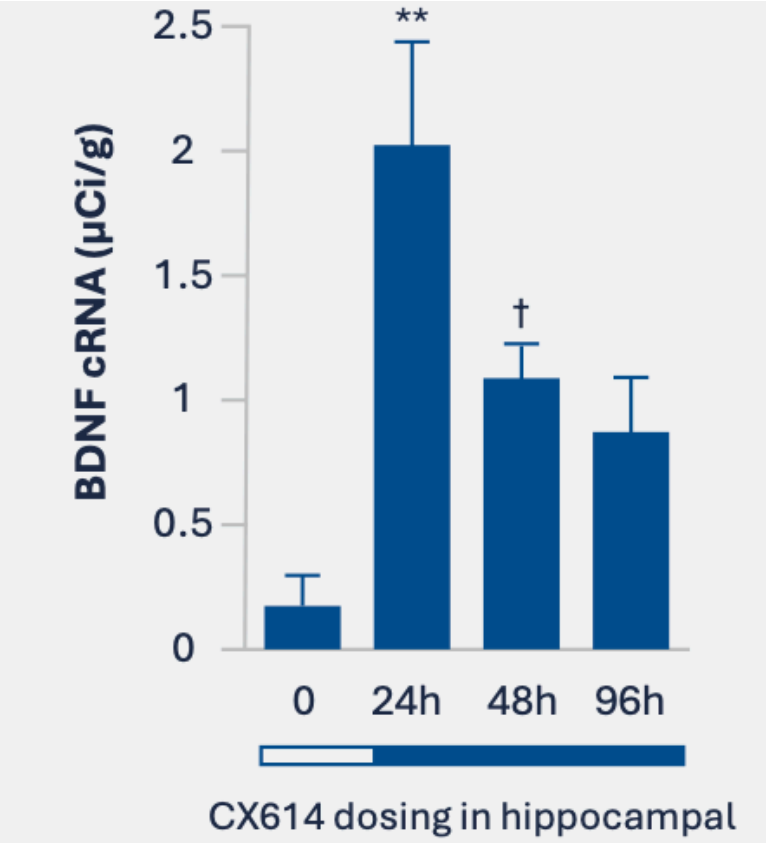
AMPA receptor potentiation



Henter I et al CNS Drugs 2021

AMPA Receptors in MDD

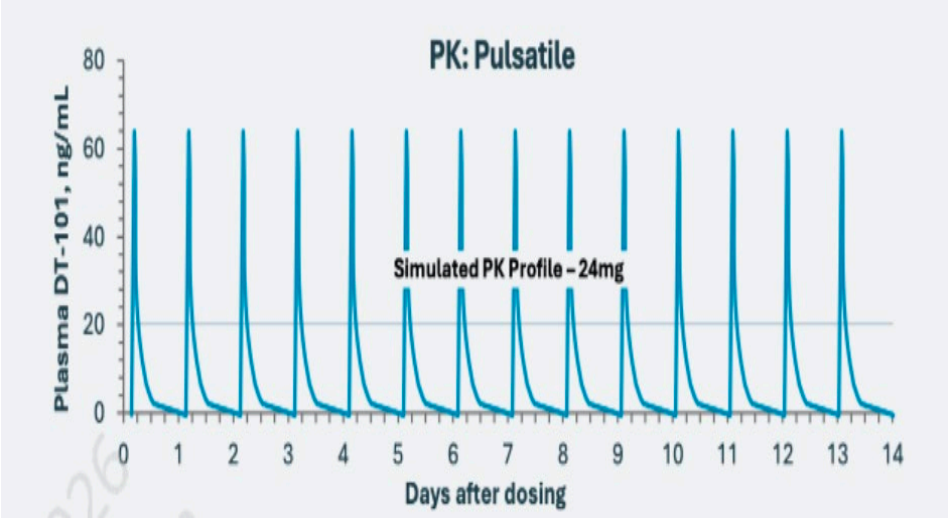
- AMPAR is central regulator of synaptic plasticity, mood, and cognition
- Ketamine efficacy driven in part by AMPAR activation
- Prolonged AMPAR PAM exposure dampens plasticity signalling
- Is *transient* AMPAR potentiation optimal for clinical benefit?
  - two active AMPA PAM antidepressant development programs

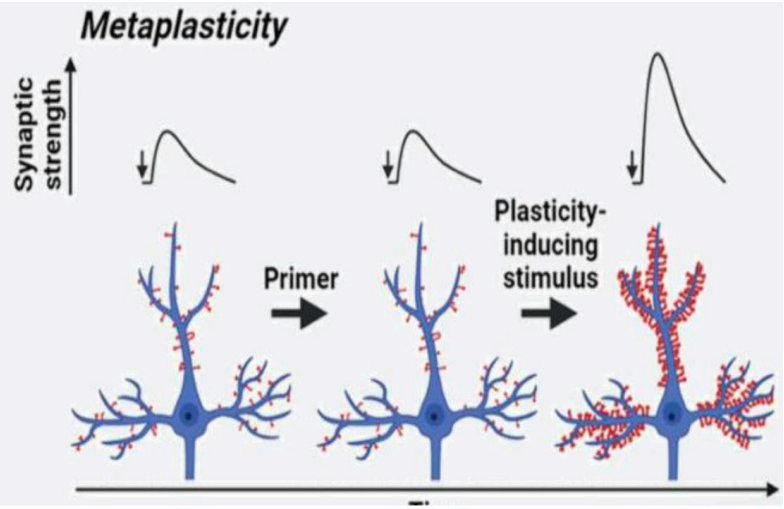


Suzuki et al 2023; Miller et al 2016; Lauterborn et al 2003

Early-Phase AMPA Receptor Antidepressant Program

- **DT-101**: AMPA receptor potentiator (positive allosteric modulator)
  - Phase 2 studies ongoing in MDD (monotherapy, adjunctive)
  - ***Pulsatile PK profile*** (ie—transient AMPA receptor engagement critical for driving synaptic plasticity)
  - Pulsatile exposure primes neuronal circuits, amplifying response to subsequent stimuli
  - Dose-dependent modulation of cortical oscillatory activity across paradigms (visual gamma, ASSR, resting state)



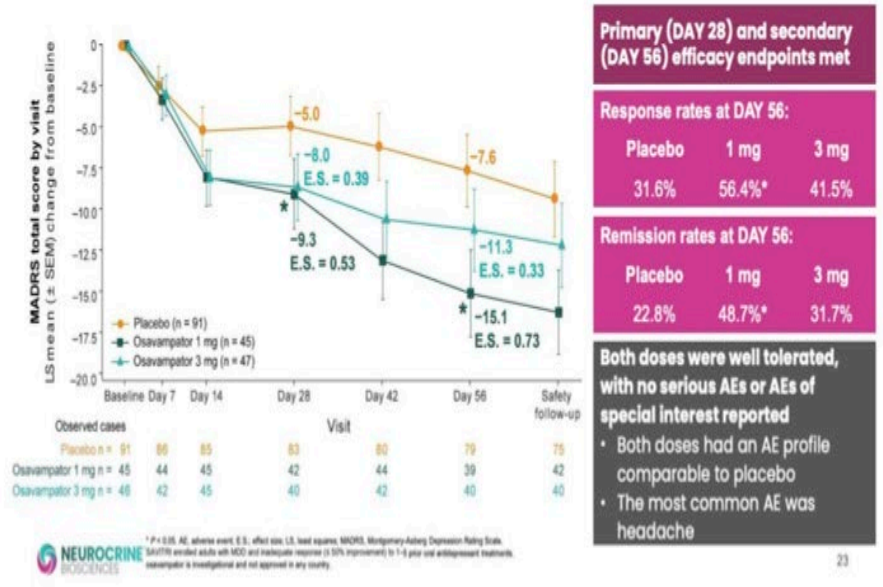


Brown et al Mol Psychiatry 2024;Draig Therapeutics, ASCP 2026

AMPA Positive Allosteric Modulator: Phase 3 Antidepressant Program

- AMPA receptor positive allosteric modulator: **osavampator** (NBI-1065845)
  - Positive phase 2 adjunctive trial in 183 adults with MDD
    - **1 mg** dose demonstrated improvement over placebo of -4.3 (p-value = 0.0159) at day 28 and 7.5 (p-value = 0.0016) at day 56.
    - 48.7% remission rate

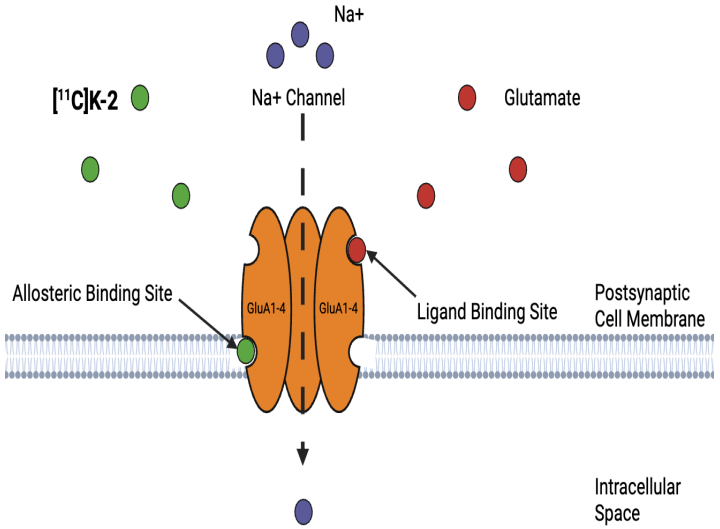
Osavampator (Neurocrine) Phase II data

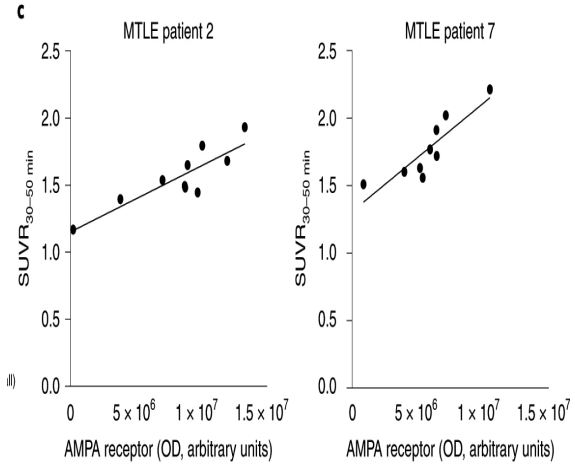


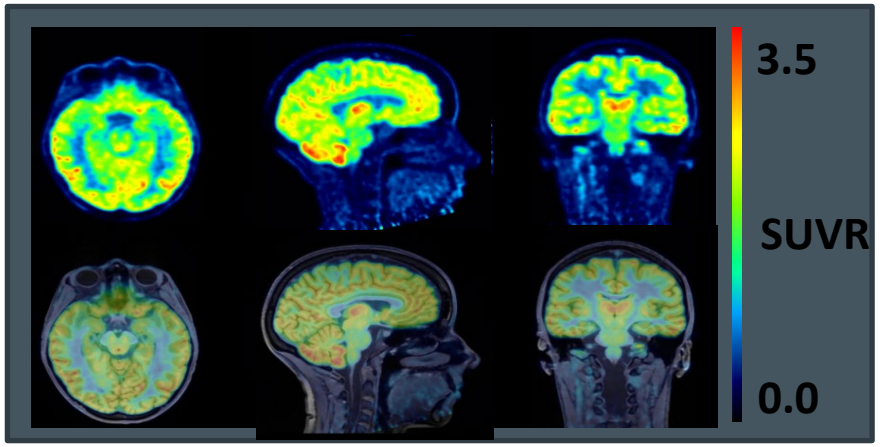
Neurocrine SAVITRI trial press release Sept 22, 2025

AMPAR Target: [C11]K2 PET

- novel ligand that binds to the allosteric binding site on GluA1-4 receptors on the post-synaptic cell membrane.
- Target validity was tested in patients receiving surgery for temporal lobe epilepsy.
- [C11]K2 uptake was positively correlated with AMPA receptor density in surgical samples (Miyazaki et al, 2020)

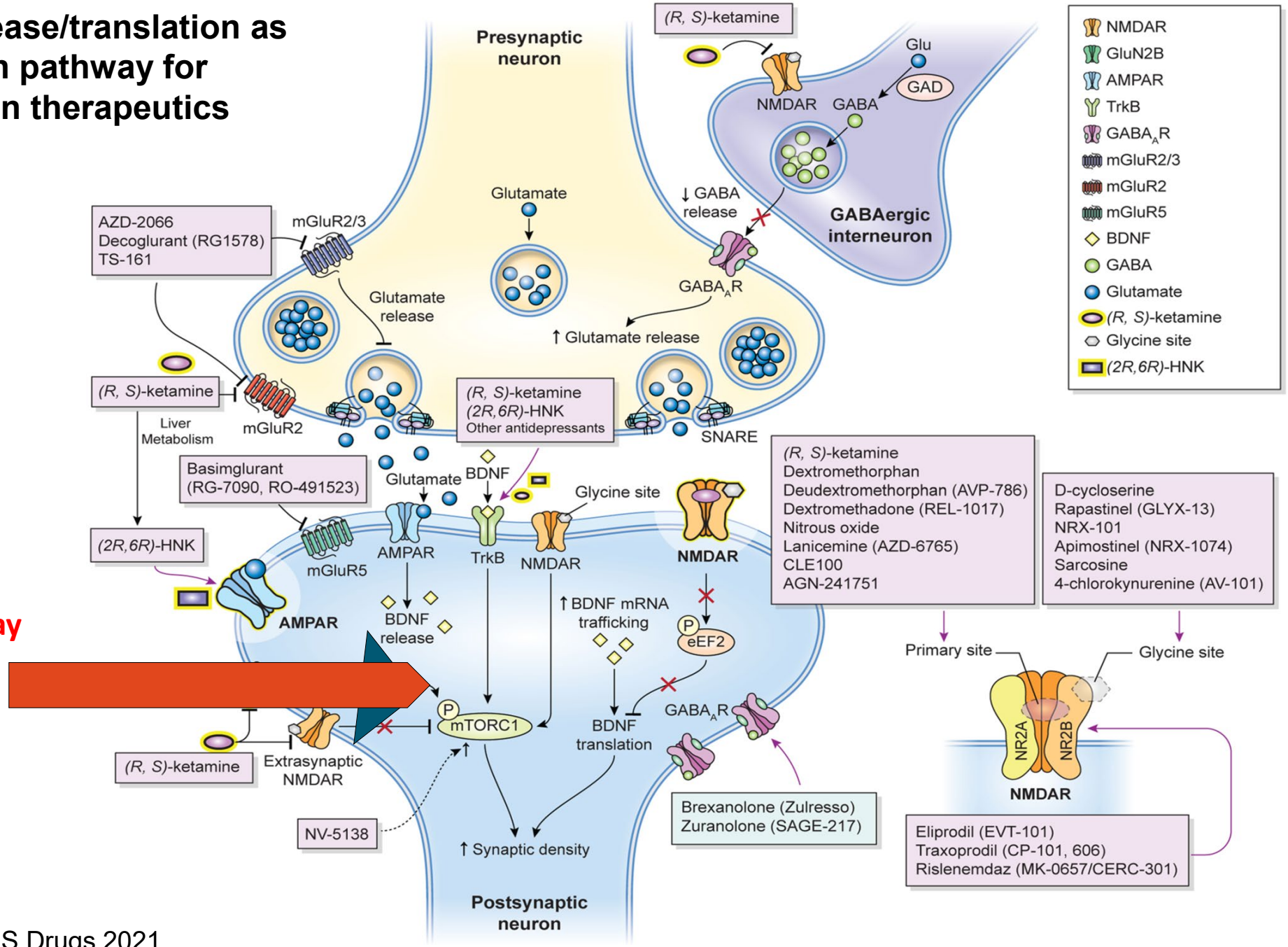






[C11]K2 Standard Uptake Value Ratio; Healthy Control; IND 161438

BDNF release/translation as a common pathway for depression therapeutics

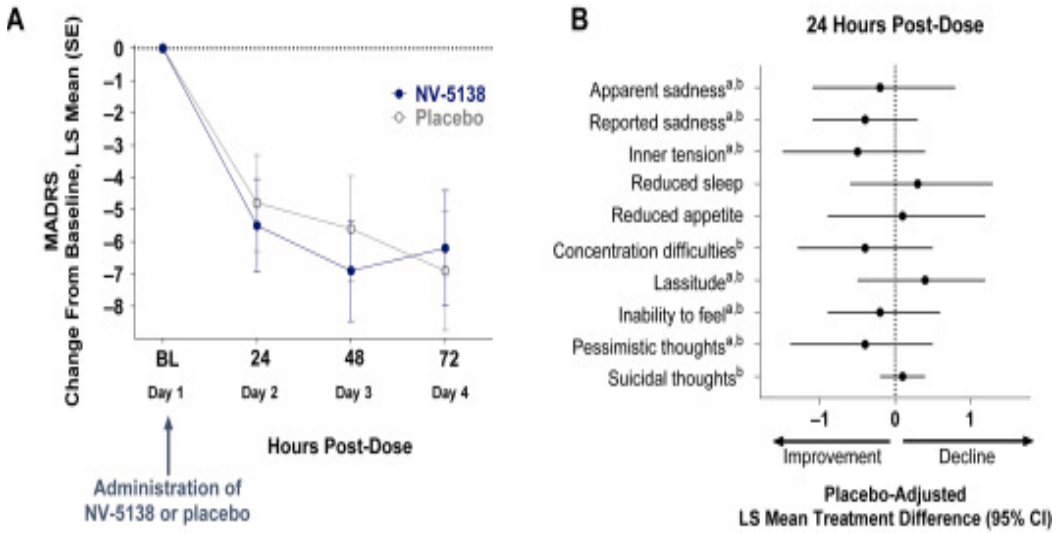


mTORC pathway

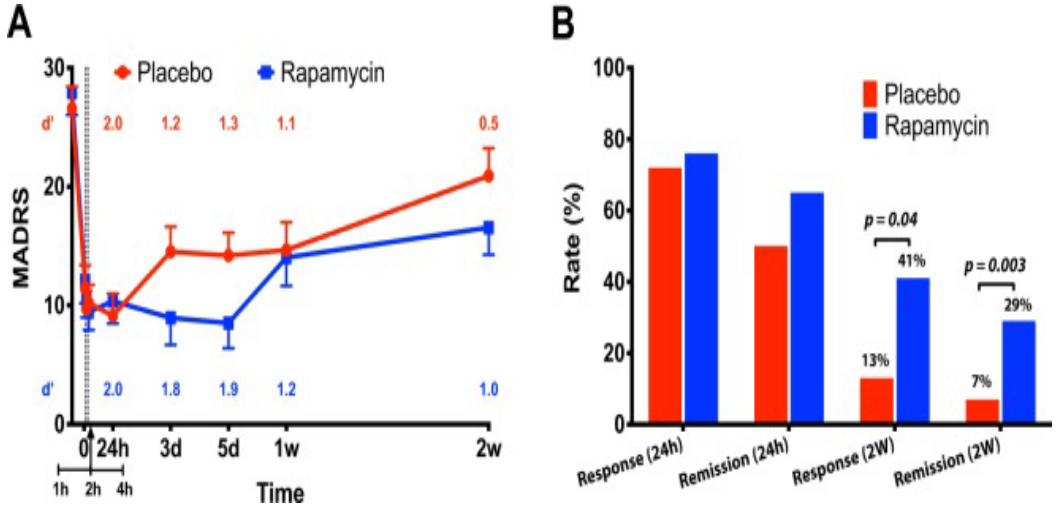
Henter I et al CNS Drugs 2021

Targeting mTORC1: mammalian target of rapamycin complex 1

- Activation of ***mTORC1,*** producing synaptogenesis and downstream activation of brain-derived neurotrophic factor.
  - mTORC1 activator (**mefluleucine/SPN-820**):
    - Phase 2b study of 227 TRD patients (negative, 2/2025)
  - Temsirolimus + ketamine (**FREE001**)
    - 20 patients randomized to pretreatment with oral **sirolimus** (6 mg), an mTORC1 inhibitor, or placebo 2 hours prior to IV KET (0.5 mg/kg) in a double-blind cross-over design
    - The mTOR inhibitor temsirolimus (**prodrug of SIR**) is under investigation in combination with KET for adjunctive treatment in TRD



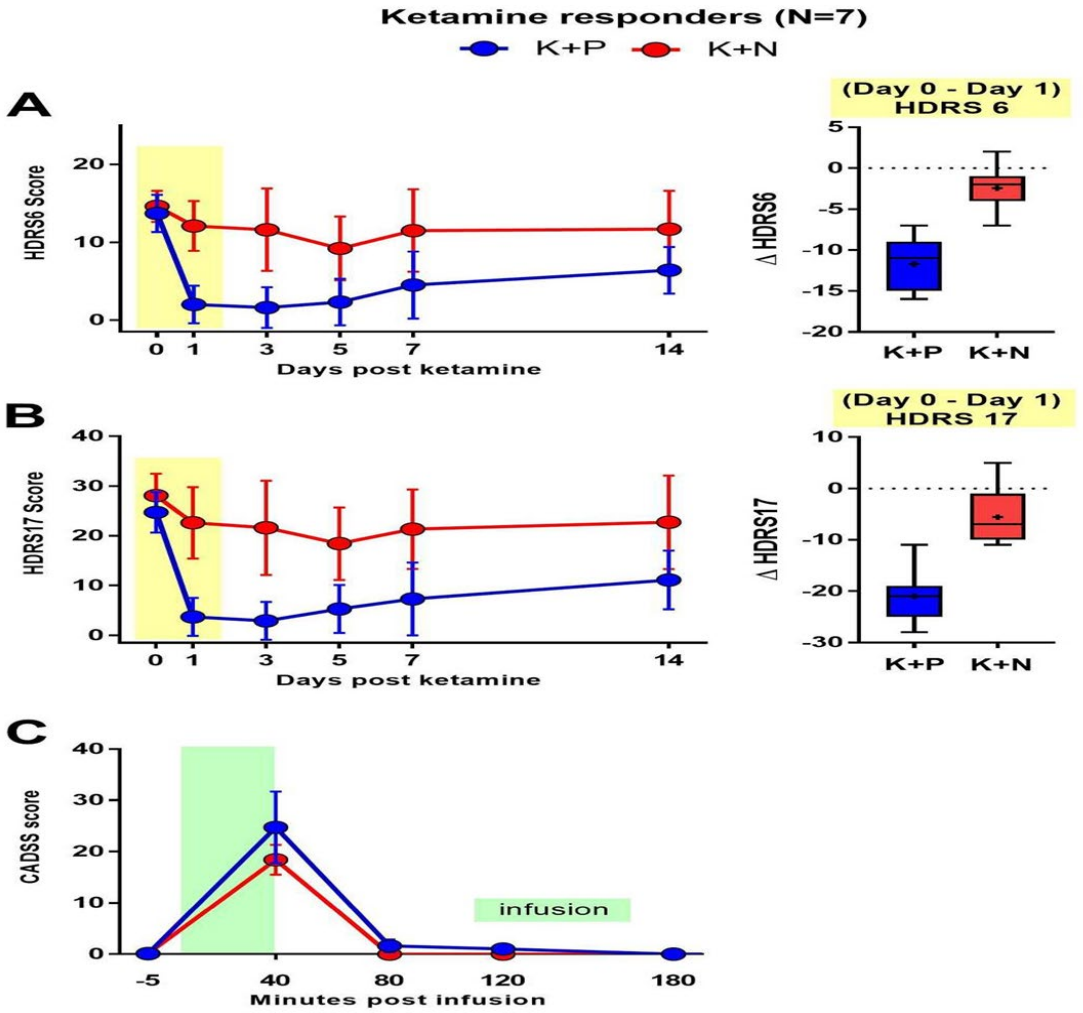
Targum S et al *J Psych Research* 2026



Abdallah et al *Neuropsychopharmacology* 2020

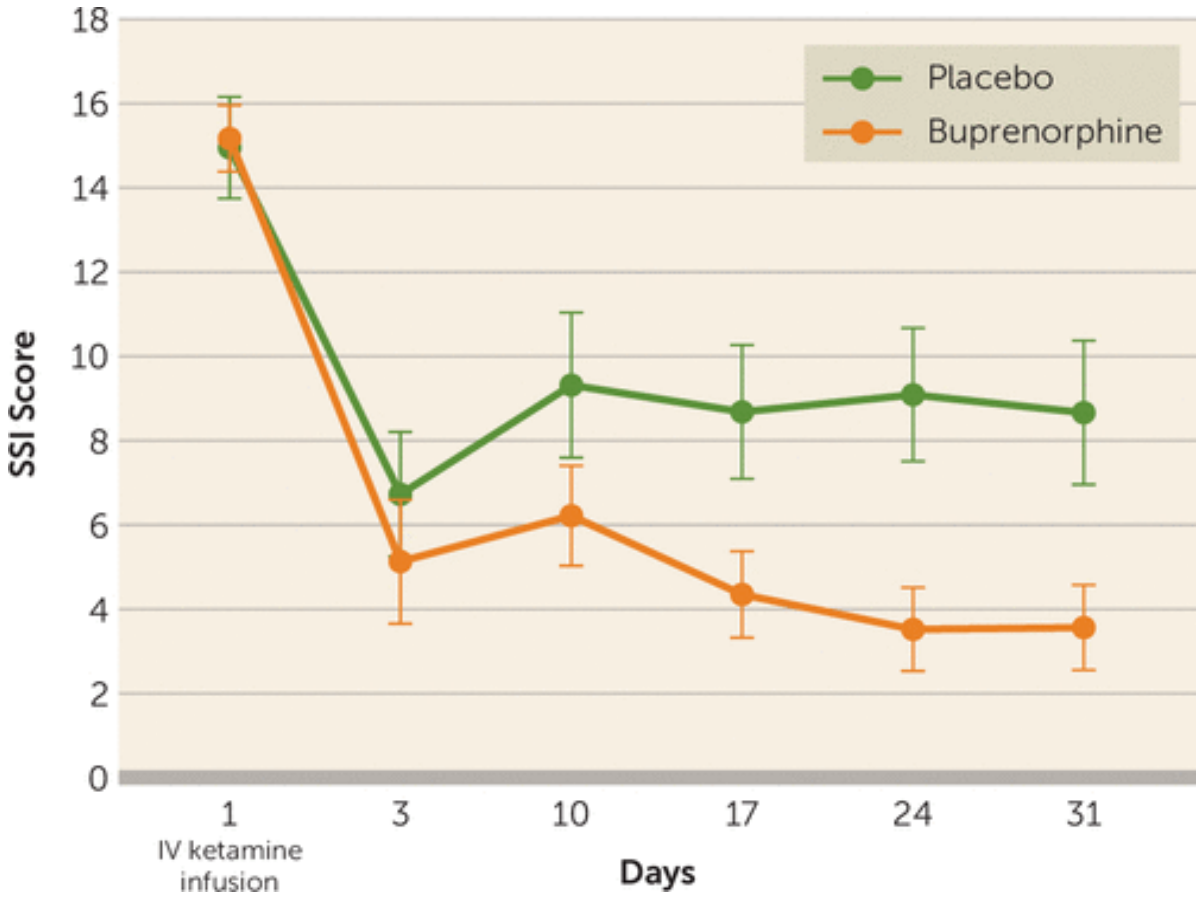
Opioid receptor antagonism attenuates antidepressant effects of ketamine

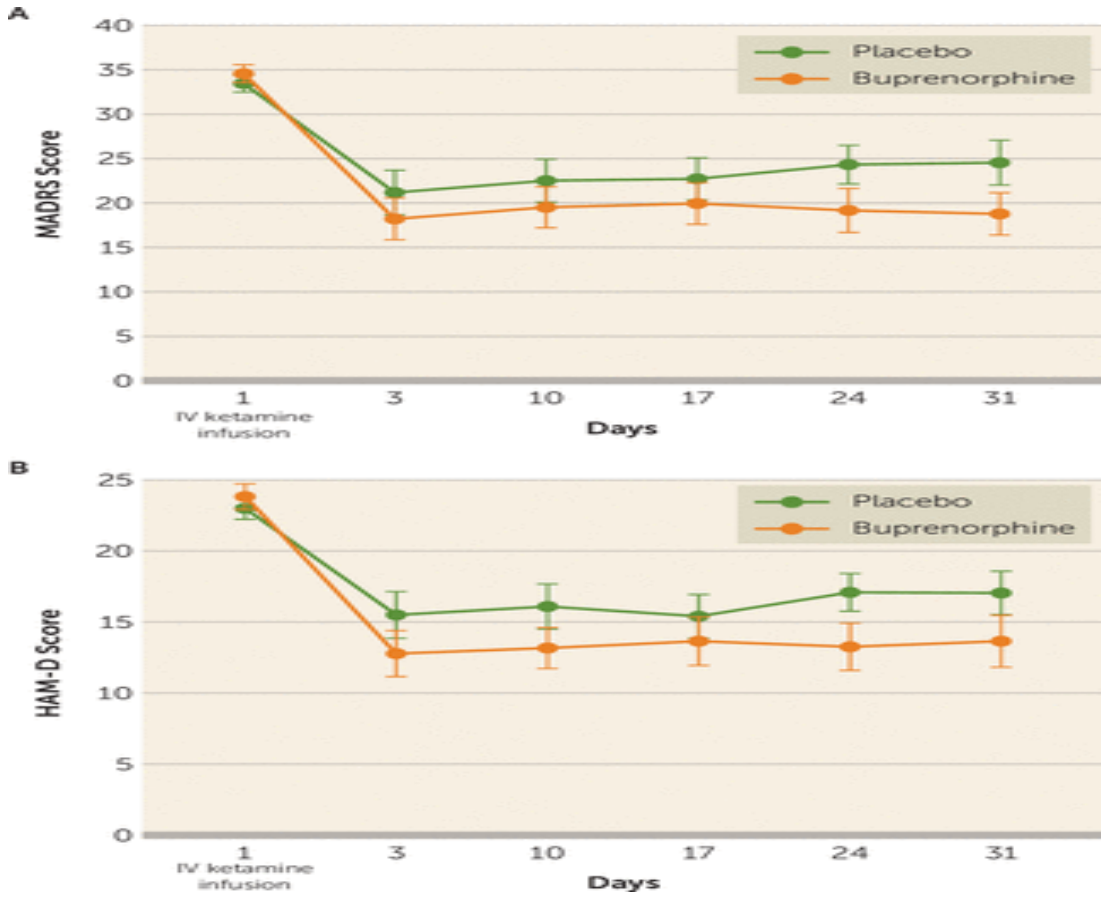
- 12 patients with TRD received two ketamine infusions (0.5 mg/kg), separated by about 30 days
- Pretreatment with naltrexone (50 mg) or placebo
- 24 hr post ketamine-- significant differences in HAM-D reduction
  - Nal+ KET: ⇓⇓ 5.6 pts
  - PBO+ KET: ⇓ 22.3 pts
- No significant differences in acute dissociative response



Williams N, et al *Am J Psychiatry* 2018

Low-Dose Buprenorphine Following Ketamine Treatment for Suicidal Ideation in Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial



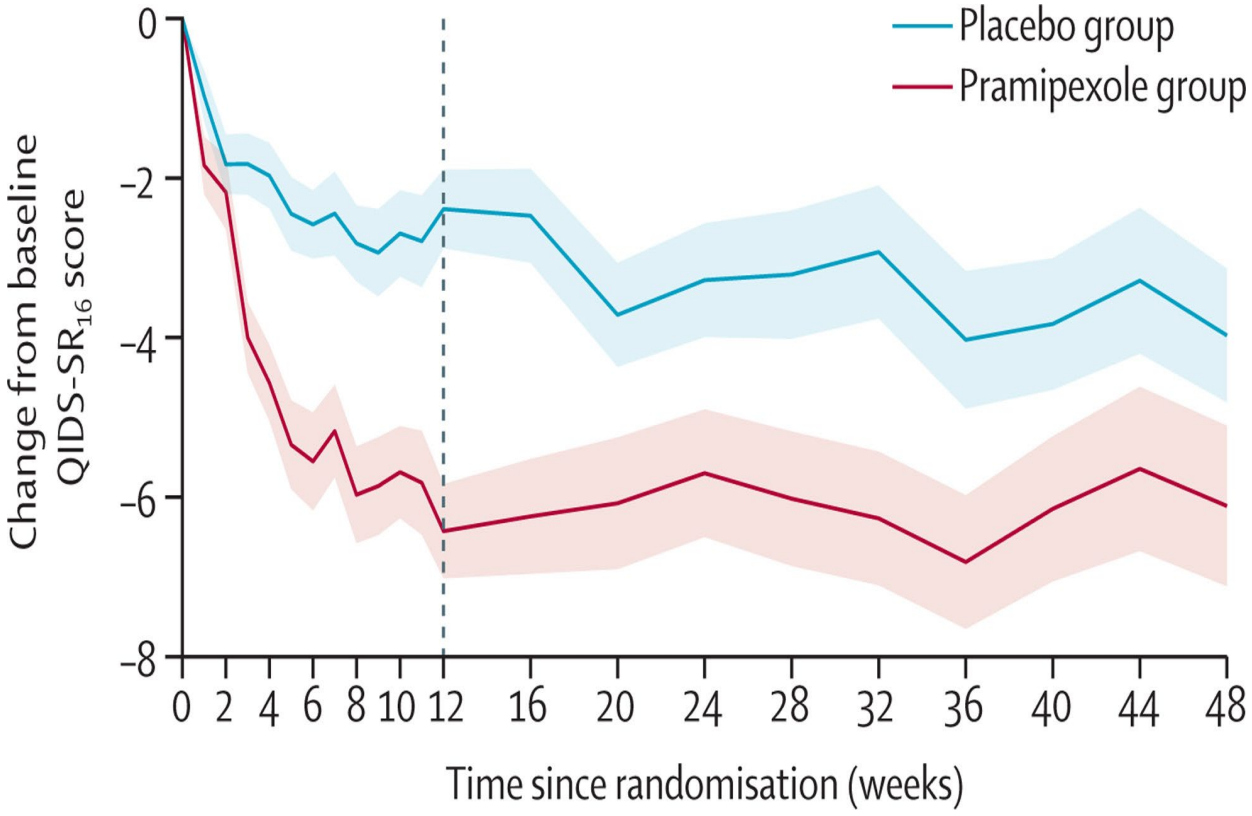


Tucciarone JM et al Am J Psychiatry 2026

Beyond Glutamatergic Antidepressant Drug Targets

Repurposed Drugs for New Depression Indications

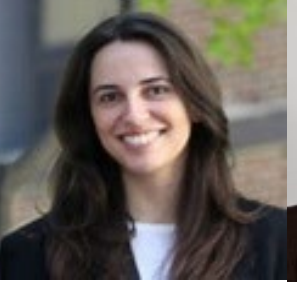
- D3/D2 + 5-HT3 antagonist (**ALTO-207**): ***pramiprexole*** + ondansetron for TRD
- Methylated derivative of ***amisulpride*** (**LB-102**): selective antagonism of D_2, D_3, and $5HT_7$ receptors
- ***Agomelatine*** (melatonin 1/2 receptor agonist + 5HT2C antagonist) (**ALTO-300** and **GlyphAgo**)



M Browning et al Lancet Psychiatry 2025

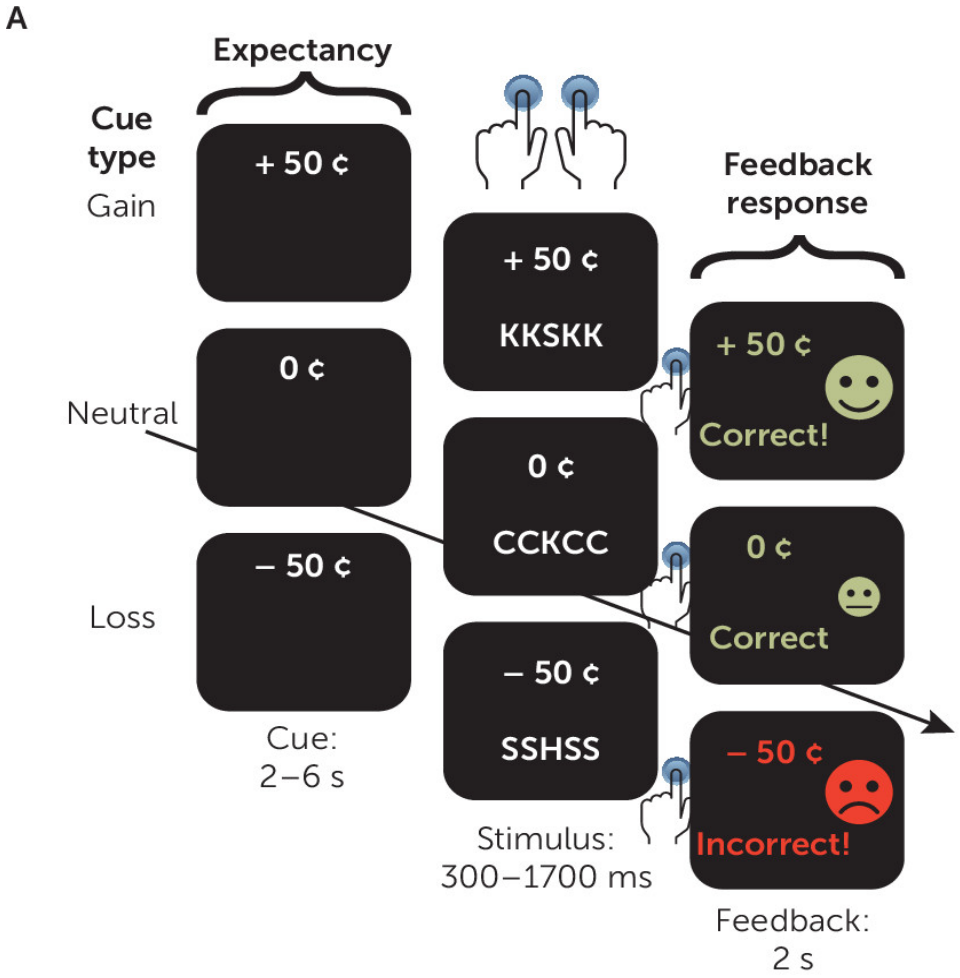
Novel Mechanism Antidepressant Development Programs

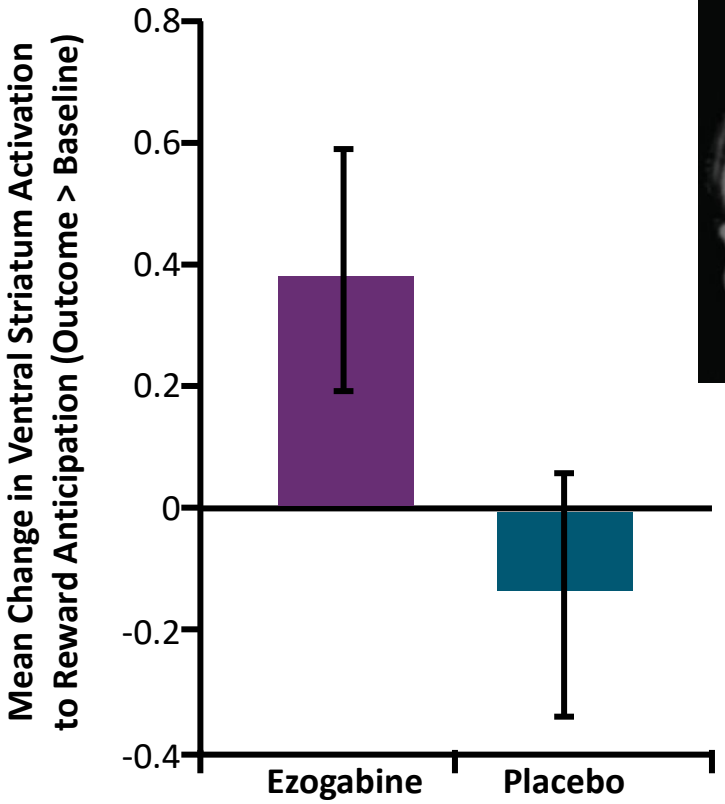
- **Phase 3**
  - **KCNQ2/3 (K_v7.2/K_v 7.3) Channel Opener: Encukalner (XEN1101)**
    - voluntary enrollment pause in Phase 3 trials (Sept 2026) for neuropsychiatric AEs
  - Orexin-2 Antagonist (**seltorexant**): adjunctive MDD with insomnia symptoms
  - ~~Kappa Opioid Receptor antagonist: **Navacaprant**~~
- **Early Phase**
  - Thyroid receptor beta (TRβ)-selective agonist (elunetirom, **ABX-002**)
  - Kappa-opioid receptor antagonist: **icalcaprant**
  - Muscarinic-1 receptor antagonist (**JNJ-5120**): negative Ph 2 trial (Sept 2026)
  - Glyph Allopregnanolone (**SPT-300**): oral prodrug of allopregnanolone
  - ~~Neuroplastogen (**DLX-001, Zalsupindole):** non-hallucinogenic 5HT2A agonist~~

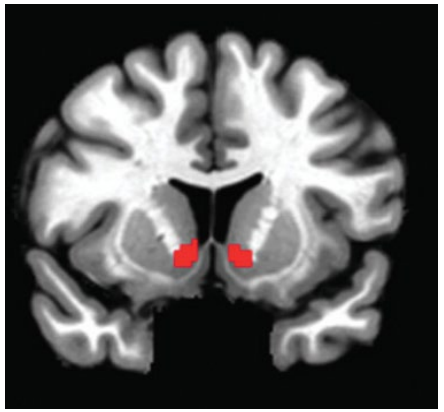




KCNQ2/3 Potassium Channel Positive Allosteric Modulator "Opener" and Reward Circuit Activity





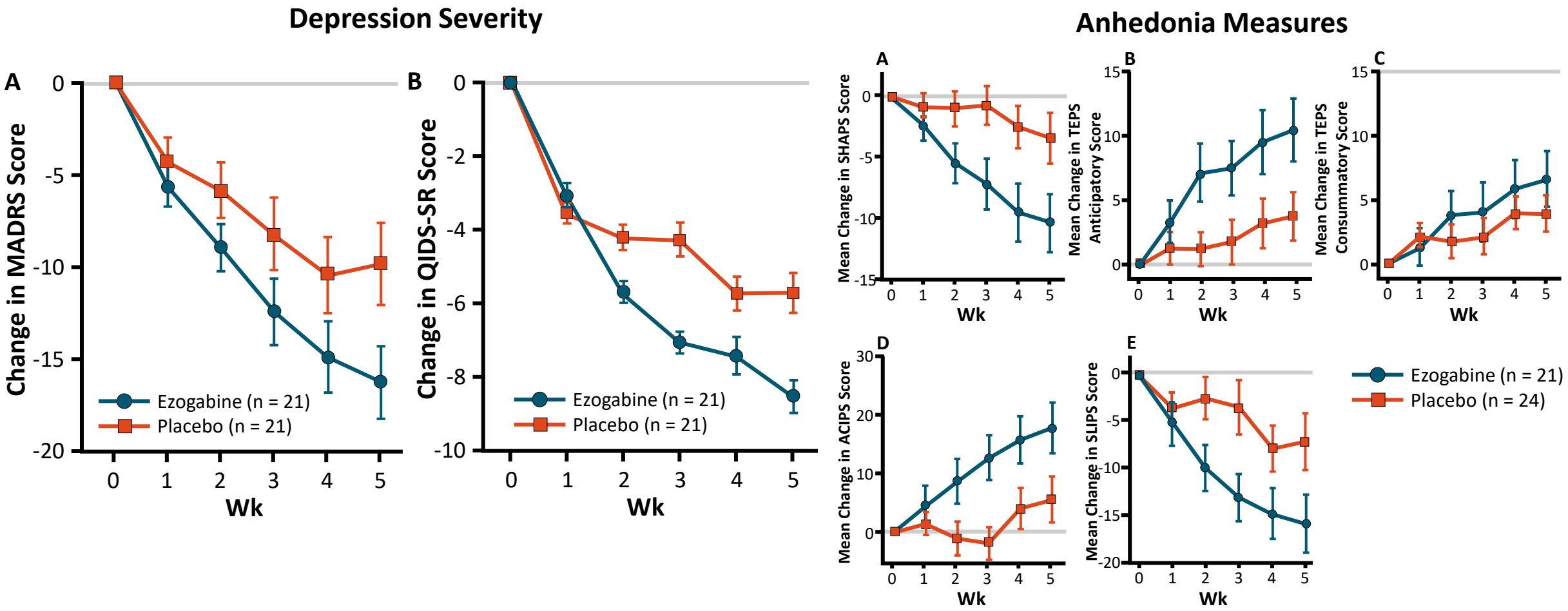


Nucleus Accumbens ROI

N = 45.

Costi S et al *Am J Psychiatry*. 2021;178:437.

KCNQ2/3 Channel Opener Ezogabine and Reward Circuit Activity: MDD With Anhedonia

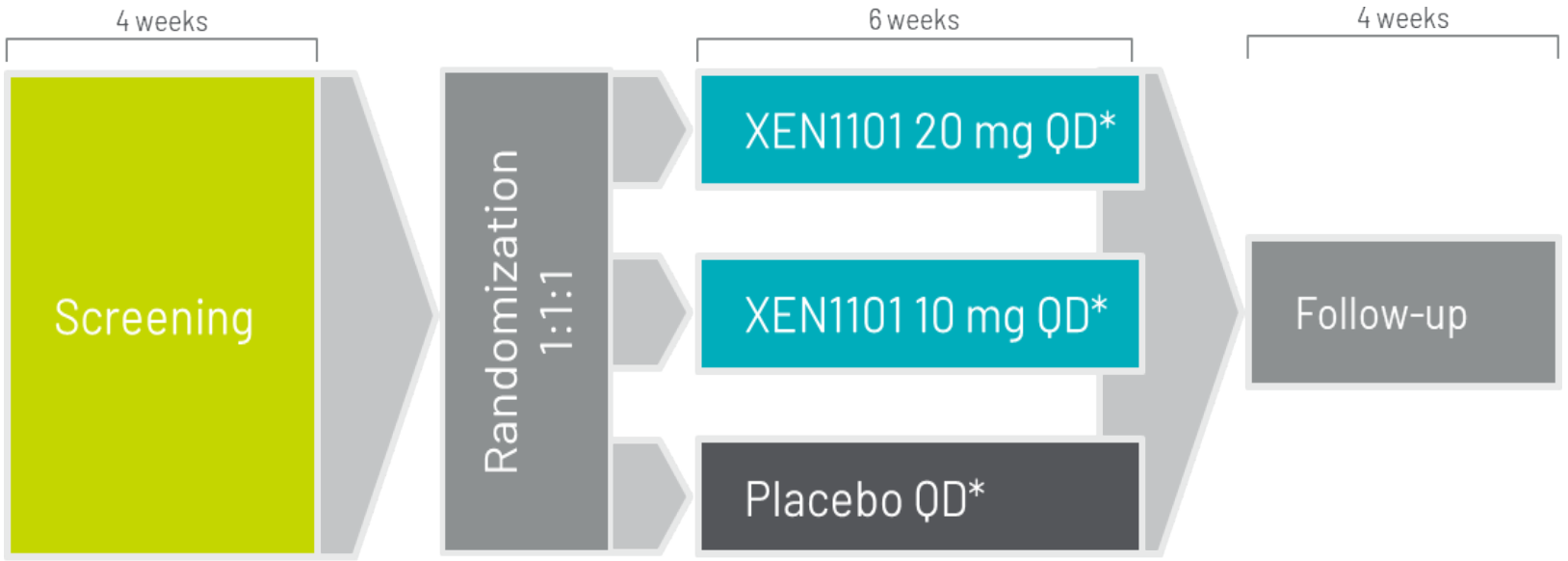


N = 45.

Costi et al. Am J Psychiatry. 2021;178:437.

Encukalner: Second Generation Potassium Channel Opener

A Proof-of-Concept, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 in Major Depressive Disorder



- **Primary Endpoint**
  - **Montgomery-Åsberg Depression Rating Scale (MADRS) score change through Week 6**
- **Key Secondary Endpoints**
  - **Snaith-Hamilton Pleasure Scale (SHAPS) score change through Week 6**

Azetukalner, a Kv7 Potassium Channel Opener, in MDD

JAMA Network Open

RCT: Azetukalner, a Novel K_V7 Potassium Channel Opener, in Adults With Major Depressive Disorder

POPULATION

57 Males, 111 Females



Adults with moderate to severe major depressive disorder (MDD) in a current depressive episode

Mean age, 47.2 y

SETTINGS / LOCATIONS



20 US sites

INTERVENTION

168 Participants with MDD



56 Placebo
Taken orally once daily with food for 6 wk with no titration

56 Azetukalner 10 mg
Taken orally once daily with food for 6 wk with no titration

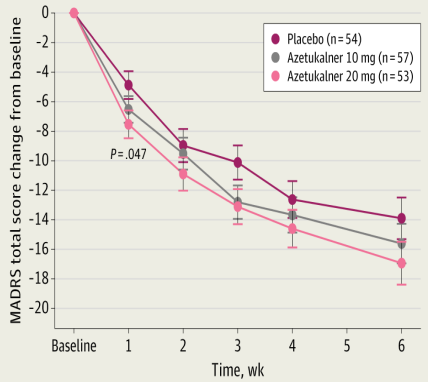
56 Azetukalner 20 mg
Taken orally once daily with food for 6 wk with no titration

PRIMARY OUTCOME

Change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score at 6 wk. MADRS is a 10-item clinician-rated scale (range, 0-60; 20-34 indicates moderate to severe depression; >35 indicates very severe depression).

FINDINGS

Least squares mean change in MADRS total score at 6 wk with azetukalner 20 mg (-16.94) vs placebo (-13.90) was clinically meaningful but not statistically significant (-3.04 points; $P=.14$)

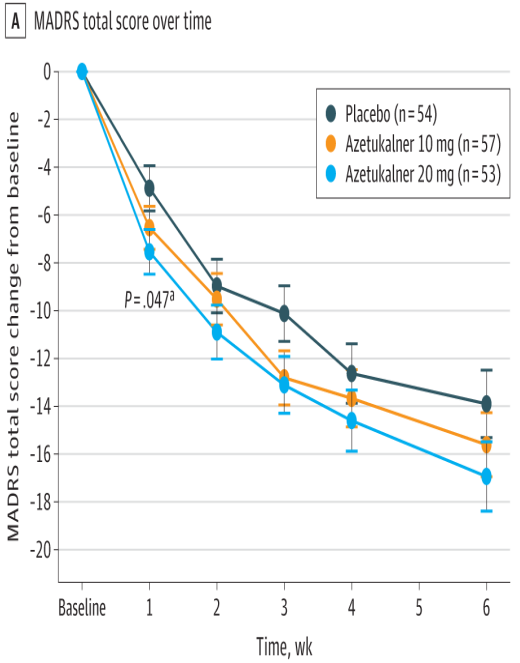


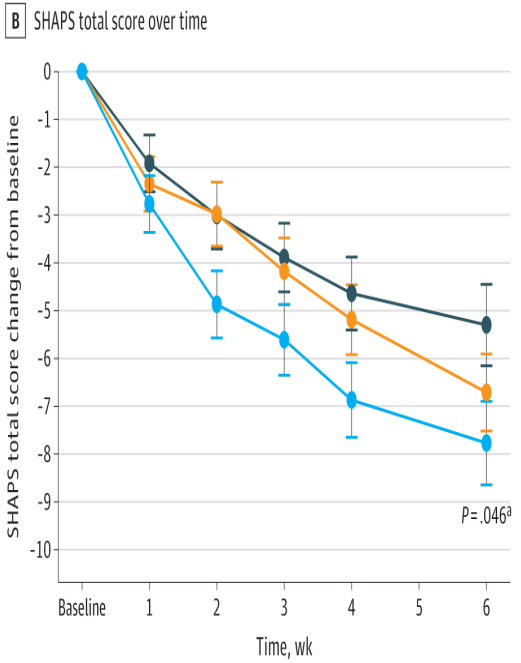
Least squares mean change (SE) in MADRS total score

Placebo: -13.90 (1.41)
Azetukalner 10 mg: -15.61 (1.34); $P=.38$
Azetukalner 20 mg: -16.94 (1.45); $P=.14$

Butterfield NN, Luzon Rosenblut C, Fava M, et al. Azetukalner, a novel K_V7 potassium channel opener, in adults with major depressive disorder: a randomized clinical trial. *JAMA Netw Open*. 2025;8(5):e2514278. doi:10.1001/jamanetworkopen.2025.14278

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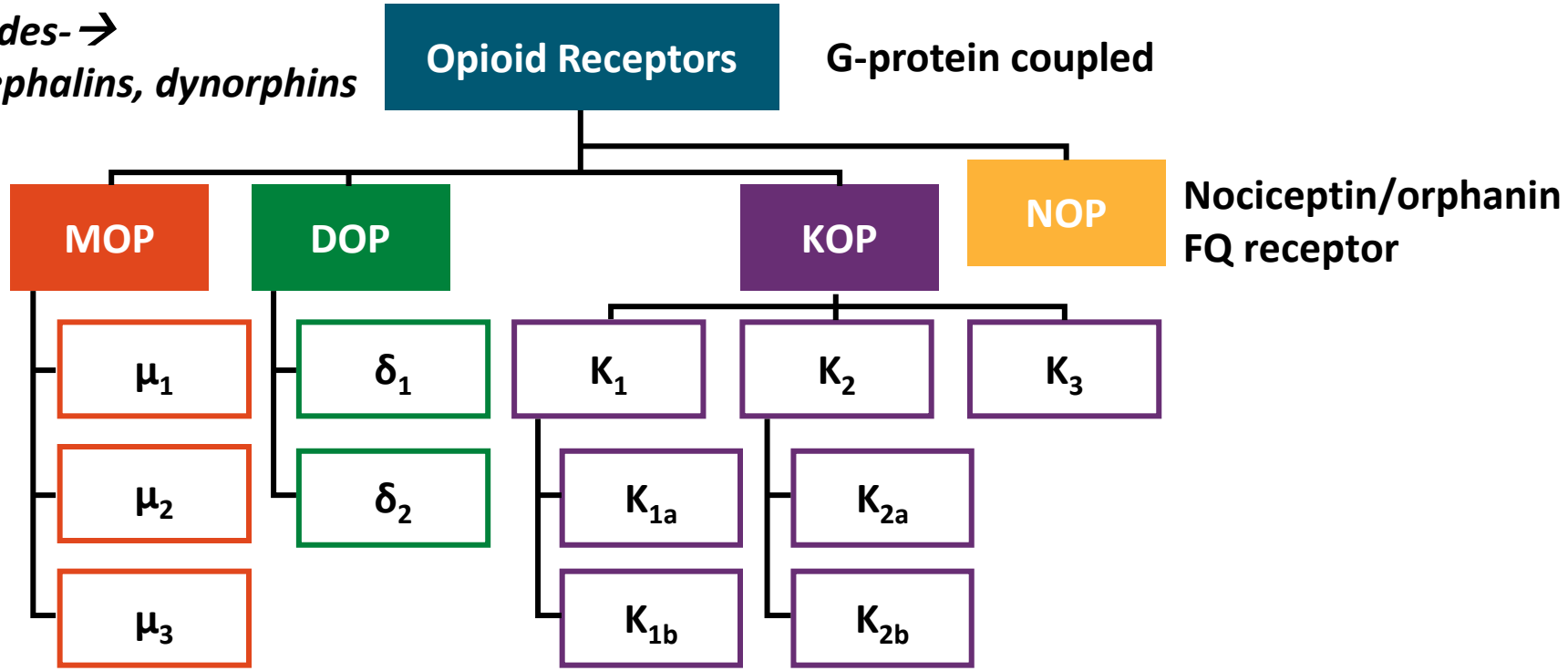


20 mg dose: HAM-D at Week 6 (-3.08 pts; p<0.05)

Butterfield NN, et al *JAMA Netw Open* 2025

Pharmacologic Classification of Opioid Receptors

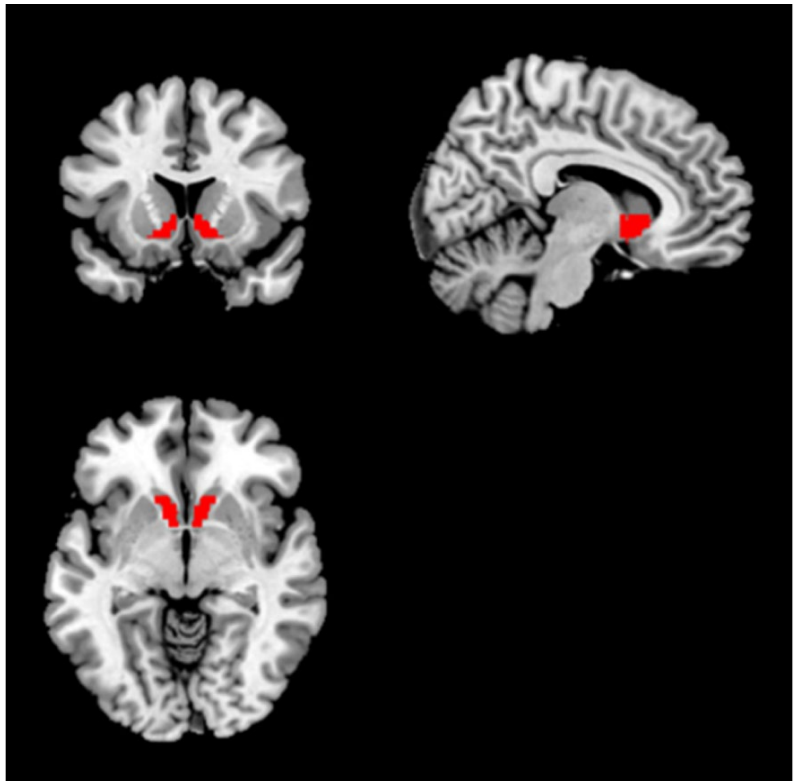
Endogenous peptides-→
B-endorphin, enkephalins, dynorphins

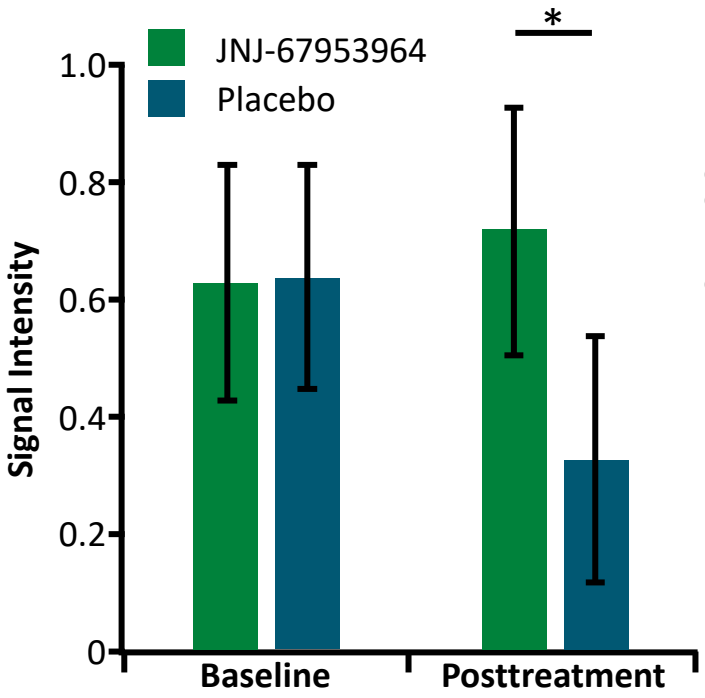


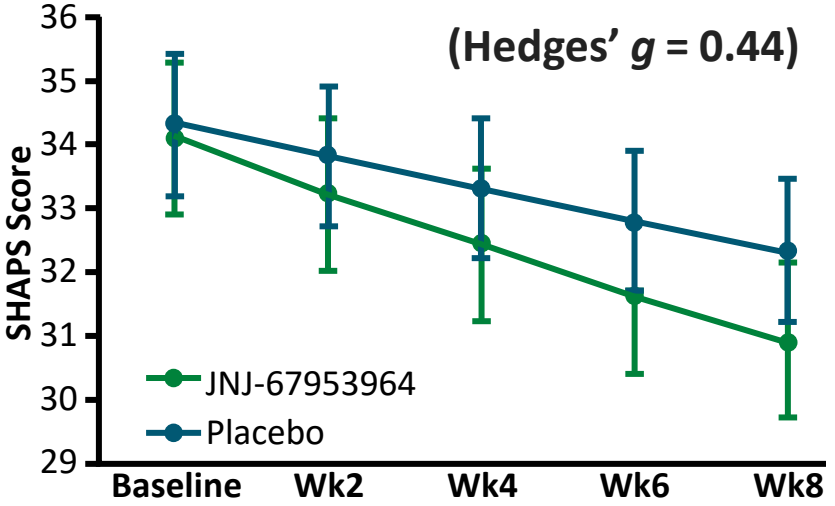
Pharmacologic classification of the opioid receptor family

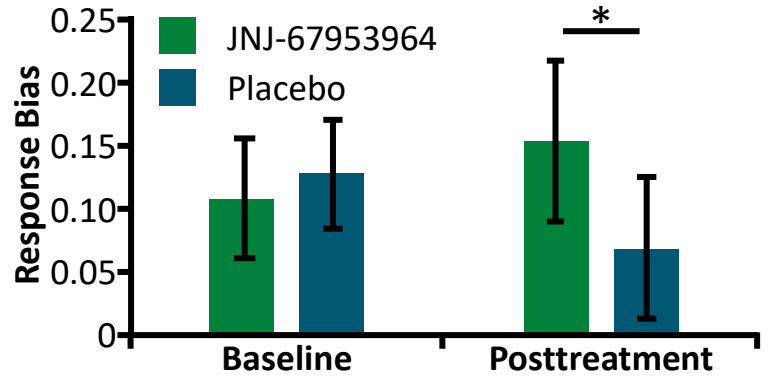
Dietis et al. Br J Anaesth. 2011;107:8.

“Fast-fail” Approach: Evaluating κ-opioid Antagonism (Aticaprant) for Anhedonia







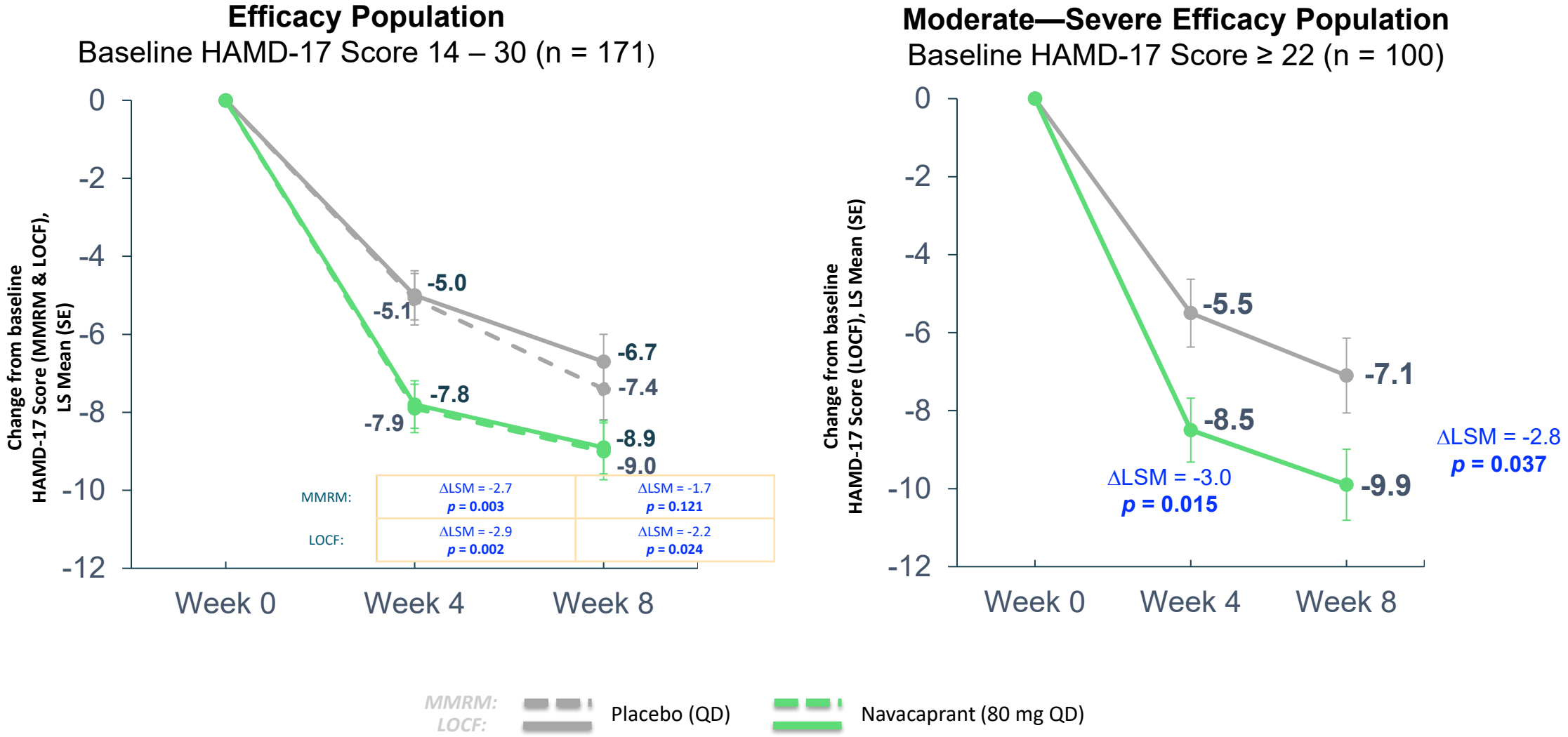


Primary outcome: **mean fMRI ventral striatal activation in anticipation of rewards in the monetary incentive delay task**

N = 89.

Krystal et al. Nat Med. 2020;26:760.

Navacaprant Phase 2a Trial: Change from Baseline in HAMD-17 Score



Mathew SJ et al, *J Clin Psychopharmacol* 2025

HAMD-17 = Hamilton Depression Rating Scale – 17-item version; LOCF = last observation carried forward; LSM = least squares mean; MMRM = mixed model repeated measures; QD = once daily; SE = standard error

Psychedelics and Psychedelic-Assisted Psychotherapy

Psyche (soul, spirit, or mind) and delos (clear or manifest)

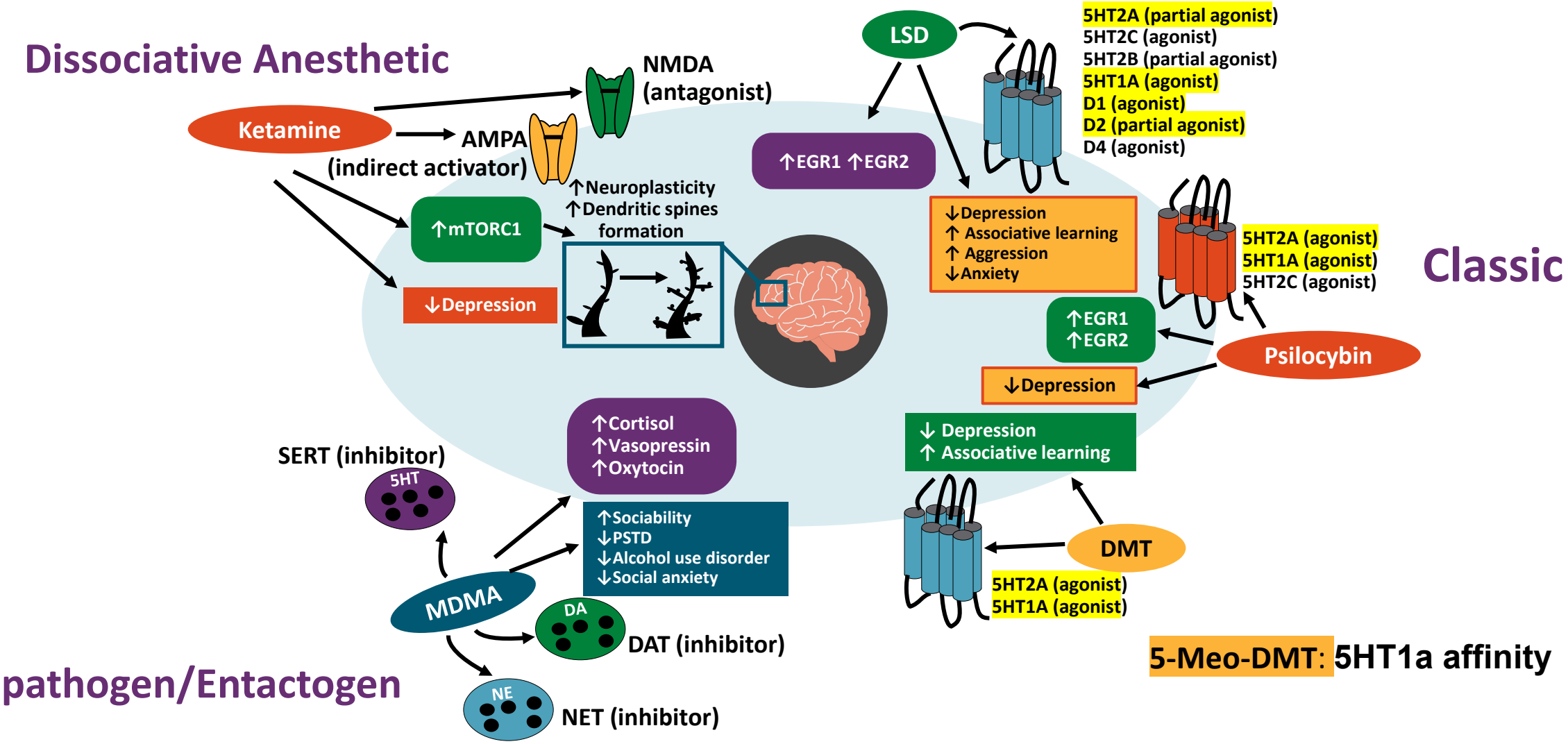
5-MeO-DMT, derived from venom of Sonoran Desert toad



Psilocybin: Plant alkaloid derived from tryptamine precursors

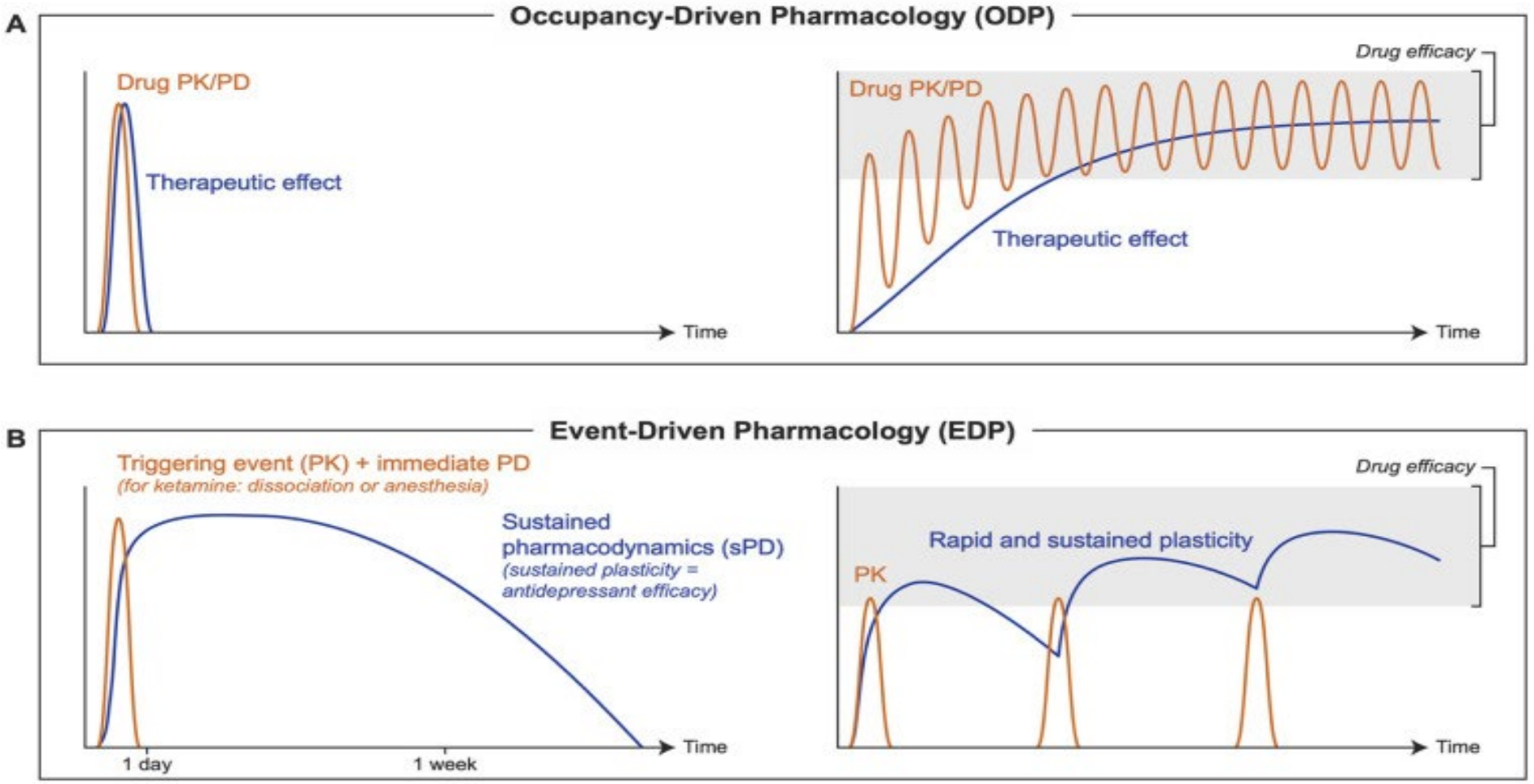


Pharmacologic Targets of Psychedelics



De Gregorio et al. J Neurosci. 2021;41:891.

Event-Driven Pharmacology: implications for dose frequency and meta-plasticity



Stable receptor occupancy over extended time

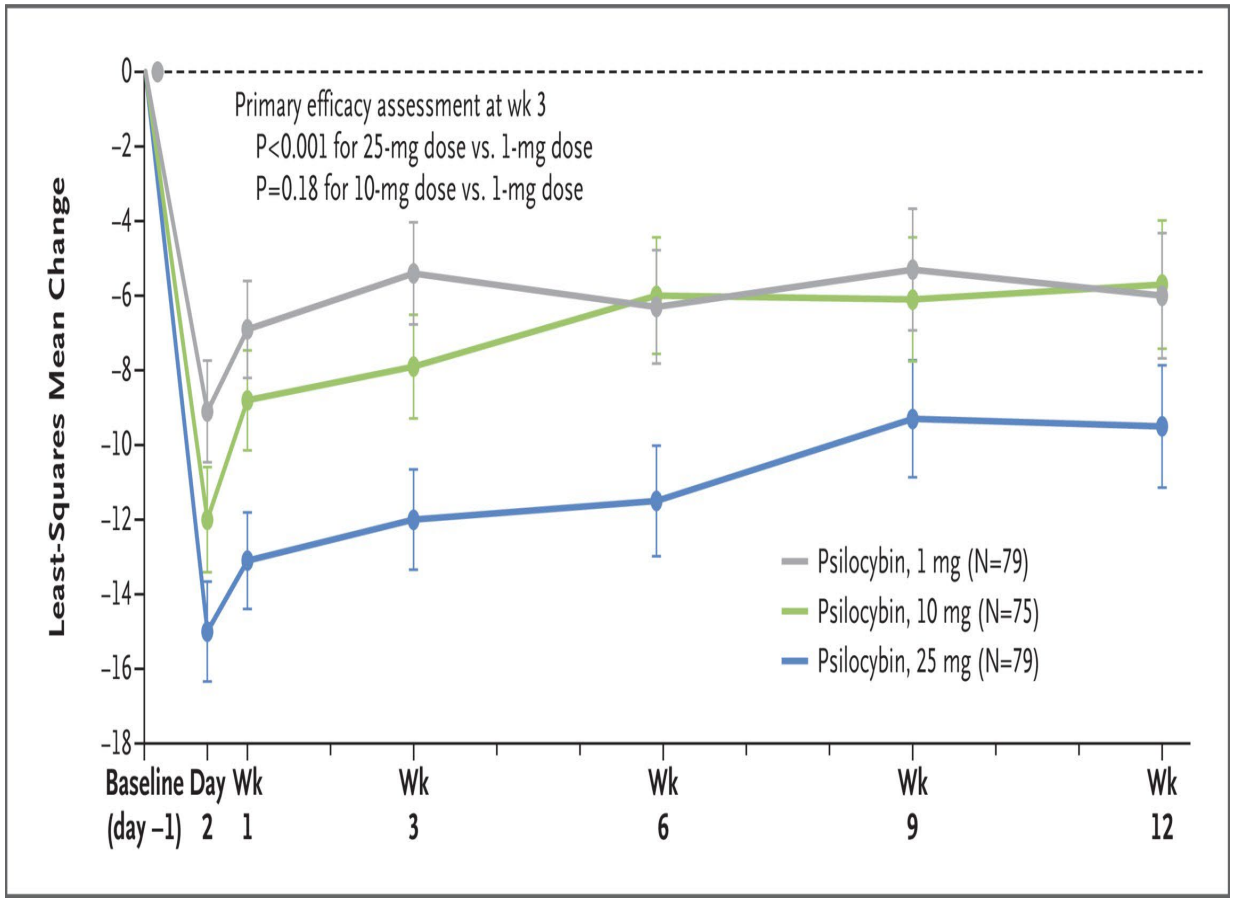
Transient receptor occupancy, followed by complete drug elimination

Gould TD, Mathew SJ, Fava M, Shekhar A, *J Psychopharmacology* 2026

Psychedelics: Recent Developments in MDD/TRD

- **Psilocybin and derivatives**
  - **COMP360**/Usona Institute: Phase 3 trials in TRD/MDD
  - **Deupsilocin (HLP003):** deuterated psilocin analog for adjunctive MDD in Phase 3
- **Mebufotenin (5-MeO-DMT) or DMT (Dimethyltryptamine)**
  - **Mebufotenin** (5-MeO-DMT) **GH001**: inhalational administration
  - **BPL-003** (intranasal mebufotenin benzoate): Phase 3 trials in TRD
  - **VLS-01 (DMT)**: oral transmucosal film for TRD (Phase 2b)
  - **Bretisilocin (GM-2505):** analogue of DMT, IM (duration is 60-90 min), q2wk
- **Lysergide D-tartrate (LSD)**
  - **DT120:** orally disintegrating tablet (ODT): Phase 3 in MDD

Single-Dose Psilocybin for a Treatment-resistant episode of major depression: Phase 2b Trial of COMP360



Goodwin GM et al NEJM 2022

Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
Primary efficacy end point			
Change from baseline to wk 3 in MADRS total score			
Least-squares mean	−12.0±1.3	−7.9±1.4	−5.4±1.4
95% CI of the least-squares mean	−14.6 to −9.3	−10.6 to −5.2	−8.1 to −2.7
Least-squares mean difference vs. 1 mg	−6.6±1.9	−2.5±1.9	—
95% CI of the least-squares mean difference	−10.2 to −2.9	−6.2 to 1.2	
P value vs. 1 mg	<0.001	0.18†	—
Secondary efficacy end points			
Response at wk 3‡			
No. of participants (%)	29 (37)	14 (19)	14 (18)
Odds ratio vs. 1 mg (95% CI)	2.9 (1.2 to 6.6)	1.2 (0.5 to 3.0)	—
Remission at wk 3§			
No. of participants (%)	23 (29)	7 (9)	6 (8)
Odds ratio vs. 1 mg (95% CI)	4.8 (1.8 to 12.8)	1.2 (0.4 to 3.9)	—
Sustained response at wk 12¶			
No. of participants (%)	16 (20)	4 (5)	8 (10)
Odds ratio vs. 1 mg (95% CI)	2.2 (0.9 to 5.4)	0.7 (0.2 to 2.0)	—

* Plus–minus values are standard errors.
† This nonsignificant P value terminated significance testing on the basis of the prespecified hierarchical test procedure, and all the subsequent secondary efficacy end points are considered to be not significantly different between the 25-mg group or 10-mg group and the 1-mg group.
‡ A response was defined as a decrease of at least 50% from baseline in the MADRS total score.
§ Remission was defined as an MADRS total score of 10 or less.
¶ A sustained response was defined as a week 3 response sustained through week 12.

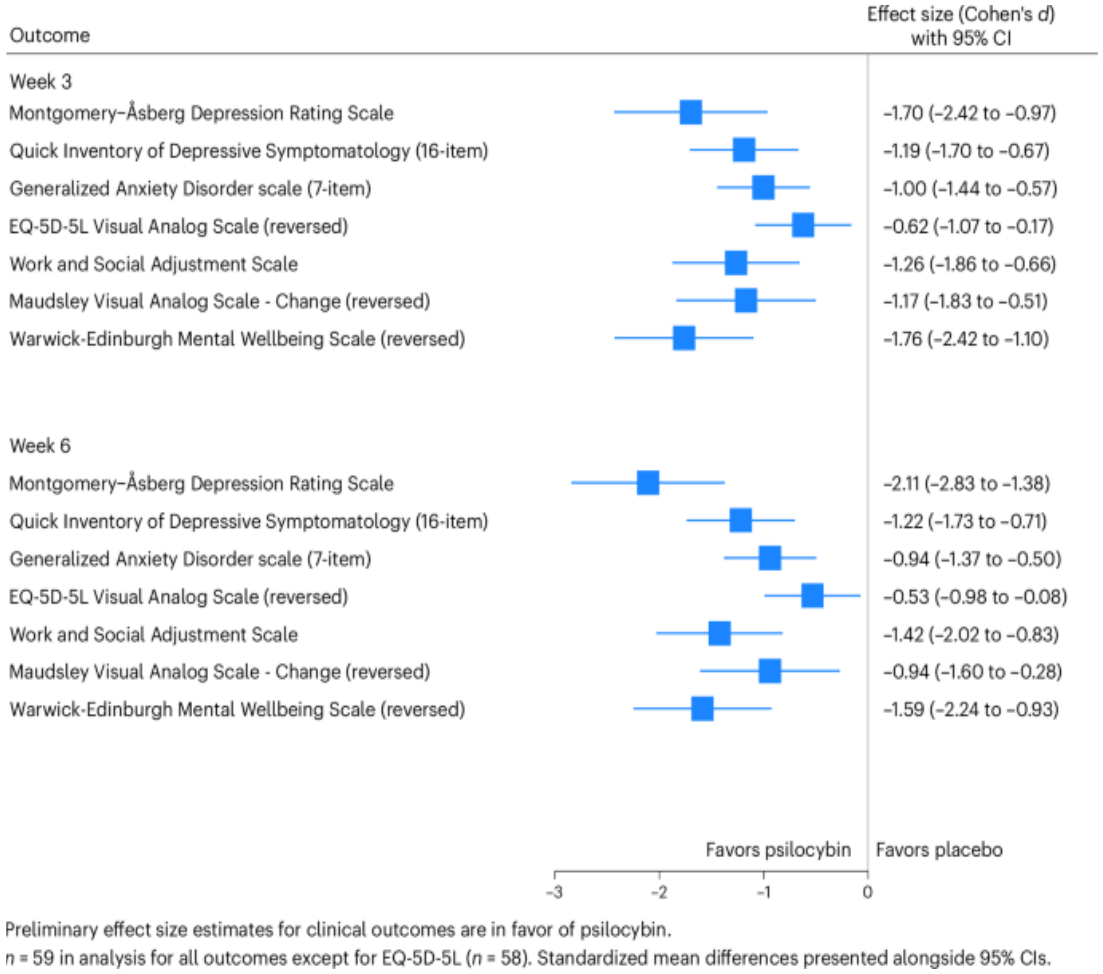
COMP360 Phase 3 Results in Treatment—Resistant Depression

	COMP005	COMP006
Dose	Single dose	Multiple dose (baseline + 3 weeks)
Sample size	258	581
Trial arms	25 mg, placebo	25 mg, 10 mg, 1 mg
Primary endpoint	Week 6	Week 6
Durability effect	26 weeks	26 weeks
Drug-placebo difference at primary endpoint	**-3.6** ($p < 0.001$)	**-3.8** ($p < 0.001$)

Compass Pathways, press release 2025, 2026; TRD sample primarily patients with 2 or 3 failed trials and majority had episode duration > 2y

Psilocybin-assisted therapy for treatment-resistant depression in a public healthcare setting

- UK randomized placebo controlled trial (n=60) in TRD, sponsored by NHS Foundation Trust
- 25 mg psilocybin vs placebo, followed by 6 hr session, then 6 integration sessions across 6 weeks
- No emerging suicidality or mania
- Week 3 endpoint
  - MADRS -10.41 (95% CI -14.86 to -5.95)
  - Cohen's *d* = -1.70
  - Differences sustained to week 6

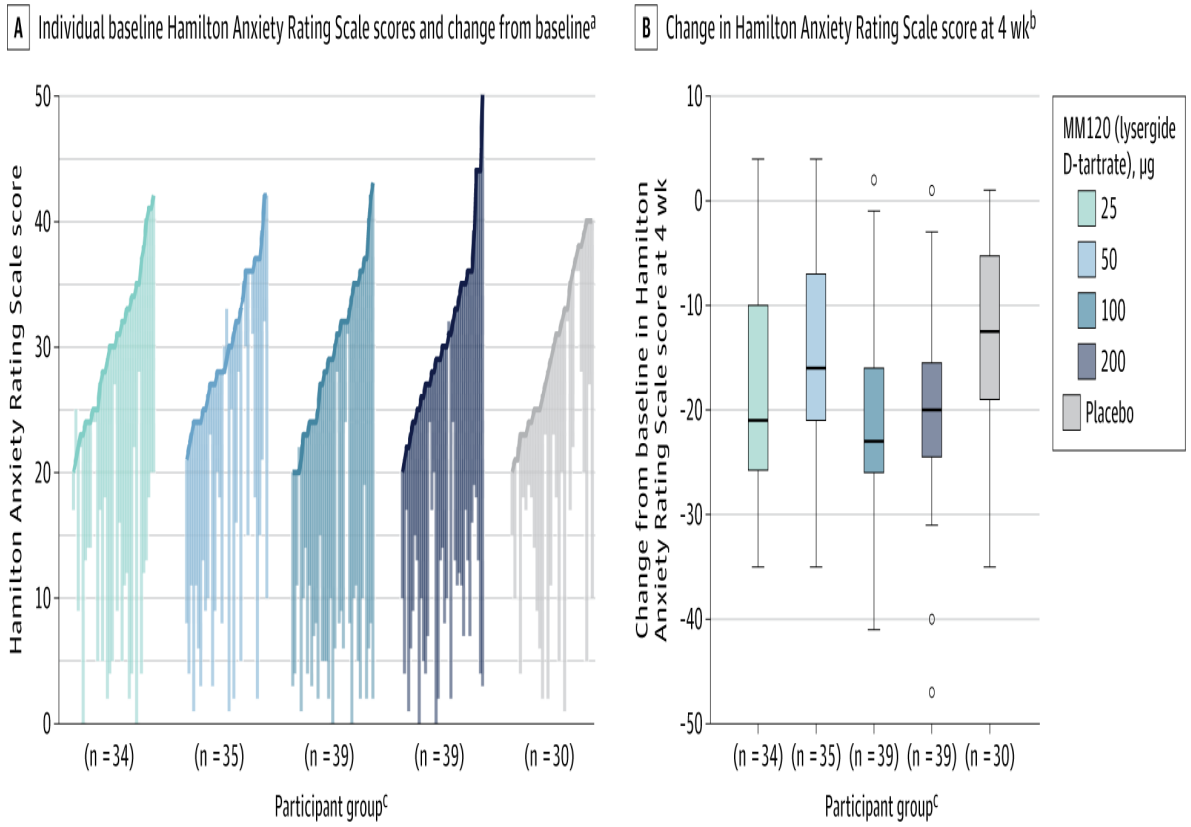


Preliminary effect size estimates for clinical outcomes are in favor of psilocybin.
n = 59 in analysis for all outcomes except for EQ-5D-5L (*n* = 58). Standardized mean differences presented alongside 95% CIs.

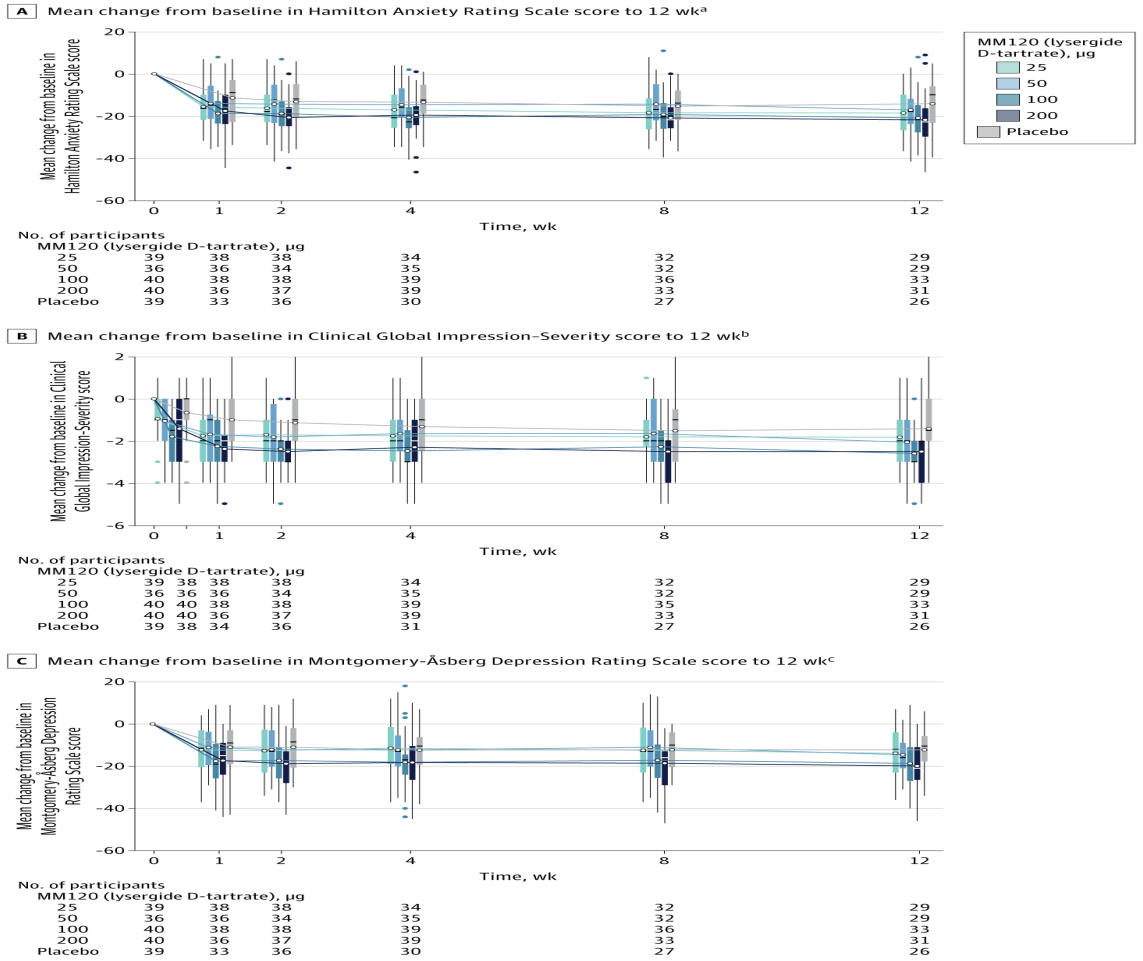
wk 6 response rate: 50% vs 3%

Rucker JJ et al Nat Medicine 2026

Single Treatment with DT120 (Lysergide) in Generalized Anxiety Disorder: A Randomized Clinical Trial (n=198)



Cohen's d = 0.81 at Week 12



Robinson R et al *JAMA* 2025

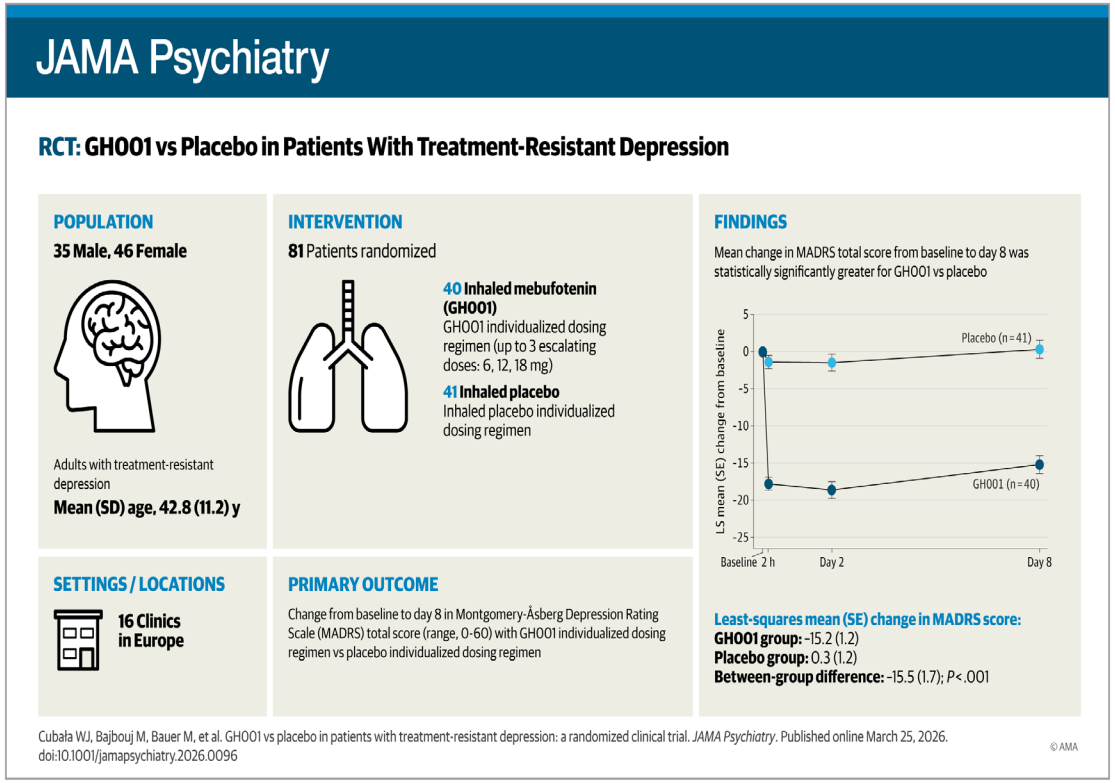
Dose-dependent improvements in MADRS

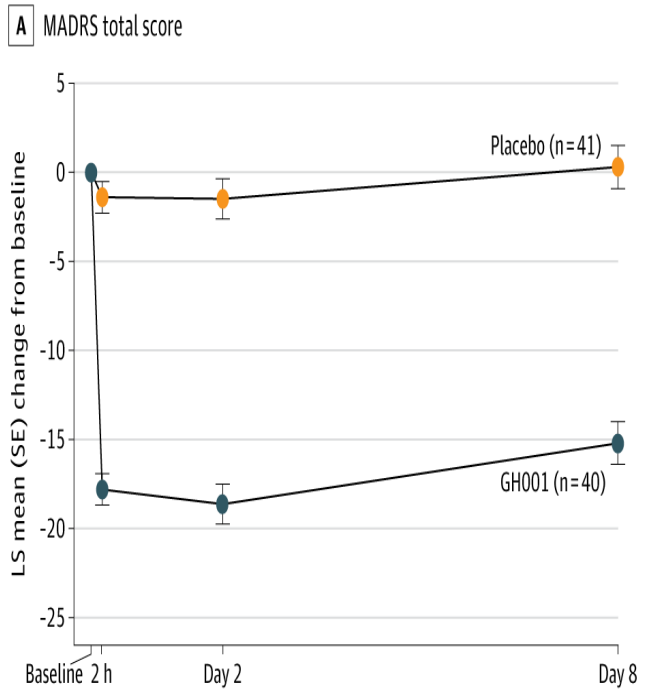
DT120 ODT: Phase 3 Program in Major Depressive Disorder

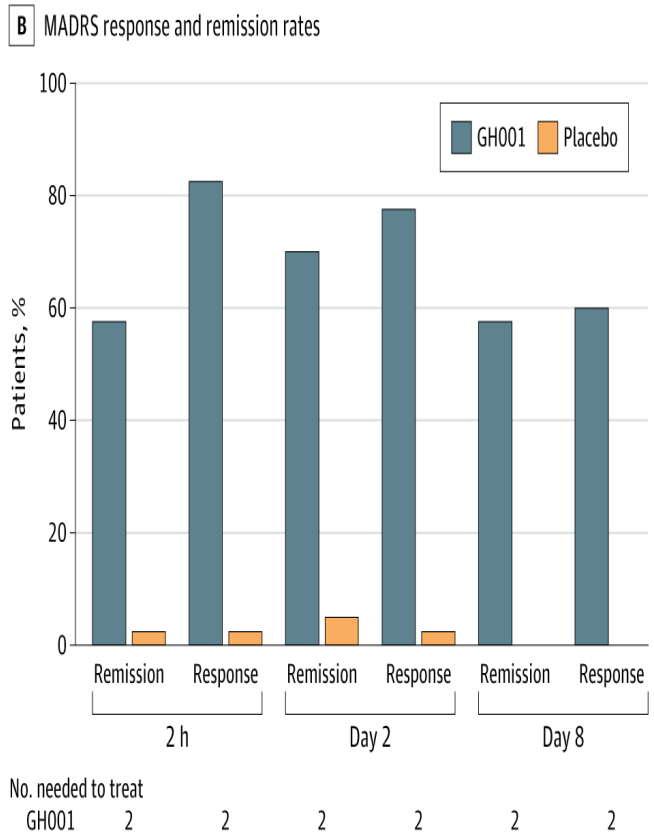
- Emerge study, n =149
  - 1:1 randomization (100 µg vs placebo)
  - 12 week DB RCT with 40 week OL extension (up to four doses)
  - About 50% of sample with 2+ past antidepressants
- Primary and key secondary endpoints
  - ***Week 6 primary endpoint***: **8.1 pt** MADRS improvement over placebo
    - **35% vs. 7% response; 24% vs 3% remission**
  - Week 1: **14.2** MADRS improvement over placebo
  - Week 12: **7.3** MADRS improvement over placebo

Definium therapeutics, press release, June 2026

Phase 2b Trial of inhaled mebufotenin (GH001) in treatment-resistant depression







Psychoactive effects 9-14 min

open-label with remitters: median time to retreatment was ***6 weeks***

Of 23 pts in remission at Day 8, 20 (87%) sustained remission across 6 months

Cubala WJ et al JAMA Psychiatry 2026

Mebufotenin Nasal Spray (BPL-003): Phase 2b Trial in TRD (n=193)

- Administered in-clinic, targets 2 hr post-dose time to discharge
- Patients with moderate to severe TRD, off antidepressants
- Primary endpoint at Week 4 (Day 29)

Treatment Arm	MADRS change from baseline	MADRS change compared to 0.3 mg	P Value
8 mg	-12.0	-6.2	< 0.01
12 mg	-11.2	-5.3	< 0.01

- Durable response through Week 8 for 8 mg and 12 mg dose
- 81% response and 67% remission at Week 16 after two doses in patients who initially received 8 mg dose

AtaiBeckley, 2026

Implementation Differences: Ketamine vs Psychedelics

	Time in Treatment Facility (hours)	Frequency of visits during maintenance phase
Esketamine nasal spray	2.5-3	Once weekly or biweekly
IV racemic ketamine	1.5-2	Highly variable
psilocybin	6-7	Every 2-3 months
LSD (DT120)	8-10	Every 2-3 months
mebufotenin	2.5-3	TBD

Key Points

- **NMDA/glutamate modulating drugs** without psychotomimetic adverse effects nor abuse liability of ketamine are of high interest, but there have been numerous failed programs over the last decade

- **AMPA receptor potentiation** is a promising mechanism that is currently in late stage testing as an oral adjunctive treatment; we now have the ability to visualize AMPA receptors in human brain with PET

- An advanced clinical program---**Kv7 Channel Openers** ---might be particularly suited to treat depression with marked anhedonia. Phase 3 programs are ongoing.

- **Psychedelics** (including psilocybin, LSD, and 5-MeO-DMT) are an active area of investigation for depression and related disorders. There are marked differences in approach in terms of time in office requirements, psychotherapy integration, route of administration, etc.