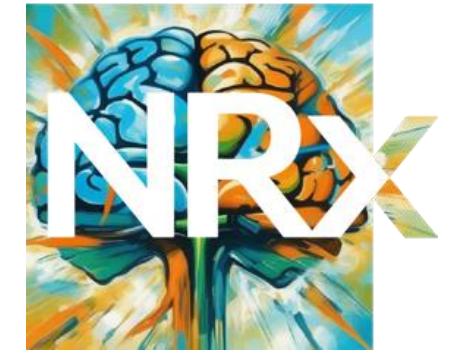


Neuroplastic Therapy
for CNS Disease
From Prediction
to Pilot to Proof
What a difference a
Year Makes

Hope
Science
Life



NASDAQ: **NRXP**



Sachs Forum 2026

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CNS Disease

The Health Challenge of Our Generation



- In the past 50 years, we have witnessed miraculous advances in treating infectious disease, heart disease, cancer, and other major causes of death
- In the past 50 years Depression, PTSD, Autism, Traumatic Brain Injury, ADHD, and other CNS conditions have become society's largest healthcare challenges

CNS Disease

A Century of Therapeutic Failure

- Psychotherapy before medication had low efficacy
- The SPECT-D Trial demonstrated that traditional antidepressants work 37% of the time
- PTSD, Autism, TBI, Cognitive Decline, OCD, and other debilitating conditions have no meaningful approved treatments
- The only FDA-approved treatment for suicidality remains Electroshock Therapy



Suicide is a National Crisis that kills >50,000 Americans every year

Over
49,000
people died by
suicide in 2022



1 death every
11 minutes



Many adults think about
suicide or attempt suicide

13.2 million
Seriously thought about suicide

3.8 million
Made a plan for suicide

1.6 million
Attempted suicide



Suicide takes our **best and brightest**

Nolan Williams

“My hope is that we are able to transform the mental health therapeutic landscape in my lifetime. We confront what I term as brain emergencies—where the brain's cognitive control circuitry is unable to suppress the neural circuitry underlying negative mood which in some people can result in severe impairment and thoughts of suicide. By studying the brain's network level differences, we aim to offer tailored solutions for those who have suffered far too long.”

- Nolan Williams, M.D.

Suicide as a short circuit in the Brain



WE HAVE LOST MORE TROOPS TO SUICIDE THAN TO COMBAT

FAILING OUR MOST INTEGRAL AND VULNERABLE SERVICE MEMBERS

VETERAN & FIRST RESPONDER MENTAL HEALTH



**MORE LIKELY TO DIE BY
SUICIDE THAN ON DUTY**

- We are part of the VA Community Cares Program
- Suicide is a strategic threat to force readiness and First Responder preparedness
- Aside from the human cost, we are losing irreplaceable personnel who are critical to National Security
- 100 Day Cabinet Meeting: Veteran Suicide is Job One



DoW(DoD) & Departments need a faster, measurable path back to full duty.

125 Drugs for Depression and They Can All Cause Suicide

For 70 years, we have been looking at the wrong neurochemical pathway (serotonin)



Mad in America
SCIENCE, PSYCHIATRY AND SOCIAL JUSTICE

EDITORIAL ▾ DRUGS ▾ EDUCATION ▾ VETERANS ▾ FAMILY ▾ MAD IN THE WORLD ▾ GET INVOLVED ▾ ABOUT ▾

The Lie That Antidepressants Protect Against Suicide Is Deadly

By Peter C. Gøtzsche, MD - November 28, 2023

3955

Editor's Note: This article is part of a special series on antidepressants. For more information, see the [introduction](#).

Abstract: The claim that antidepressants reduce suicidal behavior is a lie that has been repeated for decades. This article reviews the evidence and discusses the risks of antidepressants.

Keywords: antidepressants, suicide, serotonin, selective serotonin reuptake inhibitors (SSRIs), serotonin syndrome, akathisia, Black Box warning, serotonin hypothesis, placebo effect.

Introduction: The claim that antidepressants reduce suicidal behavior is a lie that has been repeated for decades. This article reviews the evidence and discusses the risks of antidepressants.

Conclusion: The claim that antidepressants reduce suicidal behavior is a lie that has been repeated for decades. This article reviews the evidence and discusses the risks of antidepressants.

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220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 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1103, 1104, 1105, 1106, 1107, 1108, 1109, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1260, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1274, 1275, 1276, 1277, 1278, 1279, 1271, 1272, 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Akathisia occurs in up to 15% of patients on antidepressants

Akathisia is the side effect of antidepressants most closely linked to suicide



The New York Times

By [Roni Caryn Rabin](#)
Sept. 11, 2017

- *Stewart Dolin was a successful and well-liked partner at Reed Smith in Chicago. He developed an episode of depression and was treated with Paxil. That night, his family noticed that he could not stop tapping his feet at dinner and could not sit still.*
- *In the early afternoon on July 15, 2010, Stewart Dolin walked to a Chicago Transit Authority station shortly after a business lunch with a colleague. A woman at the station noticed that Mr. Dolin was pacing and appeared to be agitated as he looked in the direction of an approaching train that was not yet in sight. When the moving train appeared, the woman watched Mr. Dolin leap in front of the train.*

In his memory, the family founded the MISSD foundation to explain akathisia to the public.
www.missd.co contains illustrative material

We are finally unlocking the neurobiology of suicide

Neuroplasticity – Making New Connections in the Brain

- Today's approved treatments, including NMDA-targeted drugs, TMS, and Hyperbaric Oxygen all drive Neuroplasticity
- Drugs like psilocybin and MDMA may provide advances, not through causing hallucination but through neuroplasticity
- Digital therapeutics and other neuromodulation technologies are likely to provide additional benefit
- EEG-guided approaches, using far less energy than TMS and focusing on electrical frequencies in the brain are around the corner

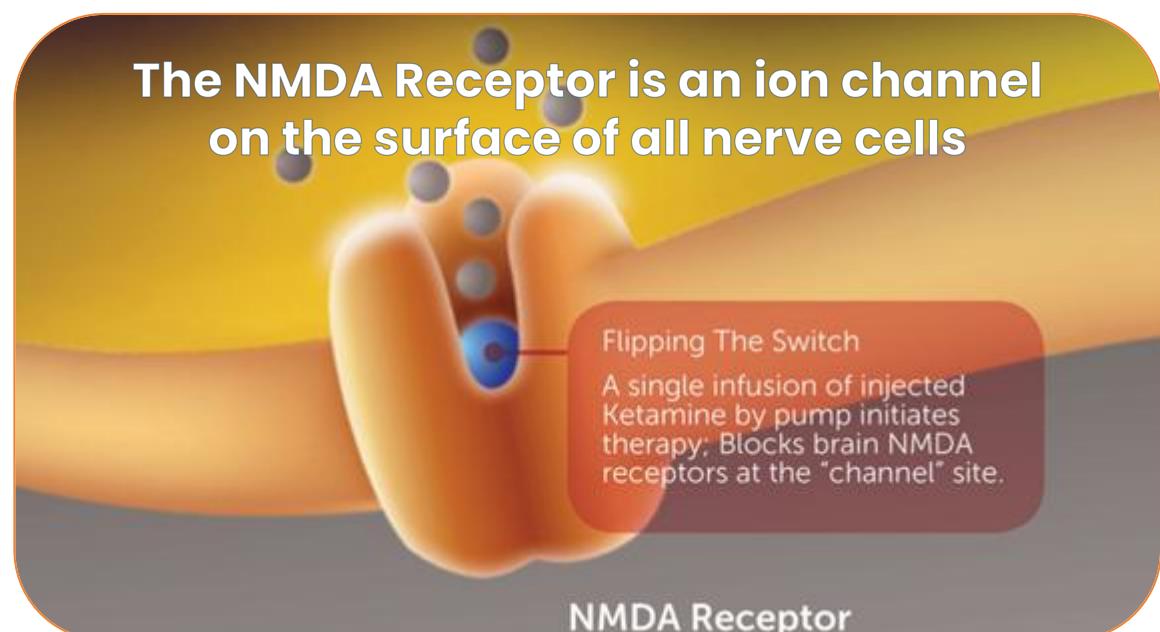


Understanding the biology of Suicide

NMDA is an ION channel that regulates Synaptic Plasticity and Speed of Thought

- › **Total Blockade**
- › **High NMDA activity**

Thoughts race uncontrollably, mania and psychosis
Low ideation, rumination, depression and suicide



NMDA Antagonists:

Modulate brain glutamate levels as seen on Magnetic Resonance Spectroscopy.

Decrease depression and suicidal ideation

Stimulate new connections between brain cells (Synaptic Plasticity)

PTSD demonstrates brain lesions with the inflammation and other characteristics of traumatic wounds



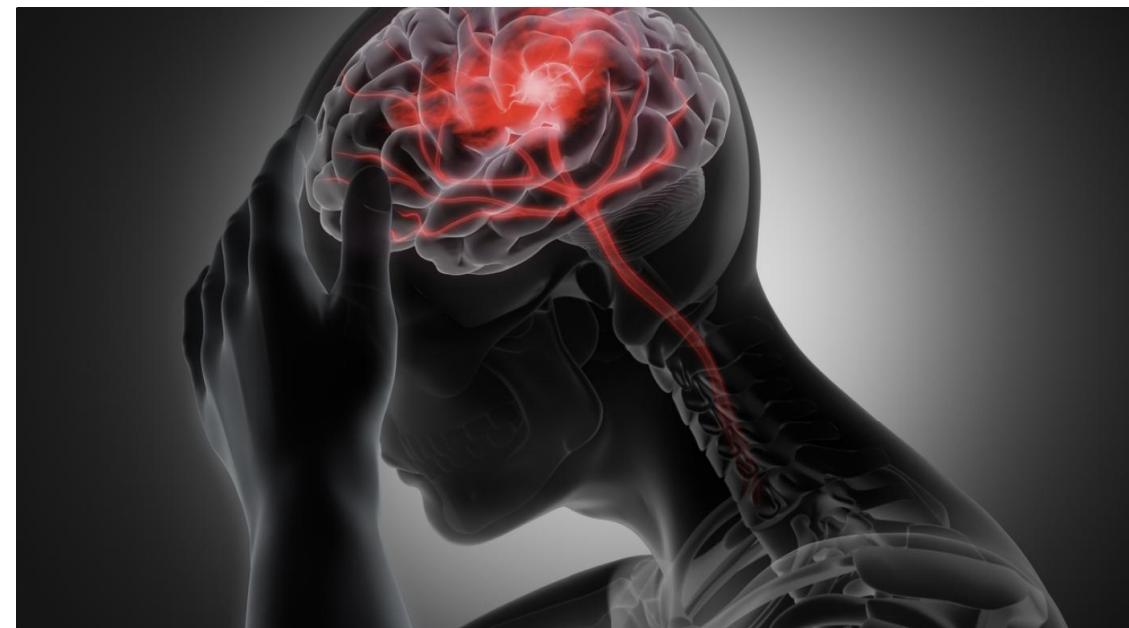
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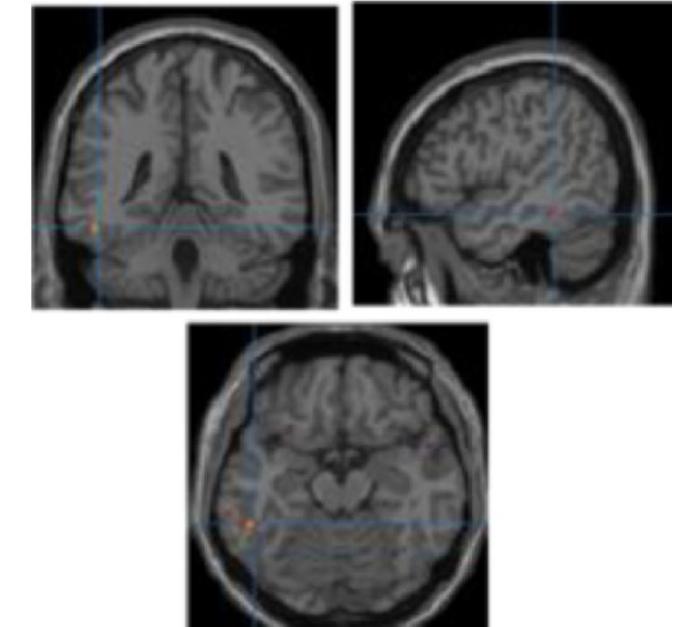
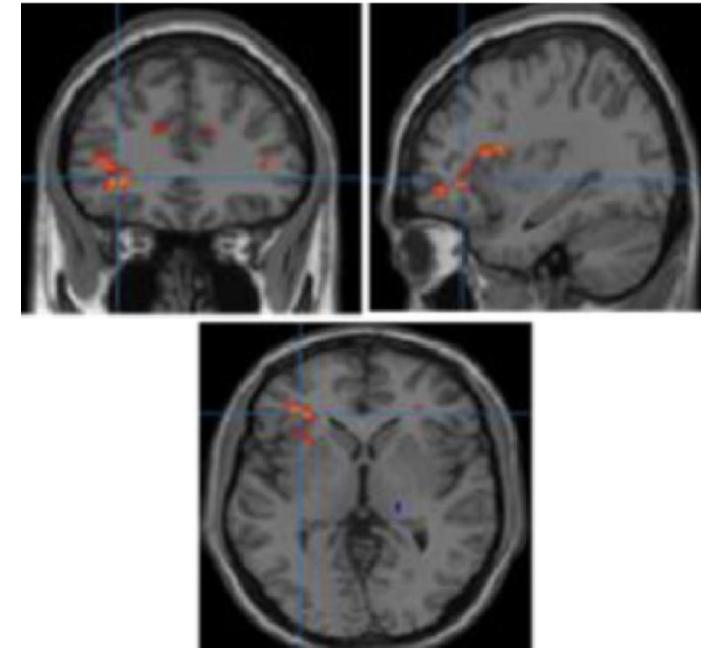
Inflammation
and PTSD

Thomas C. Neylan, MD and Aoife O'Donovan, PhD
San Francisco VA Health Care System
University of California, San Francisco



Suicidal Depression / PTSD is a Brain Wound and deserves to be treated with the same scientific commitment as any other Wound

FMRI in
Suicidal
Ideation vs.
Normal



Classifying CNS diseases that manifest as “behavioral conditions” differently from other neurological conditions denies biology

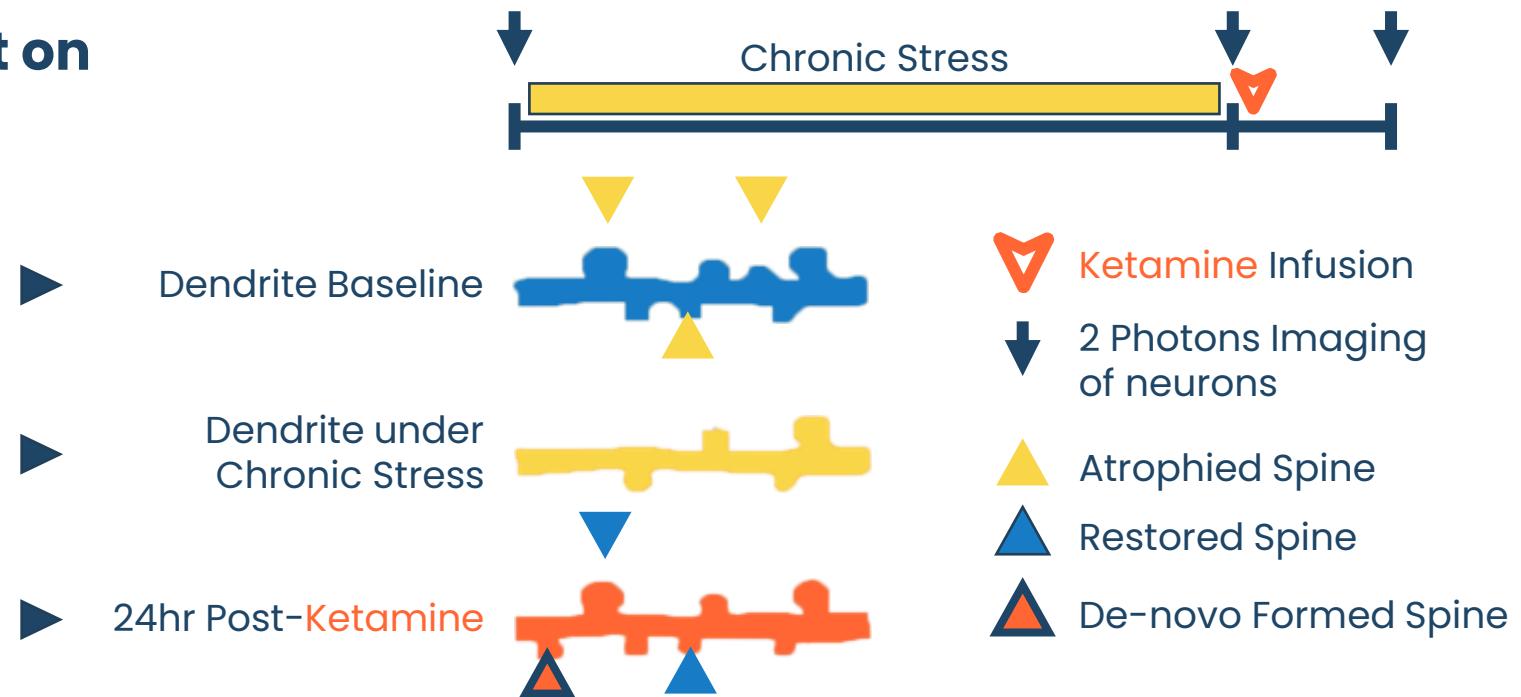
Ketamine “rewires” the brain by blocking NMDA

Ketamine’s neuroplastic effect on dendritic spines

High levels of NMDA activity are shown to cause atrophy of the “dendritic spines” that connect brain cells

Loss of dendritic spines is associated with depression-related behavior

NMDA blockade with ketamine is demonstrated to restore lost dendritic spines, while simultaneously reducing depression-related behavior



Chronic Stress

- ↑ Clustered Dendritic Spine Loss
- ↓ Ensemble Activity
- ↑ Depression-related Behavior

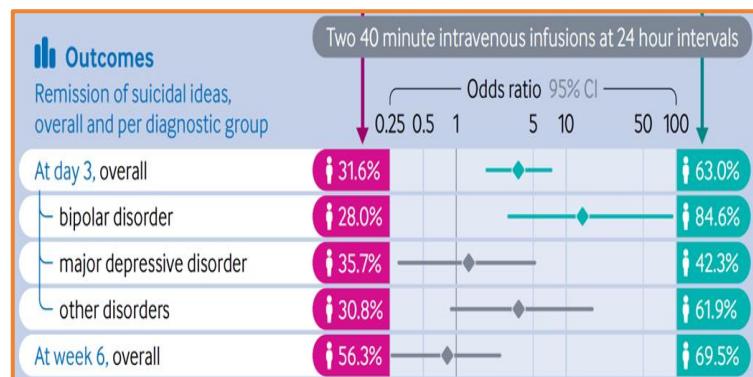
Ketamine

- ↑ Clustered Dendritic Spine Formation and Restores Spine Loss
- ↑ Ensemble Activity
- ↓ Depression-related Behavior

Established Ketamine Efficacy Data

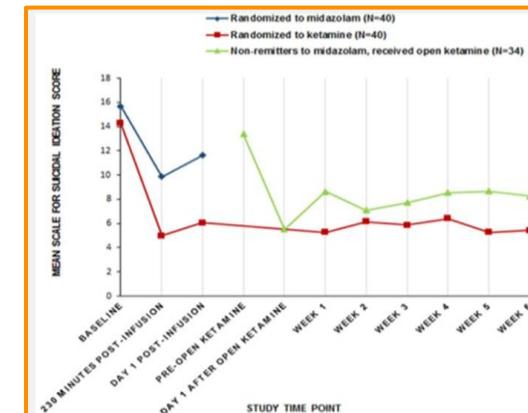
French Gov't Funded: Ketamine vs. Placebo

- 156 Patients, 7 Hospitals
- Admitted with acute suicidality
- Randomized to Ketamine vs. Placebo
- 84% remission on **Ketamine** vs. 28% on Placebo in bipolar depression subgroup
- Odds Ratio 4.6; $P<.0001$ on Primary Endpoint



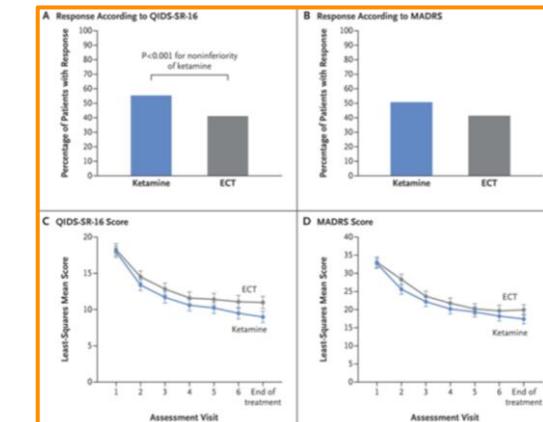
NIH Funded: Ketamine vs. Midazolam

- 96 pt. Randomization to Ketamine vs. midazolam
- Dramatic ketamine effect on suicidality and depression vs placebo (Odds Ratio 5.0; $P<.001$)
- Midazolam failures treated with open-label Ketamine and similar dramatic effect was seen with Ketamine as secondary treatment



PCORI Funded: Ketamine vs. ECT

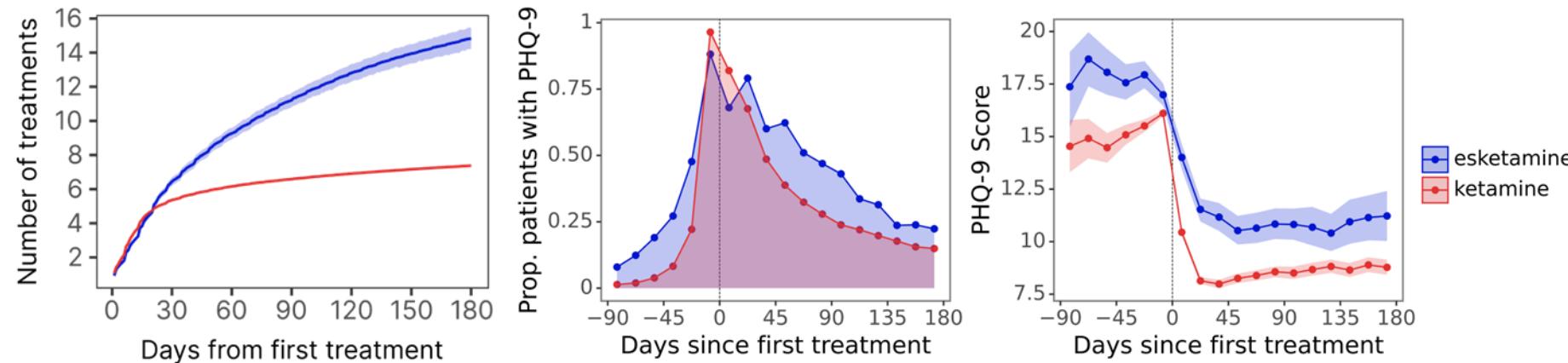
- 400 pts. superiority favoring **Ketamine** $P=.007$ (superiority is post-hoc)
- Significant memory loss in ECT vs. none with **Ketamine** (-9.7 vs. -0.9; $P<.0001$)
- 6 month relapse ECT 56.3 vs. **Ketamine** 34.5 ($P<.0001$)



>65,000 patients of Confirmatory Real World Data

IV racemic Ketamine vs. Nasal S Ketamine:

- Patients treated with ketamine required significantly fewer doses over 180 days
- Patients treated with ketamine demonstrated significantly lower depression scores (PHQ-9 scale) over 180 days of treatment

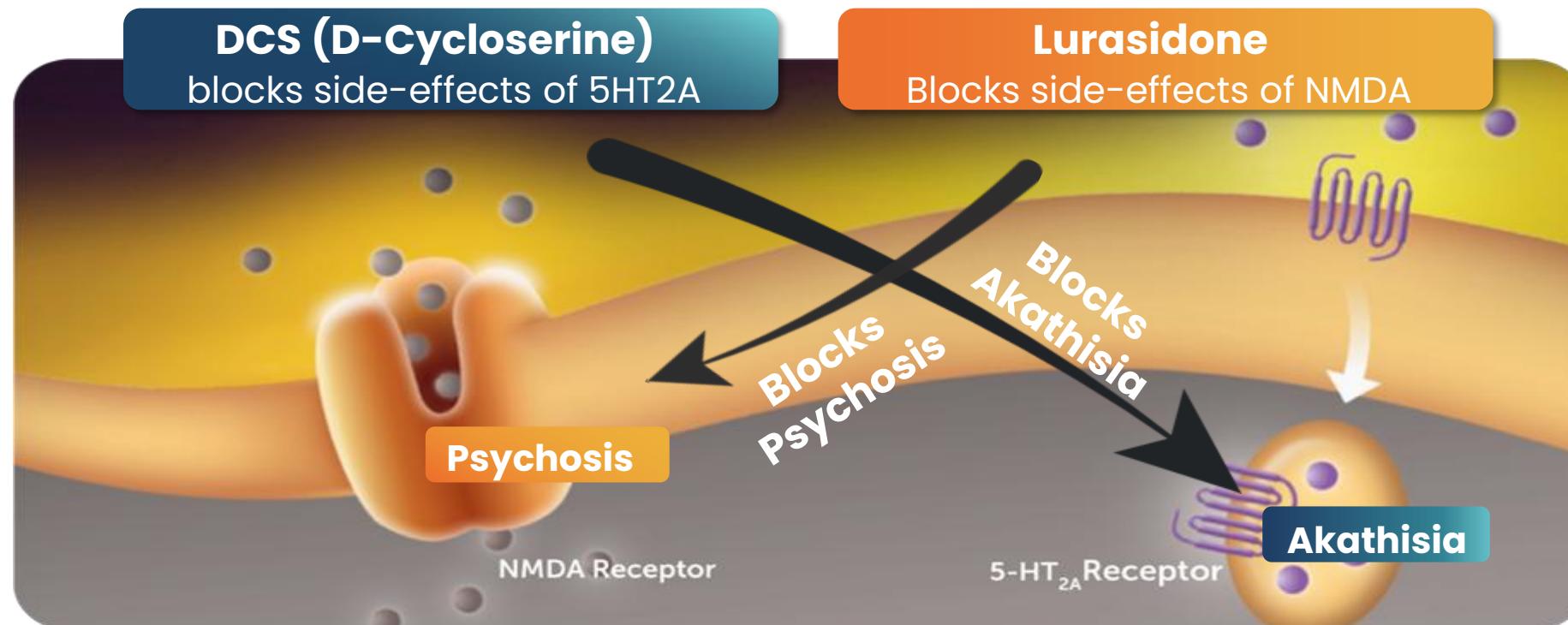


Data presented by Osmind, Inc., from medical records of more than 20,000 initial patients treated with IV Ketamine or nasal S-ketamine (ASCP June 2024)

D-cycloserine

Ketamine is a direct channel blocker/Cycloserine modulates NMDA

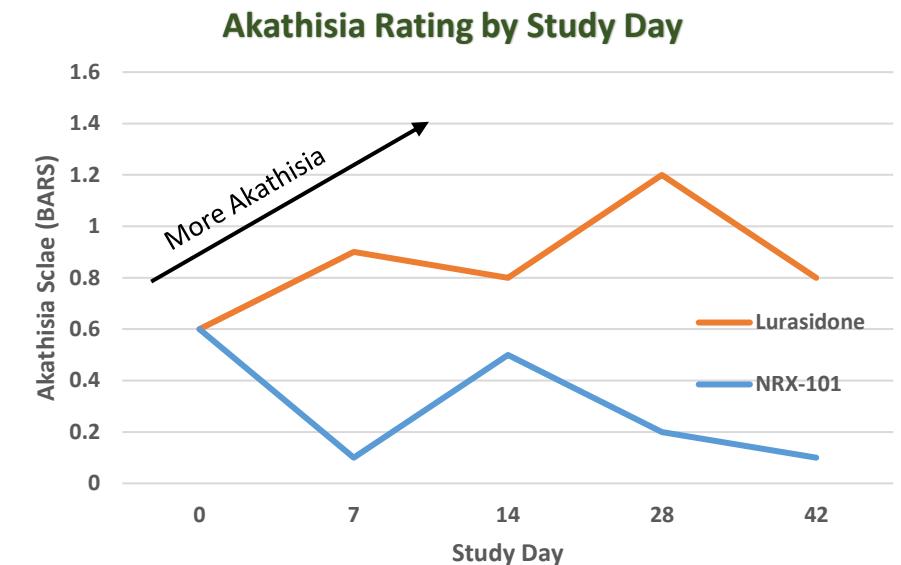
- First molecule to show antidepressant effect while directly reducing akathisia
- Unlike direct channel blockers, it is not addictive
- Hallucinogenic effects are blocked by small amounts of 5-HT_{2A} antagonists
- *Akathisia is considered by experts to be a precursor to suicide*



DCS demonstrates reduced Akathisia and Suicidality in Bipolar Depression

Phase 2b/3, randomized, double blind trial on NRX-101 vs Standard of Care (lurasidone) in Suicidal Treatment Resistant Bipolar Depression (n=93)

- Similar (50% reduction) in depression vs. SoC
- Significant reduction in akathisia vs. SoC, $p=0.03$
- Decreased Time to Sustained Remission from Suicidality on C-SSRS scale vs. lurasidone ($p<0.05$)



First clinical trial to enroll, rather than exclude suicidal patients

Transcranial Magnetic Stimulation (TMS)

Creates a potent neuroplastic effect in the brain

**TMS repairs
Brain Pathways
by causing Neuroplasticity**



TMS alone achieves remission in ~60% of patients
addition of a neuroplastic drug achieves 90% response

Although commercialized 15 years ago, TMS was a niche treatment until recently

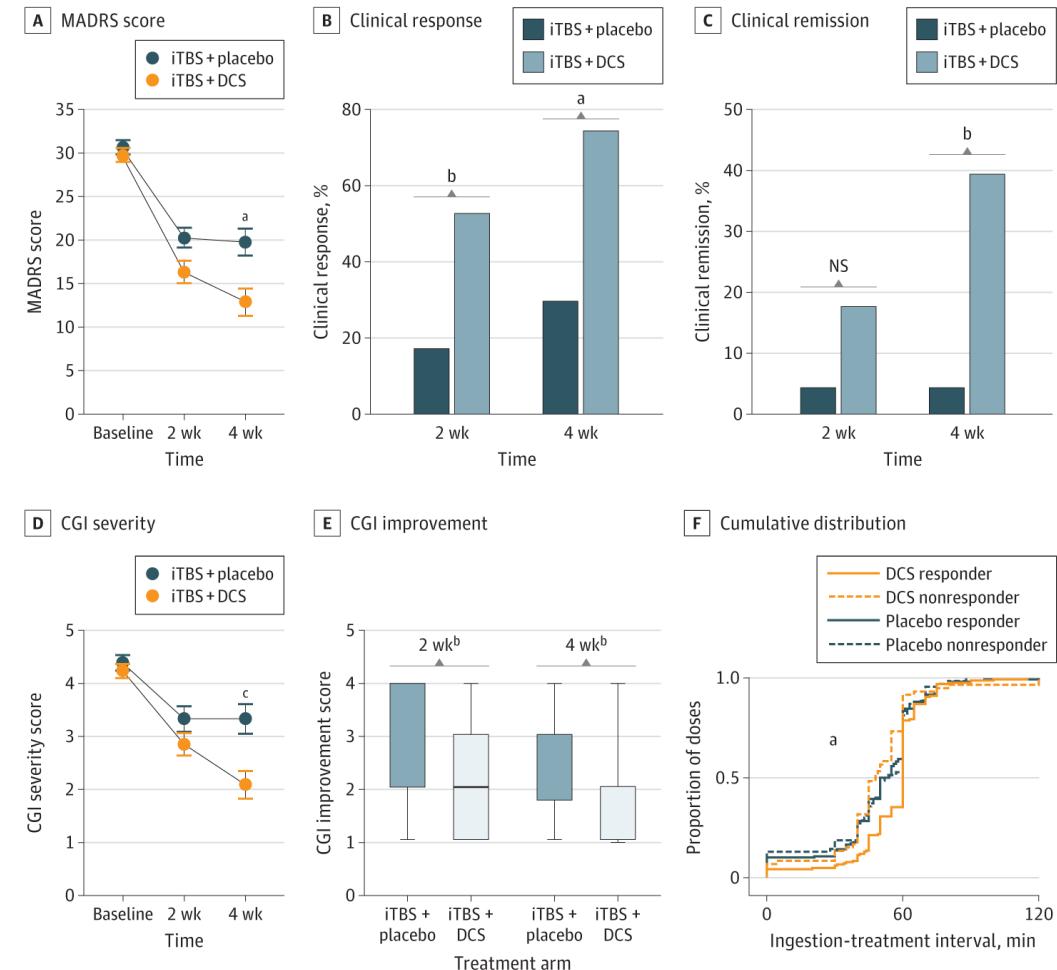
High frequency stimulation to activate
“dark areas” of the brain in depression
Low frequency stimulation to calm overly
active areas in anxiety and PTSD

Additional targets:

- OCD
- TBI
- Autism
- Parkinsons
- Cognitive Dysfunction

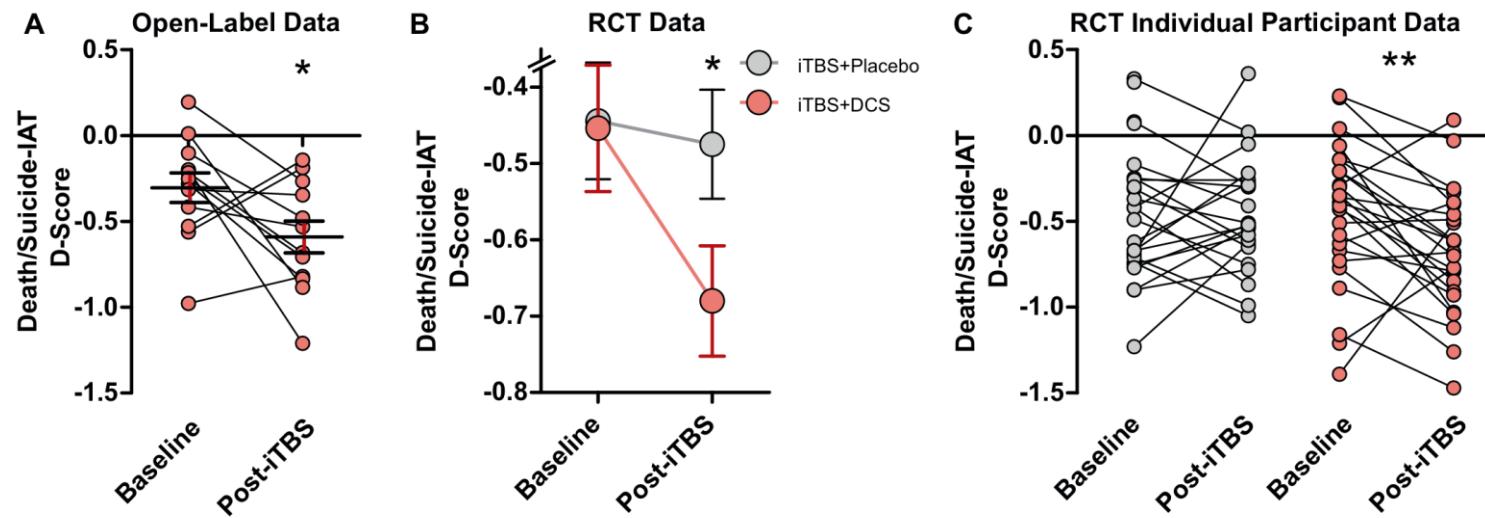
Use of D-cycloserine to Augment Theta Burst TMS

- DCS is used at neuroplastic (low) doses, not at NMDA-antagonist dose
- Randomized Trial (n=50) of DCS vs. placebo in association with Theta-burst TMS
- Patients with treatment resistant MDD
- Significant reduction in mean MADRS at 4 weeks with DCS ($P<.01$)
- > 2-fold better response ($P<.001$) and 8-fold increase in remission from depression ($P<.01$) at 4 weeks with DCS adjunctive therapy compared to placebo



Reduction in Suicidality associated with DCS + TMS

- Open label (n=12) and Randomized (n=50) trials demonstrate that DCS is superior to placebo in association with Theta-burst Transcranial Magnetic Stimulation in reducing suicidality on the IAT scale ($P<.05$)
- MADRS item 10 (suicidality) also showed statistically-significant reduction ($P<.001$)

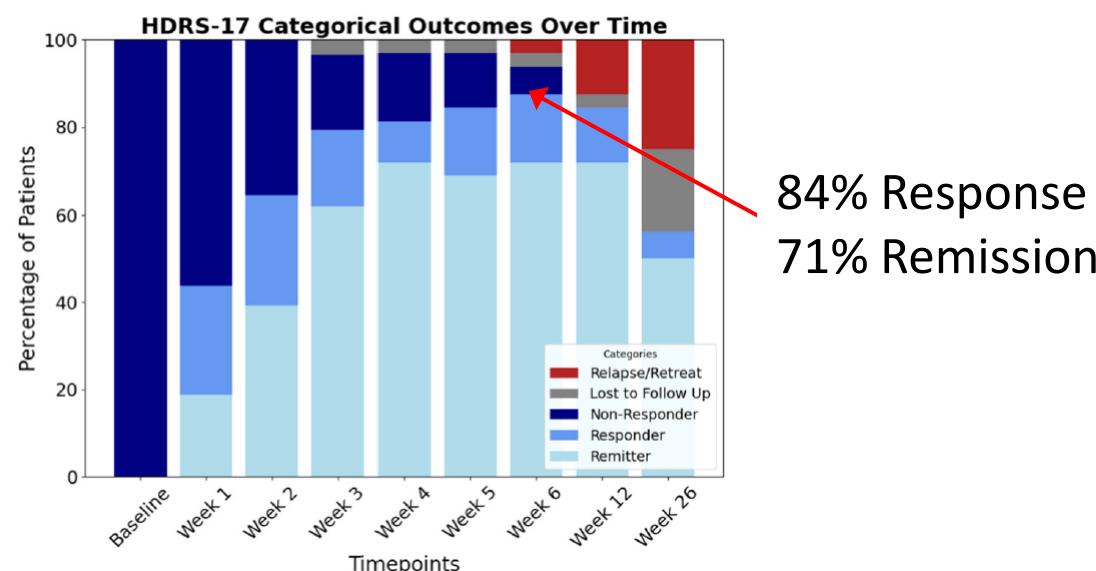


Real World Evidence: DCS + TMS for Treating Depression (TRD)



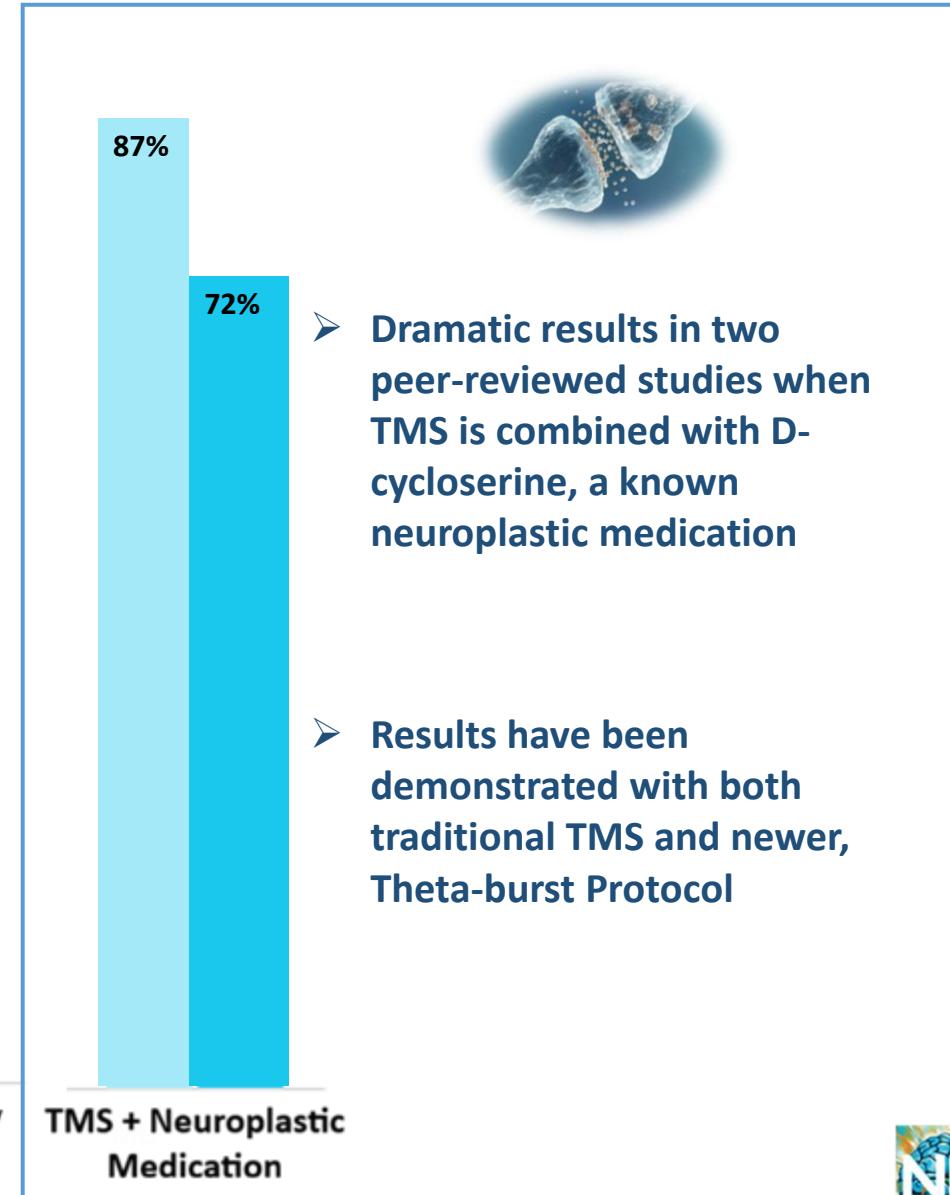
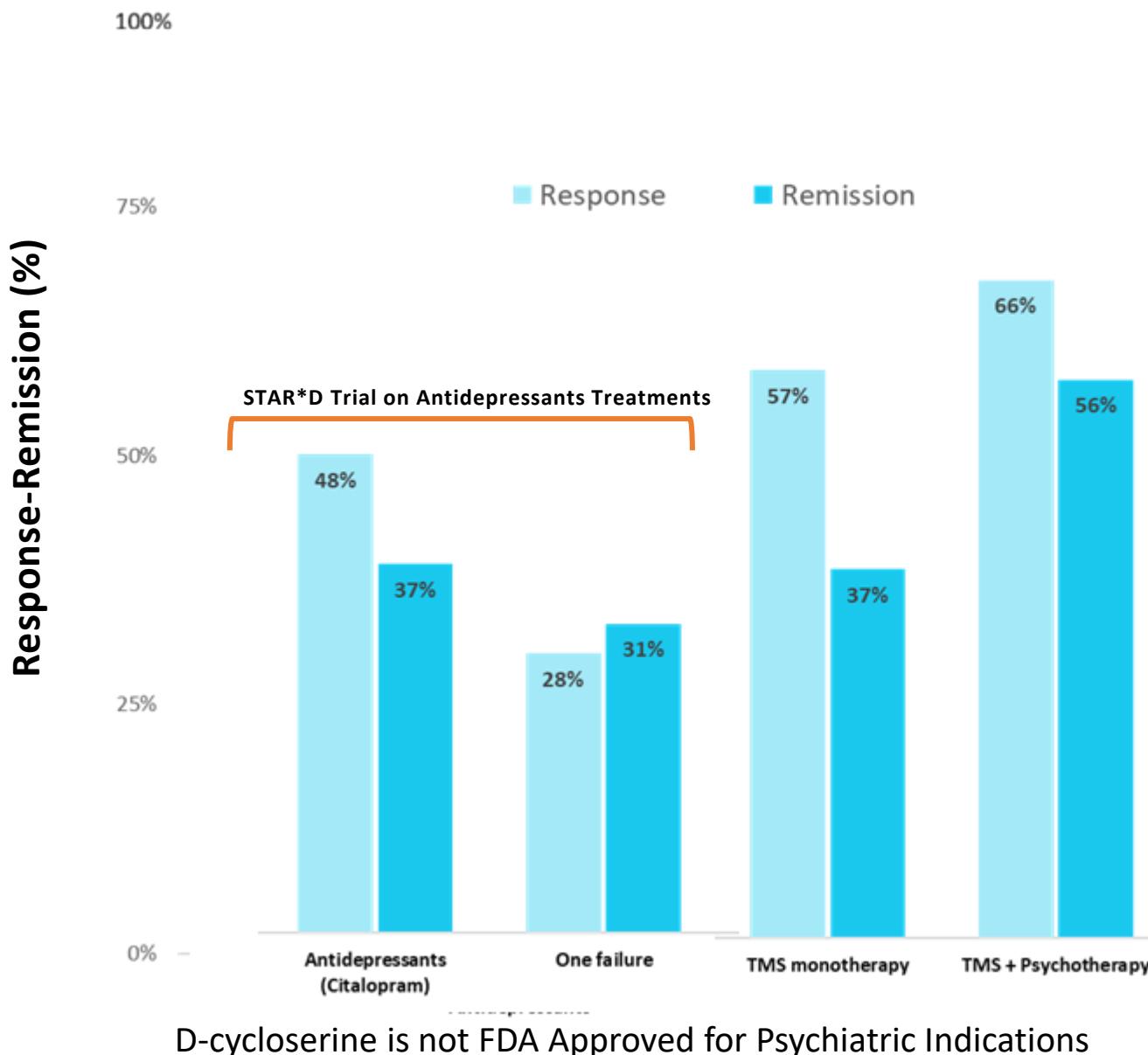
Real-world effectiveness of a single-day regimen for transcranial magnetic stimulation using Optimized, Neuroplasticity-Enhanced techniques in Depression (ONE-D): An open-label case series

Donald A. Vaughn ^a, Brooke Marino ^{a,c}, Alex Engelbertson ^c, Aleksandra Dojnov ^a, Lena Johnson ^a, Madison Stine ^c, Fidel Vila-Rodriguez ^d, Nicholas Weiss ^c, Georgine Nanos ^b, Jonathan Downar ^{a,e,f,*}



- D-cycloserine + TMS administered in a single-day protocol, 20 sessions
- No MRI or EEG guidance
- 84% Response, 71% Remission at six weeks with no additional intervention
- Note the relapse by 26 weeks without additional treatment
- Results are unprecedented in over a century of treating depression

TMS + Cycloserine Trial Results vs. Standard of Care

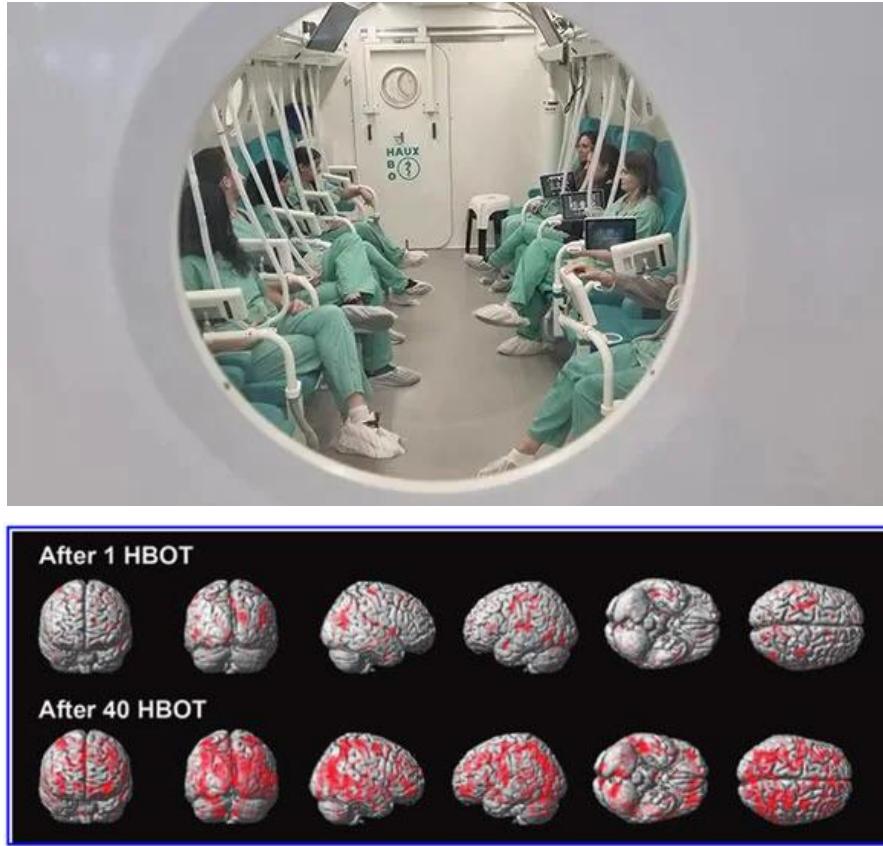




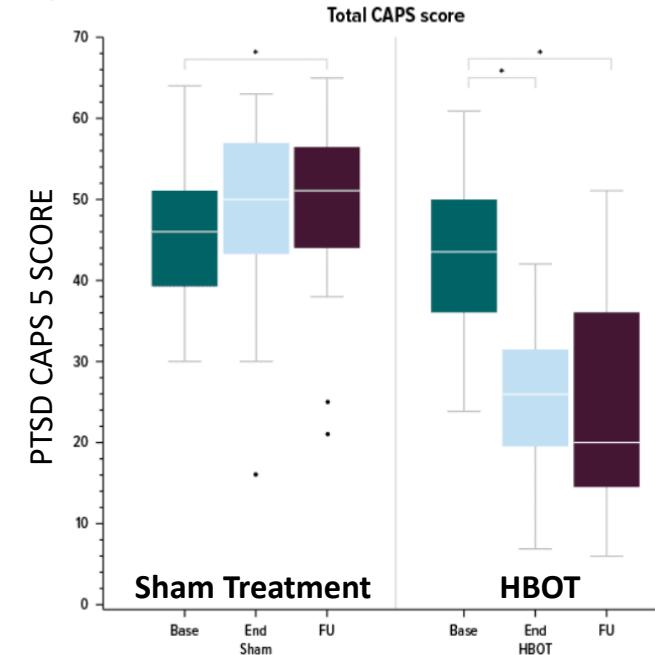
Neuronavigation: Precision targeting for TMS

“Map it before you Zap it”

Hyperbaric Oxygen Therapy (HBOT) increases brain oxygenation, stimulates Neuroplasticity and may reactivate brain stem cells



40% reduction in CAPS 5 (P<.001)



The IDF has implemented HBOT Therapy for PTSD and there is pending legislation in the US

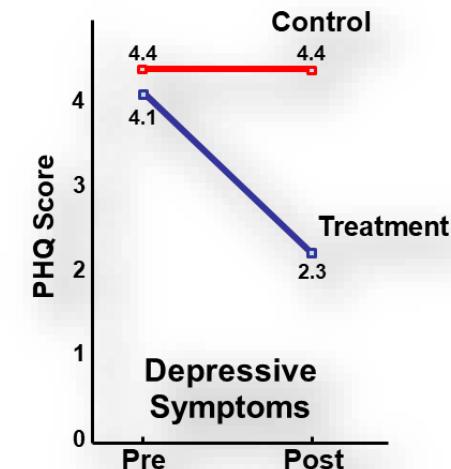
DIGITAL THERAPEUTICS:

Gamifying our way to a cure

Synchronizing Breathing and Heartrate creates Autonomic Coherence

- Discovery began with Special Forces operators who adopted meditation
- DARPA funded a project to gamify the process instead of teaching meditation
- Proven by DARPA in Riverine Warriors to improve combat performance with lower levels of serum cortisol and other physiologic indicators of stress
- Pilot projects with first responders demonstrated reduced measures of depression

Digital Therapeutics were developed in the military and shown to reduce stress and depression



Integrated Neuroplastic Care

Aim for Return to Duty in One Month

Ketamine

Rapid effect on Depression & PTSD
Effect lasts 1-2 weeks
Initiates Neuroplasticity with hours

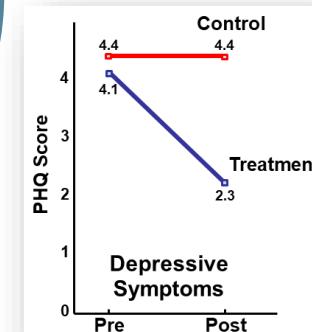


Transcranial Magnetic Stimulation

Evidence of 87% response
One Day and One Week protocols
Enhanced by neuroplastic drugs



Therapy and Medication Management



Hyperbaric Oxygen

Demonstrated by IDF to treat PTSD
Reactivates Brain stem cells in addition to neuroplastic effect

Digital Therapeutics

Developed under DARPA SBIR
Proven in Special Forces and first responders
Decreased depression, increased resilience

Integrated Neuroplastic Care

The Outcome that Matters is Return to Function

90% Success at Four Weeks in Pilot Program



REDUCE BRAIN INFLAMMATION



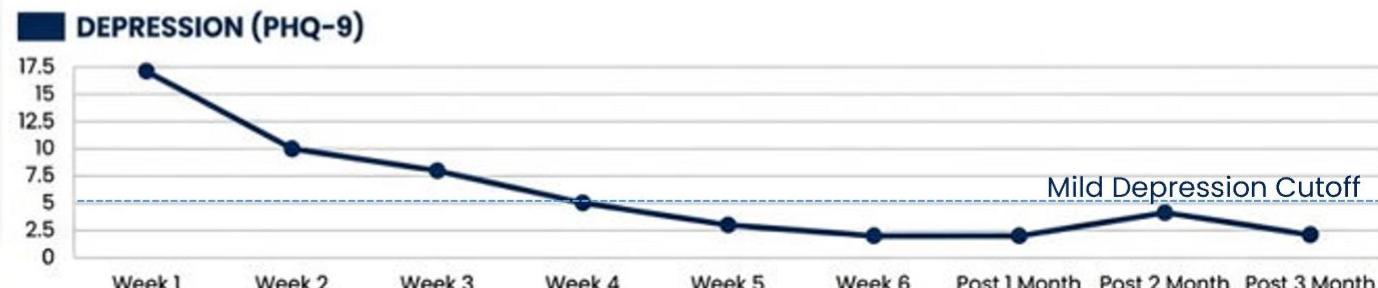
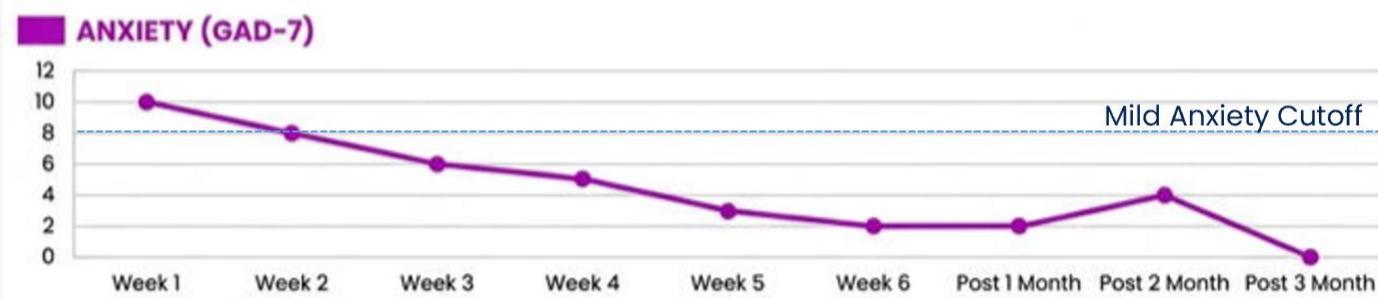
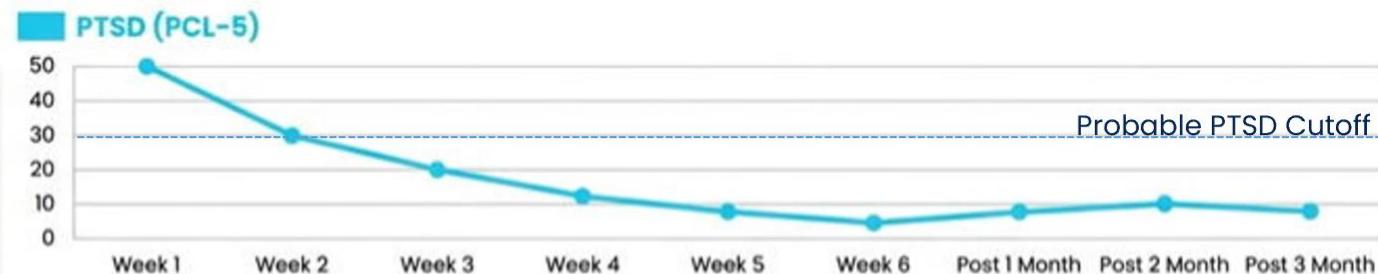
INCREASE NEUROPLASTICITY



BOOST CELLULAR ENERGY PRODUCTION



PRECISION BRAIN REWIRING



Integrated Neuroplastic Care: Cost Effectiveness

- For the first time, we are changing the survival outlook for suicidal depression and PTSD
- Integrated care for these lethal conditions costs far less than commonly reimbursed care for other lethal conditions

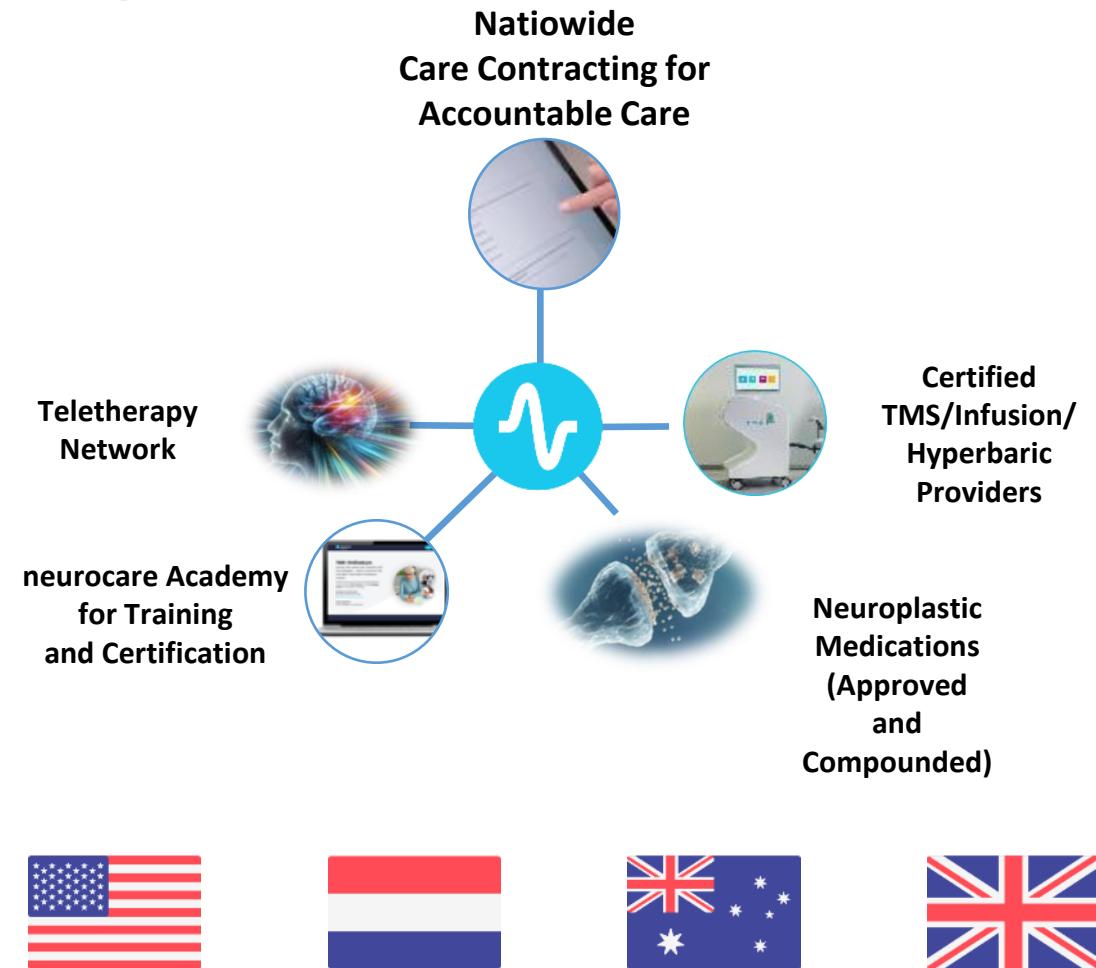
Condition	Cost per treatment episode
Suicidal Depression	< \$25,000
Cardiac Disease	~\$35,000
Breast Cancer	~\$35,000
Prostate Cancer	~\$35,000
Brain Tumor	\$150,000+

Suicidal depression and PTSD predominantly affect younger people with more years of productive life that can be saved

Cost per Discounted Healthy Year of Life saved is likely to be far lower

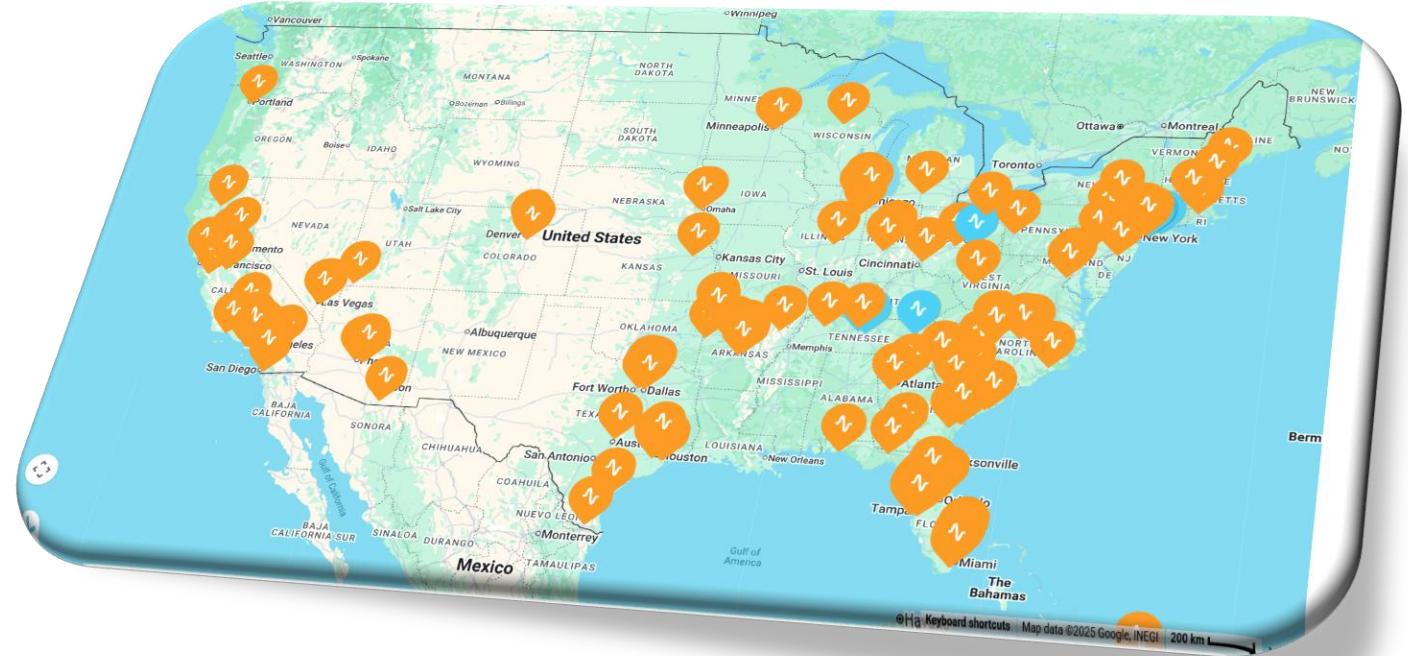
Integrated Care is the Key to Delivering Best Practice Outcomes

- ⌚ Neuroplastic drugs, TMS, and hyperbaric are today's key technologies
- ⌚ Psychedelic drugs are nearing clinical use
- ⌚ EEG-guided technologies are around the corner
- ⌚ The Market needs a Value-based Care Offering that delivers an accountable result
- ⌚ A front-end Teletherapy Network is key to enrolling and supporting the patient
- ⌚ neurocare Academy is key to maintaining standards
- ⌚ An integrated Patient Management System is key to documenting outcomes and adherence to standards



2026 Prediction: An Integrated Network of >100 Clinics

- Ability to treat >80% of Americans within driving distance of home
- Clinical response in 80%
- The TMS installed base is already in place
- The neurocare Academy insures a unique and accountable level of quality
- Definitive results for Depression and PTSD
- First results for Autism, TBI, and Cognitive decline
- The synergy created forever advances the field of neuroplastic care



• Prediction is difficult, especially when you are talking about the future -- Yogi Berra

A woman with blonde hair is holding a blue line drawing of a woman's face with wavy hair and a small sailboat in her hair. The drawing is on a white card. The background is a yellow and teal gradient.

Thank You

**For further information
Please contact:**

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jjavitt@nrxpharma.com