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New Antidepressants and the Pharmaceutical Pipeline: Where Are We Going?

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Disclosures

- Grants from NIH, Patient Centered Outcomes Research Institute, Acadia Pharmaceuticals, Allergan plc, Boehringer Ingelheim, INmuneBIO, Intracellular Therapies, Janssen Pharmaceuticals, Neurorx, Inc., Novartis International AG, LivaNova plc, Otsuka Pharmaceuticals
- Consulting to Acadia Pharmaceuticals, Allergan plc, Janssen Pharmaceuticals, Neurorx, Inc., Novartis International AG, Evecxia Therapeutics, Seelos Therapeutics, Sunovion Pharmaceuticals Inc.

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Off-Label Use of Drugs

- IV ketamine for:
  - Treatment-resistant MDD
- Medications in clinical trials
  - Ketamine
  - Arketamine
  - MIJ821
  - D-cycloserine (+ketamine+lurasidone)
    - Bipolar depression
  - L-4-Chlorokynurenine (AV-101)
  - Dextromethorphan + quinidine (AVP-786) / bupropion (AXS-05)
  - Dextromethadone
  - NV-5138
  - TAK-653
  - GluR5 antagonist
  - Basimglurant
  - GluR2/3 antagonists
  - LY341495
  - MGS0039
  - Decoglurant
  - Zuranolone
  - PRAX-114
  - 3β-Methoxypregnenolone
  - JNJ-61393215
  - JNJ-42847922
  - Aticaprant
  - BTRX-335140
  - JNJ-39393406
  - Psilocybin

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Ketamine Timeline

First Synthesis 1956

1st Reports "Non-Medical Use" Early 1970's

1st Human Depression Studies Berman et al. 2000 Zarate et al. 2006

US FDA Approval TRD 2019 MDDSI 2020

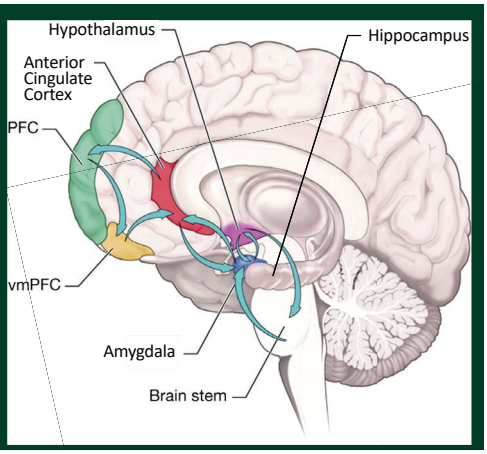
US FDA Approval 1970

First Rat "Antidepressant-like" Action 1975 (Sofia & Harakal *et al.*)

Janssen Intranasal Esketamine (Spravato™) Development Program 2012 - 2020

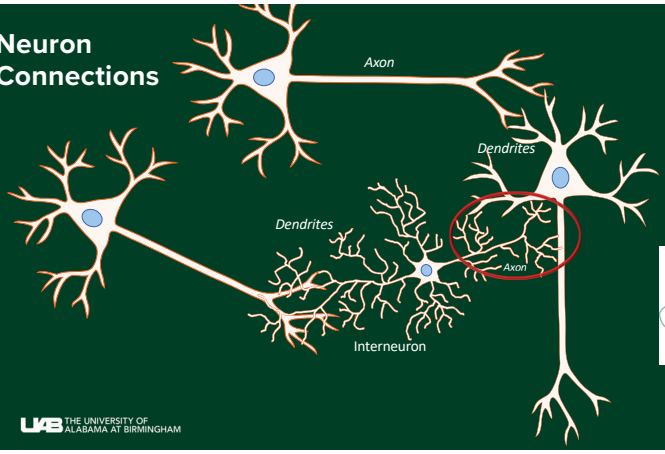
Spravato (esketamine) ©

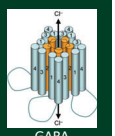
How Does the Brain Regulate Emotion? ("Functional Connectivity")



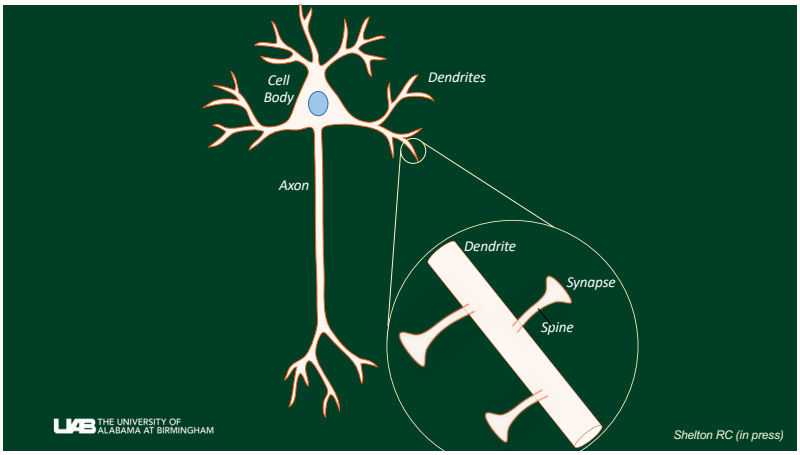
Tost H, Meyer-Lindenberg A. PNAS 2010; 107:17071-17072

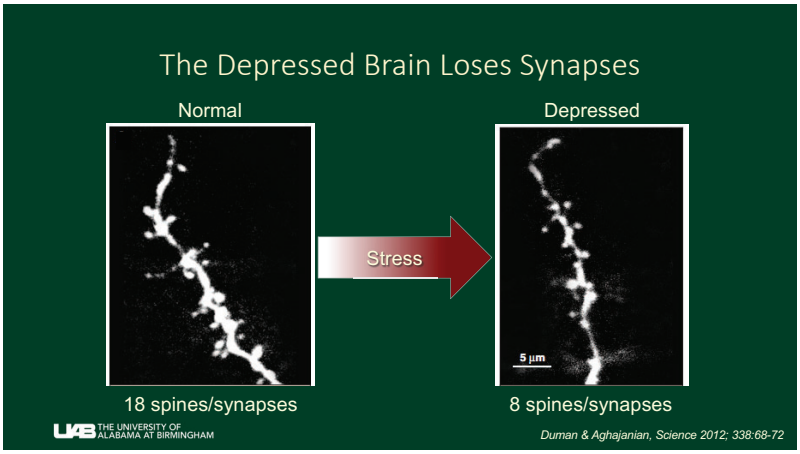
Neuron Connections



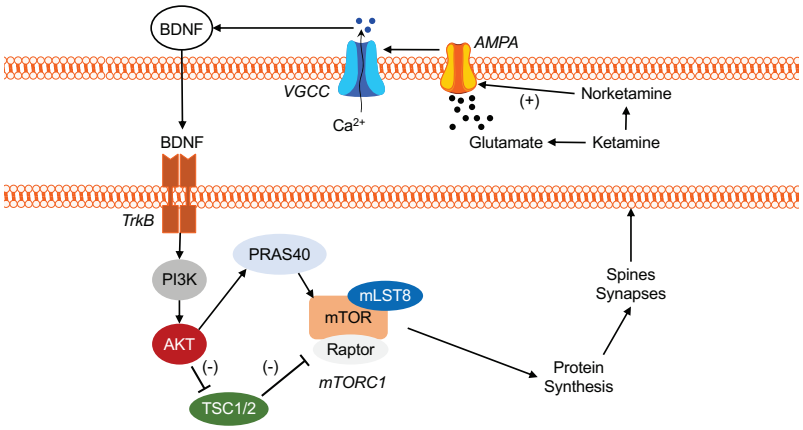


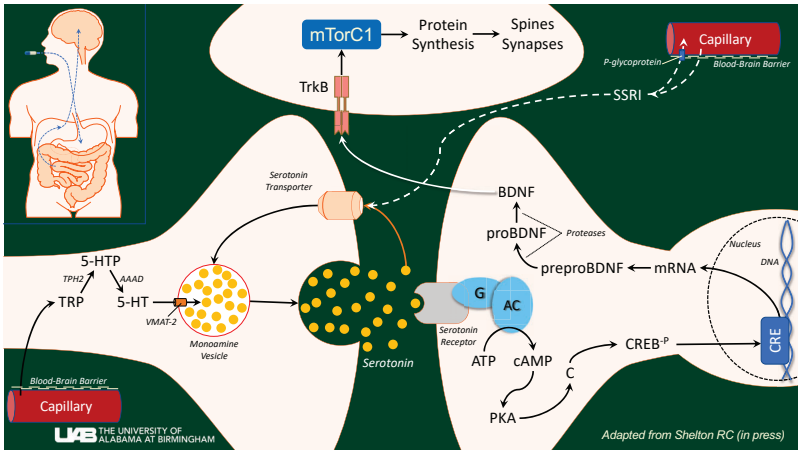
GABA Receptor





GABA-r = Gamma aminobutyric acid receptor
Glutamate
AMPA-r = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
NMDA-r = N-methyl-D-aspartic acid receptor
mTORC1 = Mammalian (molecular, mechanistic) target of rapamycin complex 1
BDNF = Brain derived neurotrophic factor
TrkB = Tyrosine (tropomyosin) receptor kinase B


BDNF
AMPA
VGCC
Ca2+
(+)
Norketamine
Glutamate
Ketamine
BDNF
TrkB
PRAS40
PI3K
mLST8
mTOR
Raptor
AKT
(-)
(-)
mTORC1
TSC1/2
Spines
Synapses
Protein
Synthesis


mTorC1
Protein
Synthesis
Spines
Synapses
Capillary
P-glycoprotein
Blood-Brain Barrier
SSRI
TrkB
Serotonin
Transporter
BDNF
proBDNF
Proteases
preproBDNF
mRNA
Nucleus
DNA
5-HTP
TPH2
AAAD
TRP
5-HT
VMAT-2
Monoamine
Vesicle
Serotonin
G
AC
Serotonin
Receptor
ATP
cAMP
C
CREB-P
CRE
PKA
Blood-Brain Barrier
Capillary
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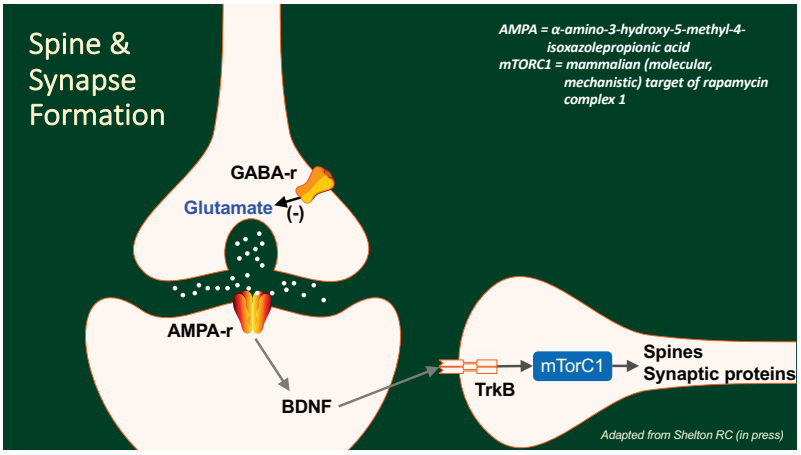
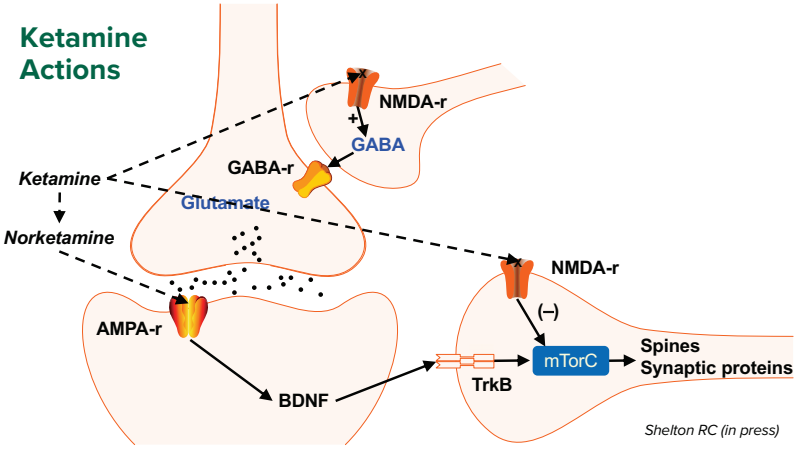
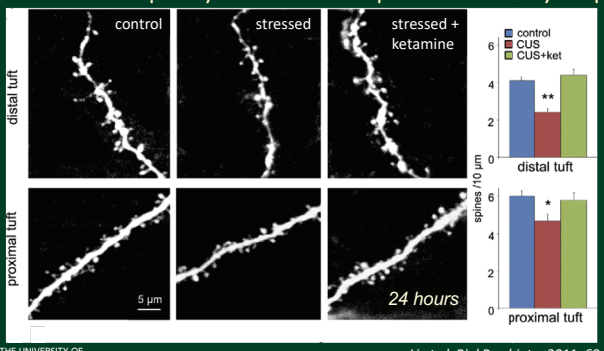
Adapted from Shelton RC (in press)


Spine &
Synapse
Formation
AMPA = α-amino-3-hydroxy-5-methyl-4-
isoxazolepropionic acid
mTORC1 = mammalian (molecular,
mechanistic) target of rapamycin
complex 1
GABA-r
Glutamate
(-)
AMPA-r
BDNF
TrkB
mTorC1
Spines
Synaptic proteins
Adapted from Shelton RC (in press)



Ketamine Rapidly Restores Spines and Synapses



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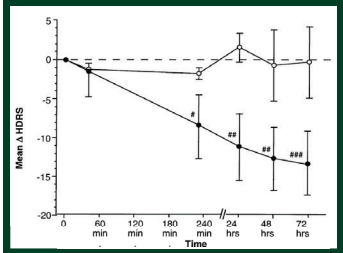
Li et al. Biol Psychiatry 2011; 69: 754-761

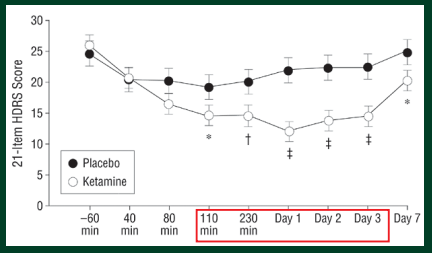
Change in Depression with Ketamine Infusion in Patients with Treatment-Resistant Depression

- N=7, MDD
- Trial design: double blind, crossover
- Ketamine 0.5 mg./kg. vs. placebo



Berman RM, et al. Biol Psychiatry 2000; 47: 351-354

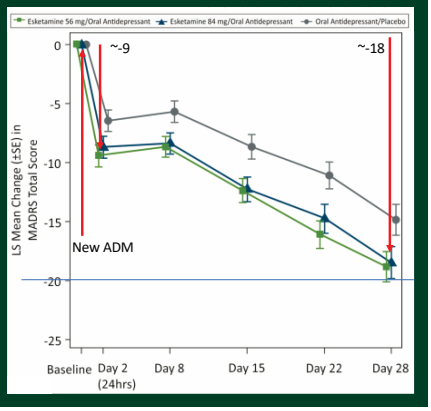
- N=18, MDD (TRD)
- 2-week drug free period
- Trial design: DB, crossover
- Treatments:
  - Ketamine 0.5 mg./kg. IV
  - Placebo (saline IV)



Zarate, C. A. et al. Arch Gen Psychiatry 2006;63:856-864

Esketamine Nasal Spray With a New Antidepressant in Treatment-Resistant Depression (Transform 1)

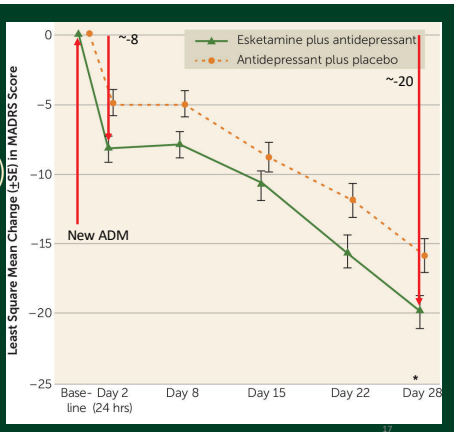
Fixed dose 56 or 84 mg.



Fedgchin M, et al. Int J Neuropsychopharmacology 2019, 22:616-630

Esketamine Nasal Spray With a New Antidepressant in Treatment-Resistant Depression (Transform 2)

Flexible dose 56/84 mg.
- *56 mg.: 33.3%*
- *84 mg.: 66.7%*

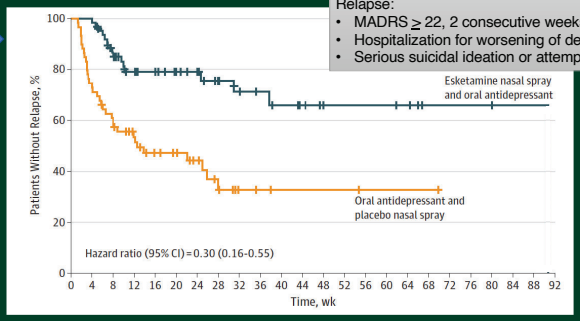


Popova V, et al. Am J Psychiatry 2019; 176:428–438

Maintenance Esketamine Treatment (SUSTAIN I)

Esketamine Responders

Relapse:
- MADRS ≥ 22, 2 consecutive weeks
- Hospitalization for worsening of depression
- Serious suicidal ideation or attempt



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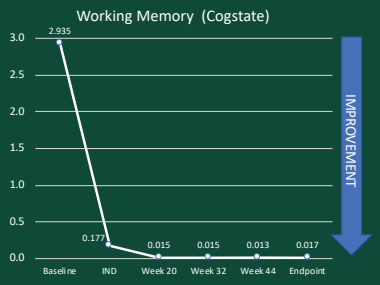
Daly EJ, et al. JAMA Psychiatry 2019;76:893-903.

Concerns with Long-Term Treatment

- Interstitial/ulcerative cystitis
  - 5 (0.6%) cases of cystitis
  - 14 (1.7%) BPIC-SS > 18
  - 7 (0.9%) BPIC-SS > 30
- Olney's lesions/cognitive effects
  - Esketamine treated patients showed improved and stable cognition in all domains
    - Reaction time, verbal learning/ memory, executive function

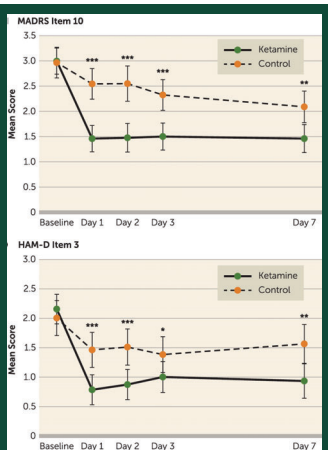


BPIC-SS=Bladder Pain/Interstitial Cystitis Symptom Score
Cogstate=Cogstate Computerized Test Battery
Olney's lesions=NMDA receptor antagonist neurotoxicity

Wajs E. et al. J Clin Psychiatry 2020;81:19m12891

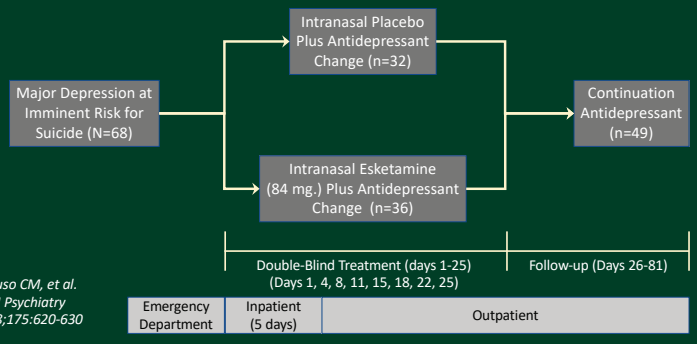
Ketamine/Esketamine Effects on Suicidal Ideation

Effects of Single-Dose Ketamine on Suicidal Ideation – Patient-Level Meta-analysis (10 Studies)



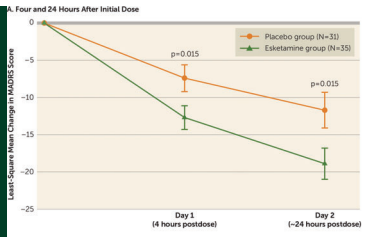
Wilkinson S, et al. Am J Psychiatry 2018; 175:150–158

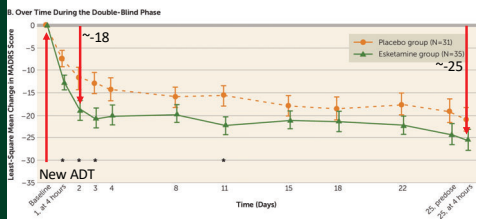
Esketamine for Major Depression with Suicidal Ideation



Canuso CM, et al. Am J Psychiatry 2018;175:620-630

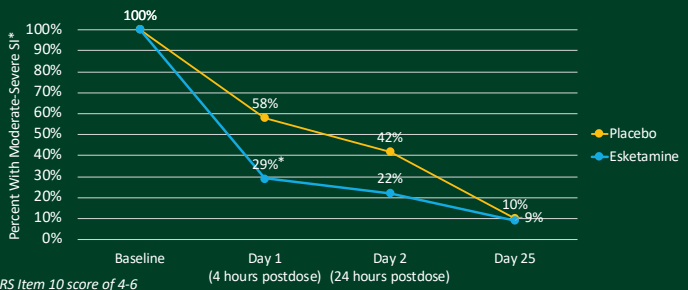
Esketamine for Major Depression with Suicidal Ideation





Canuso CM, et al. Am J Psychiatry 2018;175:620-630

Esketamine Intranasal for Major Depression with Suicidal Ideation



**MADRS Item 10 score of 4-6*

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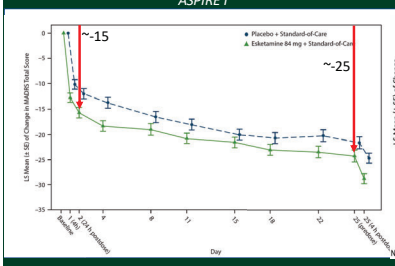
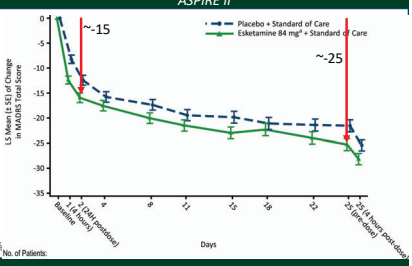
Canuso CM, et al. Am J Psychiatry 2018;175:620-630

Esketamine for Major Depression with Suicidal Ideation

ASPIRE I



ASPIRE II



Fu DJ, et al. 2020; J Clin Psychiatry 81:19m13191

Ionescu DF, et al. Int J Neuropsychopharmacol 2021; 24:27-31

Esketamine: Indication Language

- Treatment-resistant depression (TRD) in adults
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Esketamine Side Effects

	Placebo	Esketamine 56 mg.	Esketamine 84 mg.
Adverse Events	**n=113**	**n=115**	**n=116**
Dissociation	19.5%	46.1%	46.6%
Dizziness	9.7%	33.0%	27.6%
Nausea	10.6%	27.8%	31.9%
Sedation	11.5%	25.2%	25.0%
Vertigo	1.8%	20.9%	20.7%
Paraesthesia	2.7%	16.5%	9.5%
Hypoaesthesia	1.8%	12.2%	14.7%
Blood pressure increased	4.4%	9.6%	12.1%
Vomiting	1.8%	6.1%	12.1%
Tachycardia	0.9%	1.7%	2.6%

Dissociation

- "Floating"
- Feeling "disconnected"
  - From body
  - From body part(s)
    - E.G., arms, legs
  - From environment
- Vision "distorted"
- Altered colors or sounds
- Altered time perception

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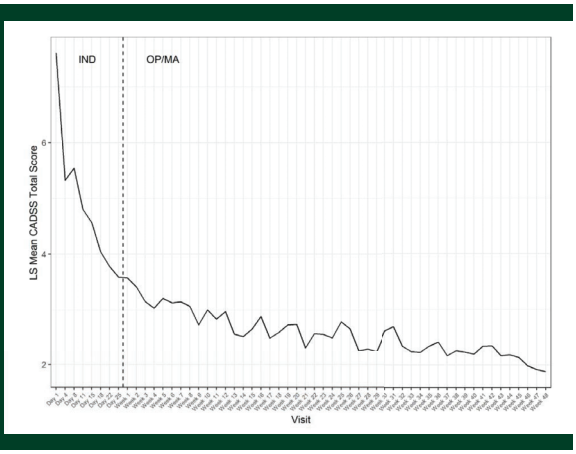
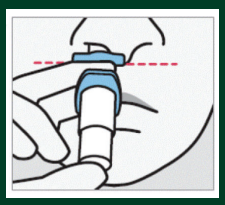
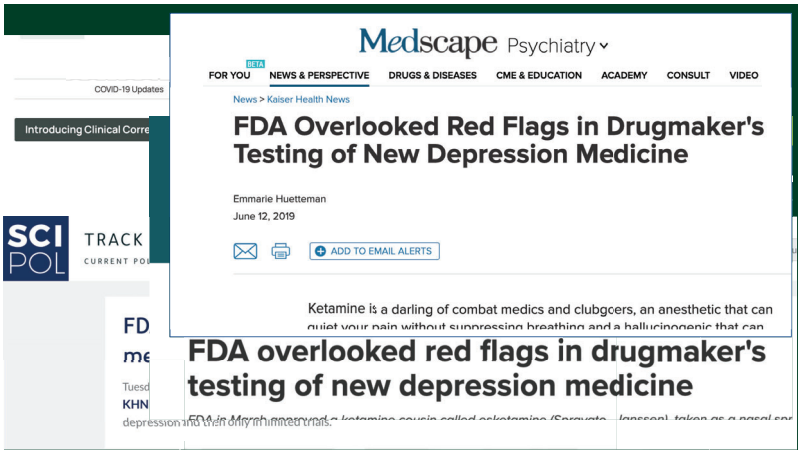
Dissociative Side Effects (Sustain II)



Wajs E. et al. J Clin Psychiatry 2020;81:19m12891



INDUCTION (twice weekly)	MAINTENANCE (once weekly)	(weekly or every 2 weeks)
WEEKS 1-4	WEEKS 5-8	WEEKS 9 AND AFTER*
Day 1 starting dose: **56 mg** Subsequent doses: **56 mg** or **84 mg**	**56 mg** or **84 mg** once weekly	**56 mg** or **84 mg** every 2 weeks or once weekly†



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News > Kaiser Health News

FDA Overlooked Red Flags in Drugmaker's Testing of New Depression Medicine

Emmarie Huetteman
June 12, 2019

ADD TO EMAIL ALERTS

Ketamine is a darling of combat medics and clubgoers, an anesthetic that can quiet your pain without suppressing breathing and a hallucinogenic that can

COVID-19 Updates

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KHN

depression and even only in limited trials.

FDA overlooked red flags in drugmaker's testing of new depression medicine

FDA in March approved a ketamine cousin called esketamine (Spravato, Janssen), taken as a nasal spr

Ketamine/Esketamine: Controversies

Esketamine for treatment-resistant depression: seven concerns about efficacy and FDA approval

With a novel mechanism of action compared with existing marketed antidepressants, esketamine has been of keen interest to mental health clinicians and researchers. On March 5, 2019, the US Food and Drug Administration (FDA) approved intranasal esketamine for treatment-resistant depression.[1] To make a proper risk–benefit analysis before prescribing, mental health clinicians should look beyond the fact of approval and consider the data

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S2215-0366(19)30394-3
See Comment page 975

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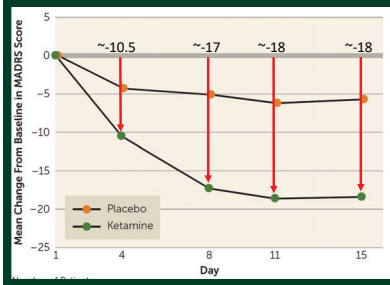
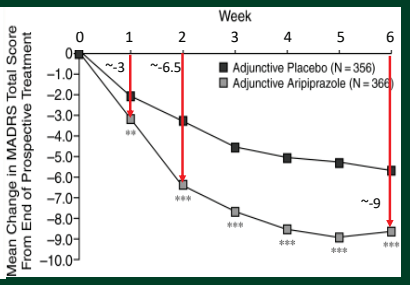
turnere@ohsu.edu

What Were the "Red Flags"?

- Esketamine failed to achieve "rapid response"

What Were the "Red Flags"?
Esketamine Failed to Achieve a "Rapid Response"





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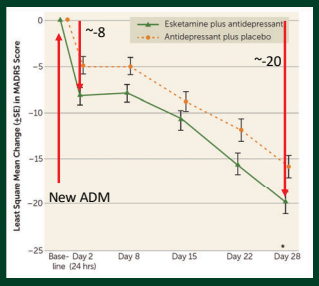
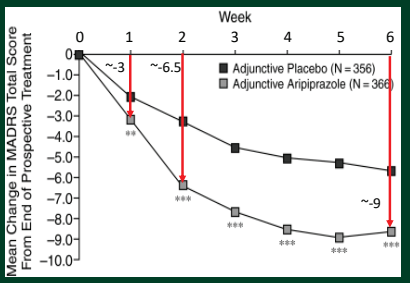
Singh JB et al. Am J Psychiatry 2016; 173:816–826;

Thase ME, et al. Prim Care Comp J Clin Psych. 2008;10:440-447

What Were the "Red Flags"?
Esketamine Failed to Achieve a "Rapid Response"





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Popova V et al. Am J Psychiatry 2019; 176:428–438

Thase ME, et al. Prim Care Comp J Clin Psych. 2008;10:440-447

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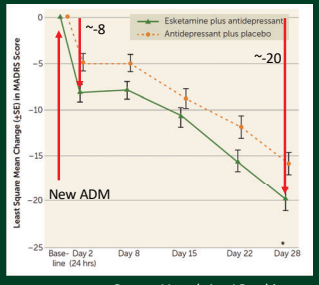
Esketamine Failed to Achieve a "Rapid Response"



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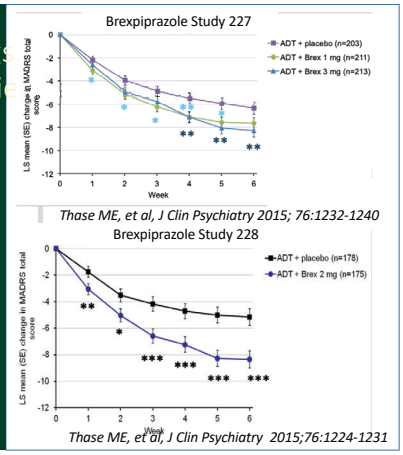
Popova V et al. Am J Psychiatry 2019; 176:428–438



Thase ME, et al, J Clin Psychiatry 2015; 76:1232-1240

Thase ME, et al, J Clin Psychiatry 2015;76:1224-1231

What Were the ”Red Flags”?

- Esketamine failed to achieve “rapid response”
- Treatment resistant depression definition: any two antidepressants
  - Versus antidepressants of two different classes
- Trials included in the approval by the FDA

Esketamine Clinical Trial Outcomes

- Synapse 1 – positive (all doses)
- Transform 1 – negative (p=.088)
  - Note: 56 mg. dose was positive
- Transform 2 – positive
- Sustain 1 – positive
  - Randomized withdrawal study
- Transform 3 (geriatric) – negative
- MDDSI PERSEVERE – positive (4 hours, days 1, 2)
- MDDSI Aspire I – positive
- MDDSI Aspire II – negative

What Were the ”Red Flags”?

- Esketamine failed to achieve “rapid response”
- Treatment resistant depression definition: any two antidepressants
  - Versus antidepressants of two different classes
  - More substantive: No more than 5 adequate antidepressant trials
- Trials included in the approval by the FDA
- No safety trials beyond 60 weeks
- 3 patient suicides in trials – all active (none placebo)
- Possible withdrawal reactions
- One of the..non-significant trials involved older patients…raising the question of esketamine’s efficacy within this important demographic.
- The mean drug-placebo difference in the single positive short-term trial was [only] 4 points on the MADRS

Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

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Objective: In addition to *N*-methyl-D-aspartate receptor antagonism, ketamine produces opioid system activation. The objective of this study was to determine whether opioid receptor antagonism prior to administration of intravenous ketamine attenuates its acute antidepressant or dissociative effects.

Method: In a proposed double-blind crossover study of 30 adults with treatment-resistant depression, the authors performed a planned interim analysis after studying 14 participants, 12 of whom completed both conditions in randomized order: placebo or 50 mg of naltrexone preceding intravenous infusion of 0.5 mg/kg of ketamine. Response was defined as a reduction ≥50% in score on the 17-item Hamilton Depression Rating Scale (HAM-D) score on postinfusion day 1.

Results: In the interim analysis, seven of 12 adults with treatment-resistant depression met the response criterion during the ketamine plus placebo condition. Reductions in 6-item and 17-item HAM-D scores among participants in the ketamine plus naltrexone condition were significantly lower than those of participants in the ketamine plus placebo condition on postinfusion day 1 and 3. Secondary analysis of all participants who completed the placebo and naltrexone conditions, regardless of the robustness of response to ketamine, showed similar results. There were no differences in ketamine-induced dissociation between conditions. Because naltrexone dramatically blocked the antidepressant but not the dissociative effects of ketamine, the trial was halted at the interim analysis.

Conclusions: The findings suggest that ketamine's acute antidepressant effect requires opioid system activation. The dissociative effects of ketamine are not mediated by the opioid system, and they do not appear sufficient without the opioid effect to produce the acute antidepressant effects of ketamine in adults with treatment-resistant depression.

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Ketamine Binds to Opioid Receptors

Site	Binding (nM)	
NMDA	0.25	
MOR_1	42	*48.4x*
MOR_2	12.1	
DOR	26.8	
KOR	28	

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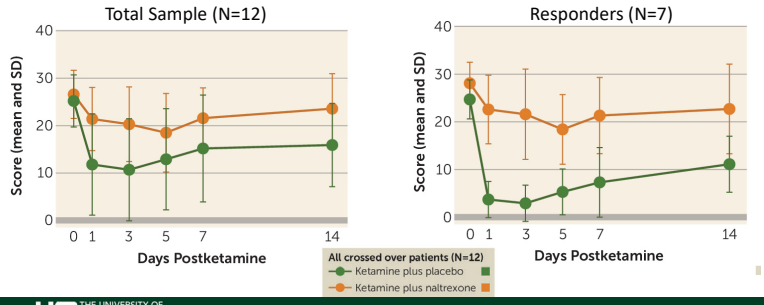
Attenuation of Antidepressant Effects of Ketamine by Naltrexone



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Attenuation of Antidepressant Effects of Ketamine by Naltrexone: What Does It Mean?

- Ketamine T½e ≅ 3 hours
  - Norketamine ≅ **12** hours

No sustained (between-dose) antidepressant benefits from mu agonists

- Ketamine is a mu modulator, not an agonist
- Norketamine is a mu antagonist
- No evidence of drug-seeking or craving
  - Clinical trials or practice (yet)
- No drug withdrawal effects

➢So, what is the mechanism? Mu – NMDA receptor modulation

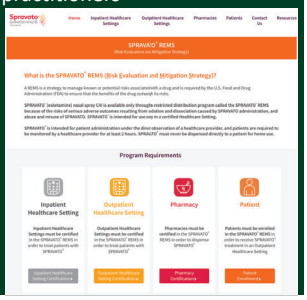
Esketamine Treatment: Substantive Concerns

- No more than 5 adequate antidepressant trials
- The number of people included in the (reported) long-term studies is relatively small
- Effects in older patients
- Unblinding of research participants
- The practical application of esketamine treatment in practice is problematic

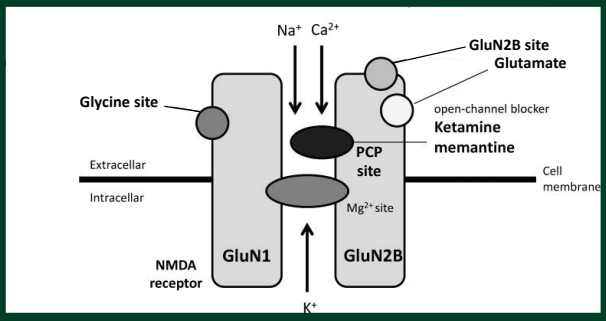
Practical Issues

- FDA mandated REMS program
  - Somewhat cumbersome for office-based practitioners
  - Requires nurse/CMA monitoring
- Prior authorization hurdles
- Drug handling and accountability
- Reimbursement issues
- Bundled payment for MDDSI
- Post-discharge treatment for MDDSI
- First year after approval <4000 treated

~6,000,000 TRD patients

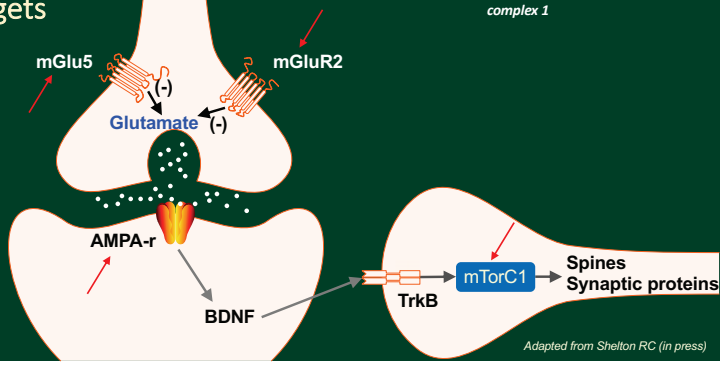


NMDA Receptor Binding Sites



Glutamate Targets

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
mTORC1 = mammalian (molecular, mechanistic) target of rapamycin complex 1

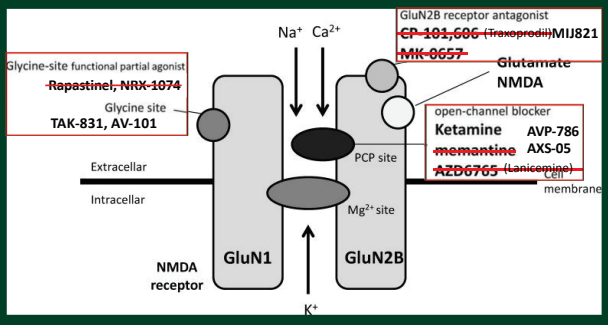


Adapted from Shelton RC (in press)

Newer GABA/Glutamate Acting Compounds

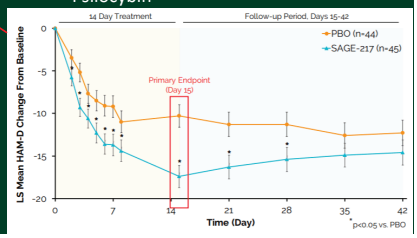
- Ketamine intranasal/IV
  - Arketamine (PCN-101)
- Selective NMDA NR2B subunit antagonist
  - MIJ821
- NMDA – glycine site agents
  - D-cycloserine (+ketamine+lurasidone)
    - Bipolar depression
  - L-4-Chlorokynurenine (AV-101)
- NMDA antagonist
  - Dextromethorphan + quinidine (AVP-786) / bupropion (AXS-05)
  - Dextromethadone (REL-1017)
- mTORC1 activator (sestrin)
  - NV-5138
- AMPA positive modulator
  - TAK-653
- D-amino acid oxidase inhibitor (D-serine potentiator)
  - TAK-831
- mGluR2/3 antagonists/NAM
  - LY341495
  - MGS0039
  - Decoglurant
- mGluR5 negative modulator
  - Basimglurant

NMDA Receptor Binding Sites



Other Pipeline Compounds

- GABA receptor positive modulator
  - Zuranolone (SAGE-217)
  - PRAX-114
- Microtubule associated protein 2 (MAP2) stimulant
  - 3β-Methoxypregnenolone
- Orexin 1/2 antagonists
  - JNJ-61393215
  - JNJ-42847922
- Kappa opioid antagonists
  - Aticaprant
  - BTRX-335140
- Alpha-7 nicotinic acetylcholine receptor positive modulator
  - JNJ-39393406
- Psychedelic
  - Psilocybin



Other Mechanistic Targets

- Short transient receptor potential channel 4/5 (TrpC4/5)
- Prostaglandin E synthase-1 (mPGES1)
- Estrogen receptor beta (ERβ)
- P2X purinoceptor 7
- Vasopressin 1B

Ketamine for Depression: Conclusions

- Ketamine is effective for TRD and MDDSI
- Intranasal esketamine has been approved for TRD and MDDSI
  - Although the trials data were mixed and somewhat controversial
- Our experience with IV ketamine and IN esketamine have been positive
- Clinical use is challenging
  - The majority of patients require long-term treatment
- Reimbursement challenges for esketamine for TRD
- No reimbursement path for MDDSI (yet)
- There is a large antidepressant medication pipeline