Rapid Acting Treatments for Depression: Ketamine and Beyond

North Carolina Psychiatric Association
2016 Annual Meeting

Lawrence Park, M.D.

Experimental Therapeutics and Pathophysiology Branch
Division of Intramural Research Program
National Institute of Mental Health

NIH Intramural Research Program
Our Research Changes Lives

one program
many people
infinite possibilities

Presenter Disclosure

Lawrence Park

The following personal financial relationships with commercial interests relevant to this presentation exist:

No relationships to disclose.

Outline

- NIMH: Experimental Therapeutics & Pathophysiology Branch
- Psychopharmacological Development
- Glutamate System and Mood Disorders
- Ketamine for Depression
- Other Glutamatergic Modulators for Depression
- Neurobiology of Suicide

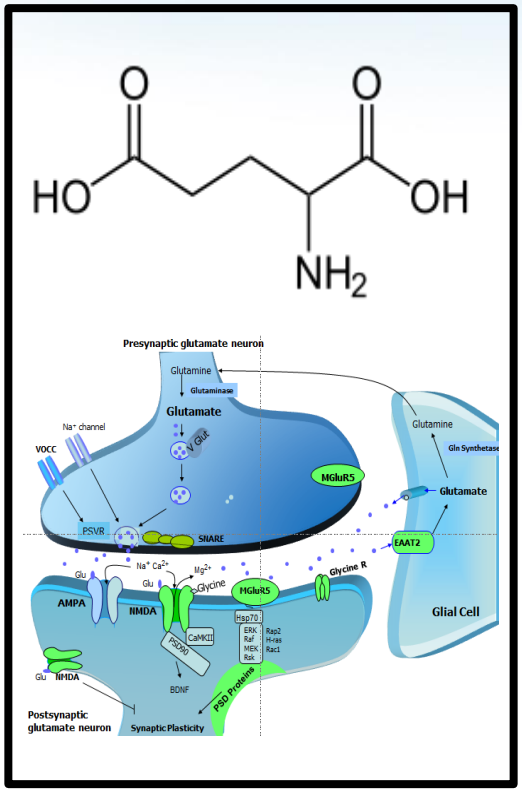
National Institute of Mental Health

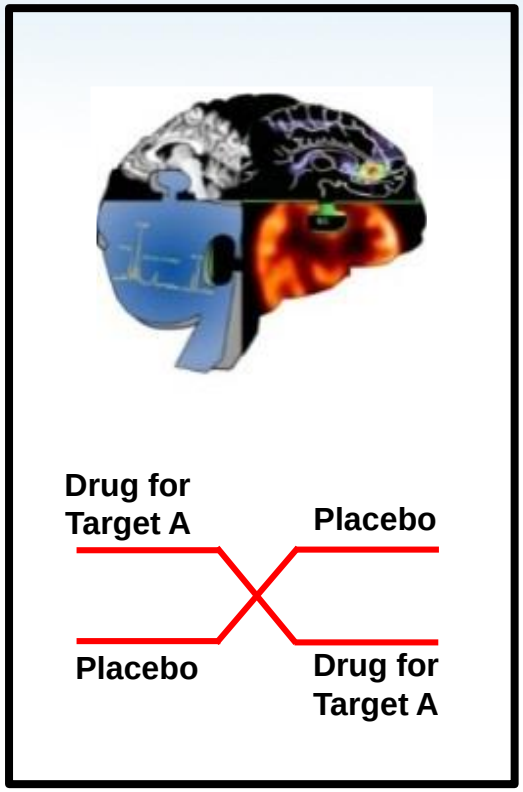
Intramural Research Program

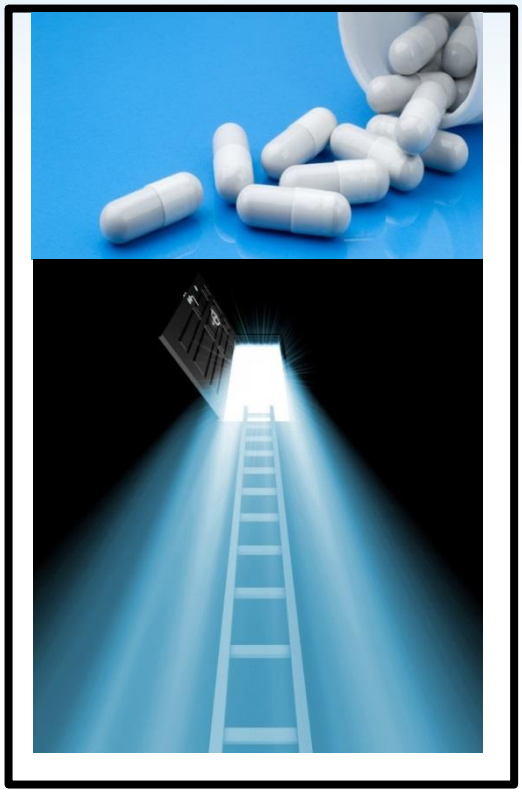
Mark O. Hatfield Clinical Research Center

- **NIH Clinical Center**
  - Dedicated research facility
  - CORE facilities
- **Dedicated Inpatient Unit**
  - Multidisciplinary team model
  - Allows for study of unmedicated subjects
- **Treatment Resistant Depression Population**
  - 24 year duration of illness
  - 50% disabled
  - 50% attempted suicide
  - 7+ antidepressants ineffective
  - 60% ECT ineffective

Experimental Therapeutics and Pathophysiology Branch

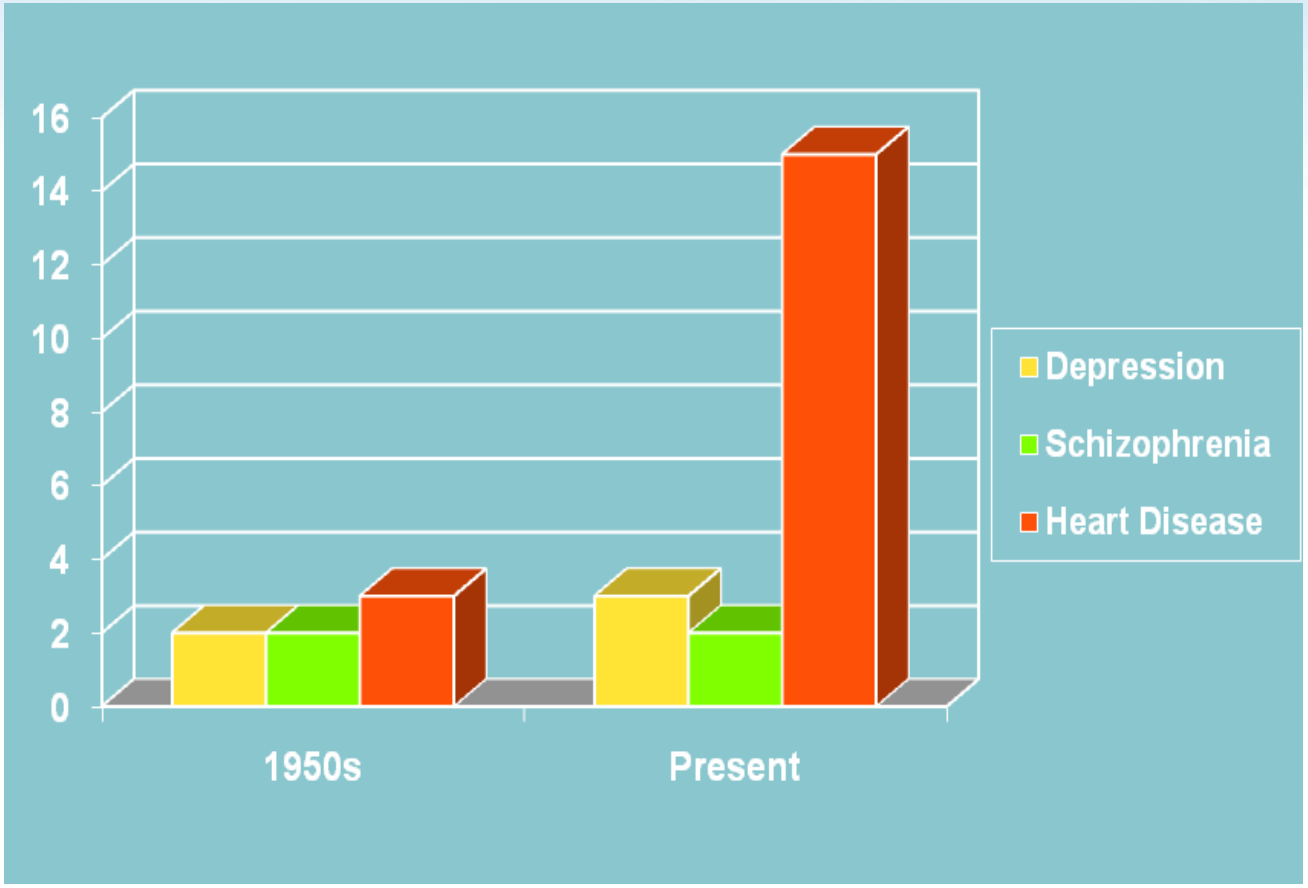






Target → **Proof of Concept (POC) Study** → **Improved Treatment**

Drug Development in the past 60 years



Need to identify new molecular targets

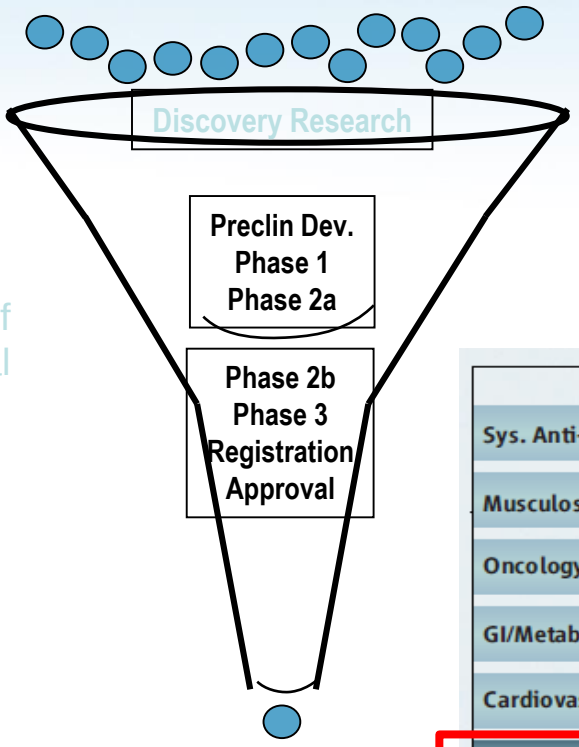
Insel and Skolnick 2006

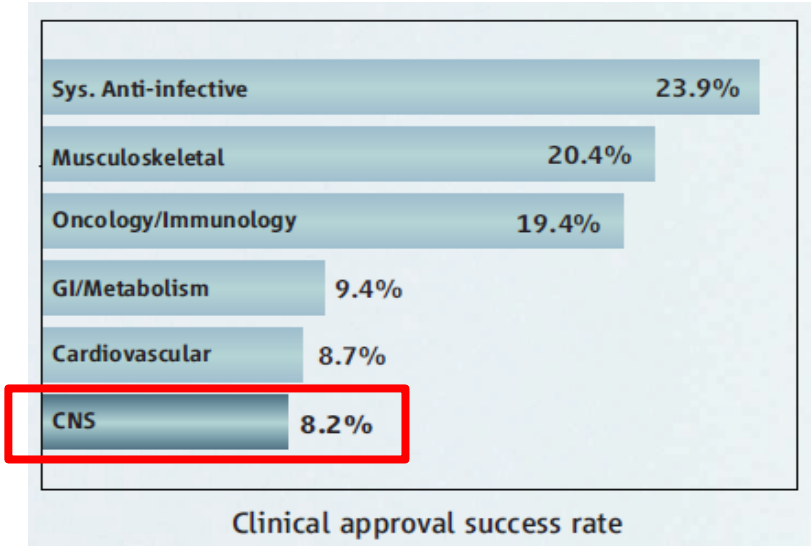
Neuroscience: Challenges in Medication Development

Time

- Higher order brain function difficult to model preclinically
- Limited segregation of patients into biological strata
- Attrition in late stages increases costs
- Sheer complexity of our brain disorders

Up to 15 years/$4-11 billion



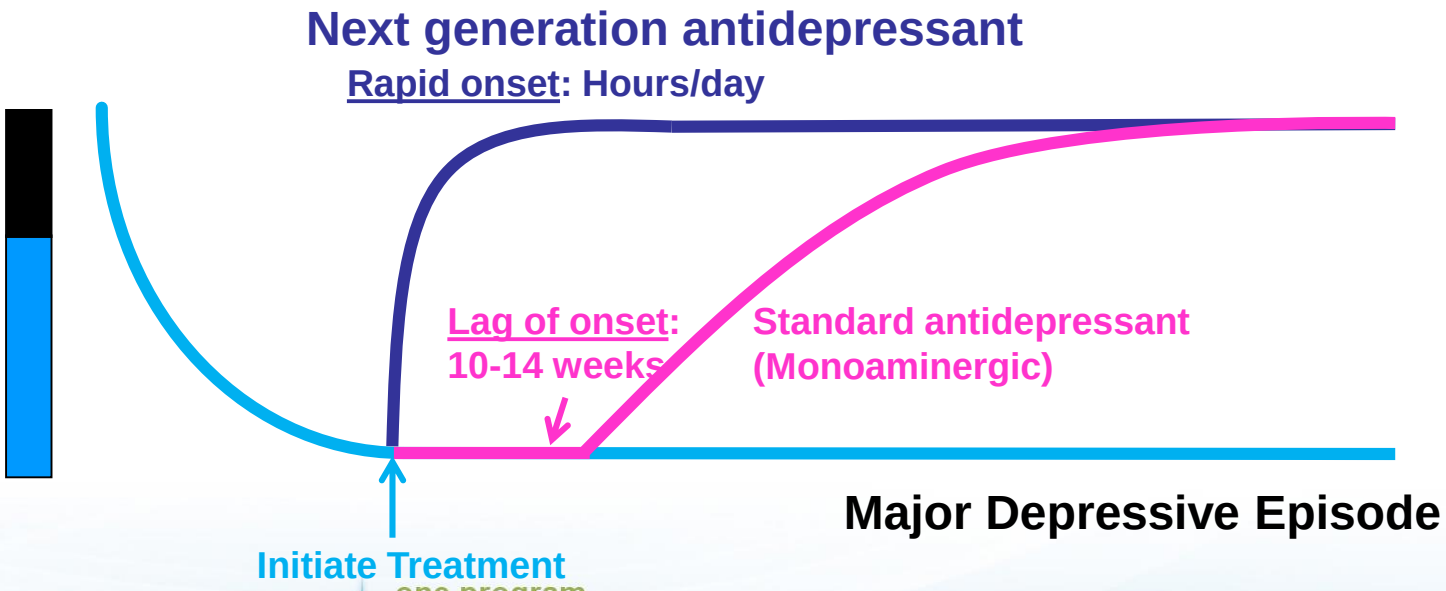


Miller Science 2010

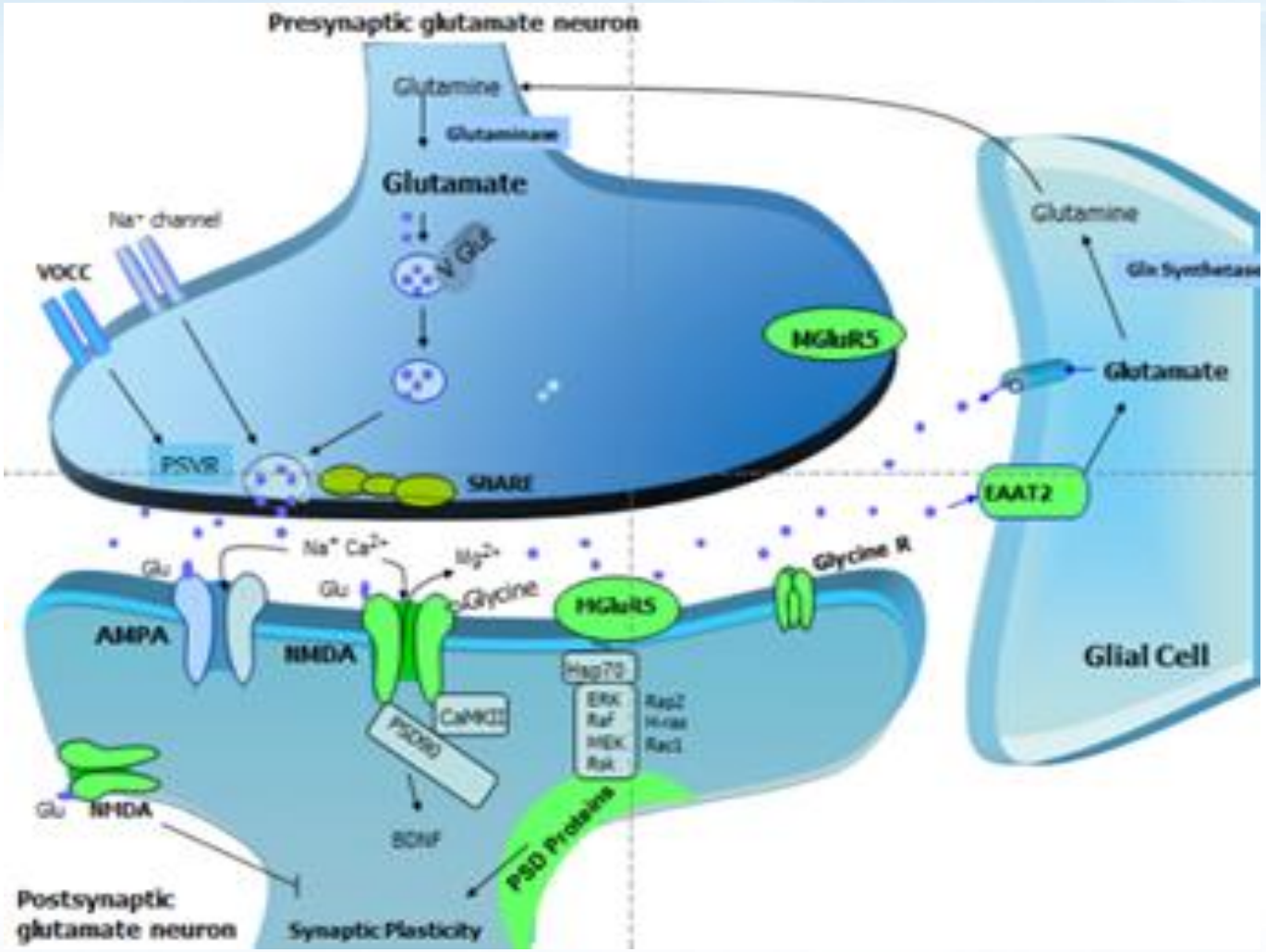
Depression: The Need for Improved Treatments

Problems with Current Antidepressants:

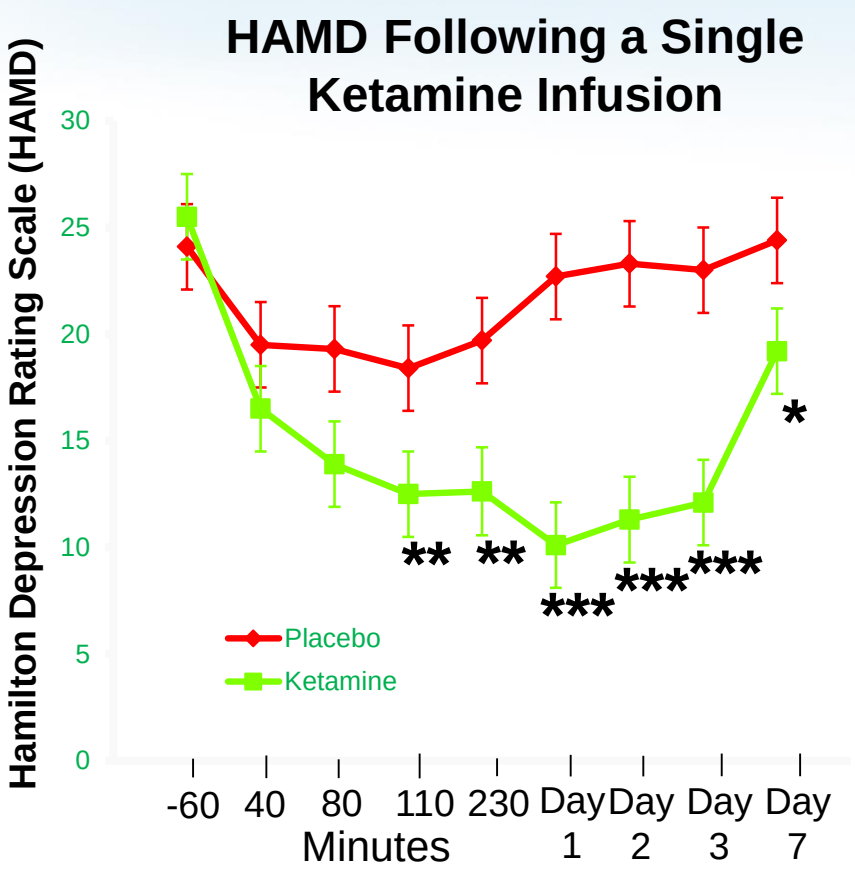
- Low remission rates
- Lag of onset of antidepressant effects
- Questionable efficacy in bipolar depression

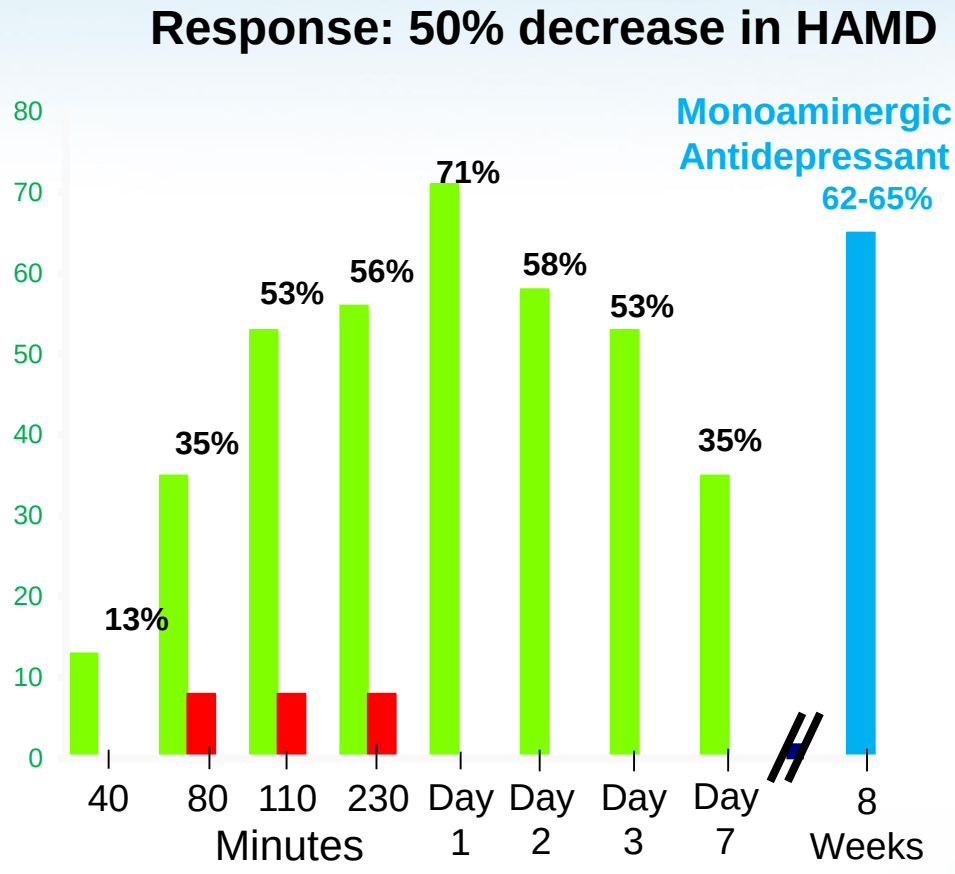


Glutamate Neuron



Rapid Antidepressant Effect of Ketamine in Unmedicated Treatment Resistant MDD (n=18)





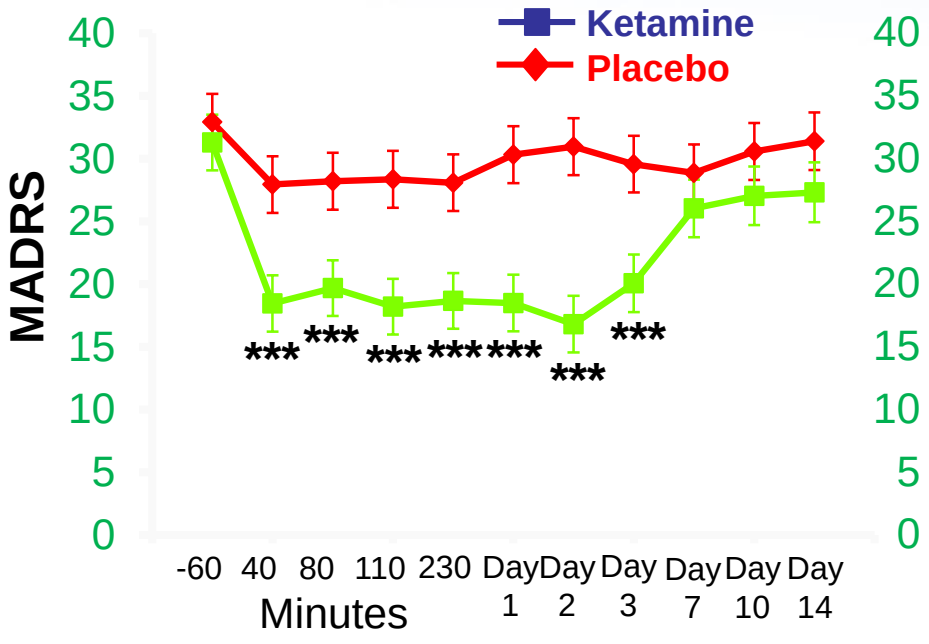
Time

***p<0.001, **p<0.01, *p<0.05

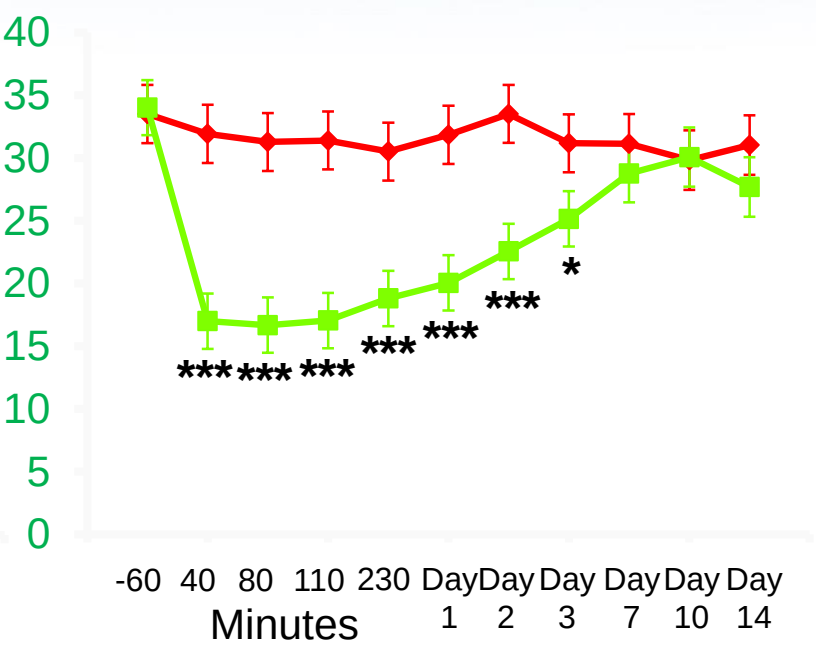
Zarate et al. Arch Gen Psychiatry 2006

Rapid Antidepressant Effect of Ketamine in Treatment Resistant Bipolar (BP) Depression

First BP Study of Ketamine (n=18)



Replication BP study (n=15)



Time

Diazgranados et al. Arch Gen Psych 2010

Zarate et al. Biol Psych 2012

***p<0.001, **p<0.01, *p<0.05

Development of Ketamine Research/Treatment

1 Ketamine in Clinical Practice Settings: research/off-label use

- U.S. government patent (depression)
  - Licensed by J&J (Esketamine) FDA 'breakthrough therapy designation'
- Off-label use of ketamine worldwide
  - >12 companies developing glutamatergic modulators for depression
  - >40 NIMH grants

2 Develop ketamine-like drugs (without dissociative side effects) → More NMDA subunit selective drugs

3 Understand ketamine's mechanism of action from synapses through a range of systems

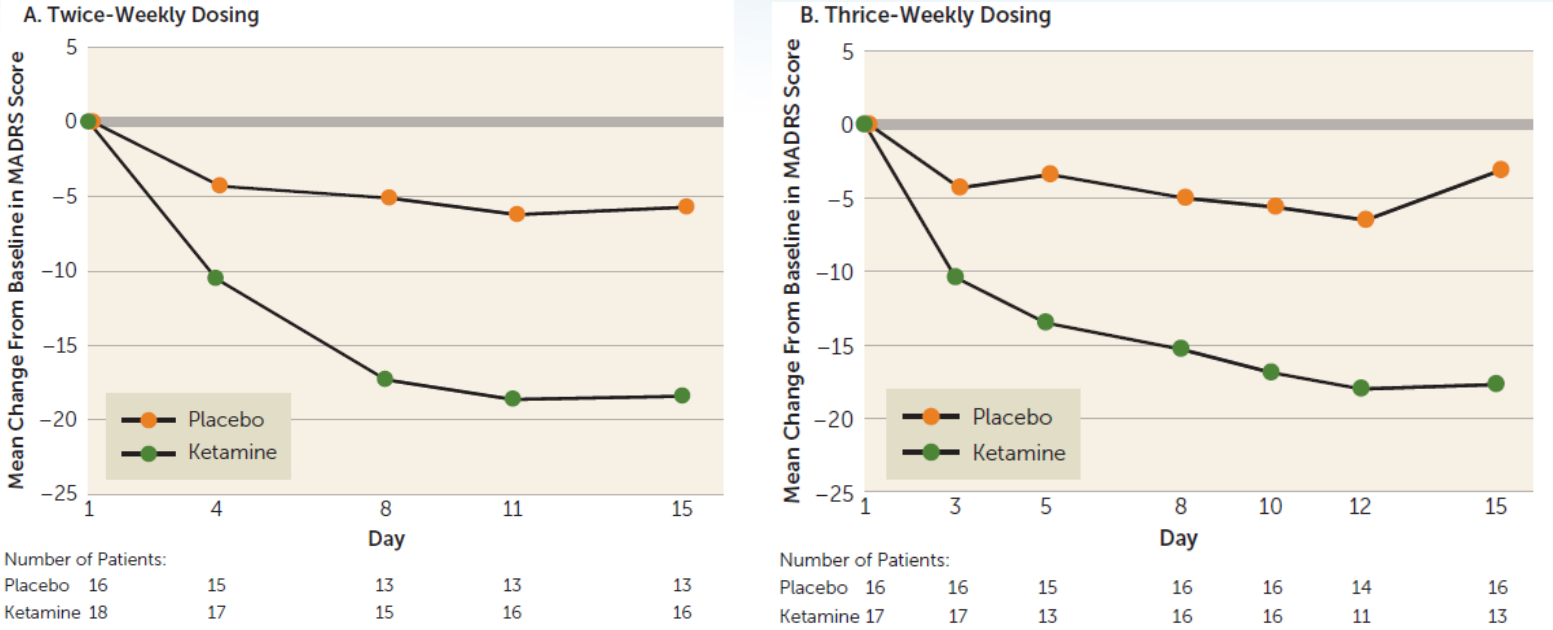
4 Is there more to the story with the "ketamine paradigm": ketamine's metabolites →

Intramural & Extramural Collaboration

- University of Maryland
- NCATS
- NIA
- UNC
- NIMH

Zanos et al. Nature 2016

Repeat Dose IV Ketamine



Singh et al. Am J Psych 2016

Candidate Glutamatergic Modulators for Depression

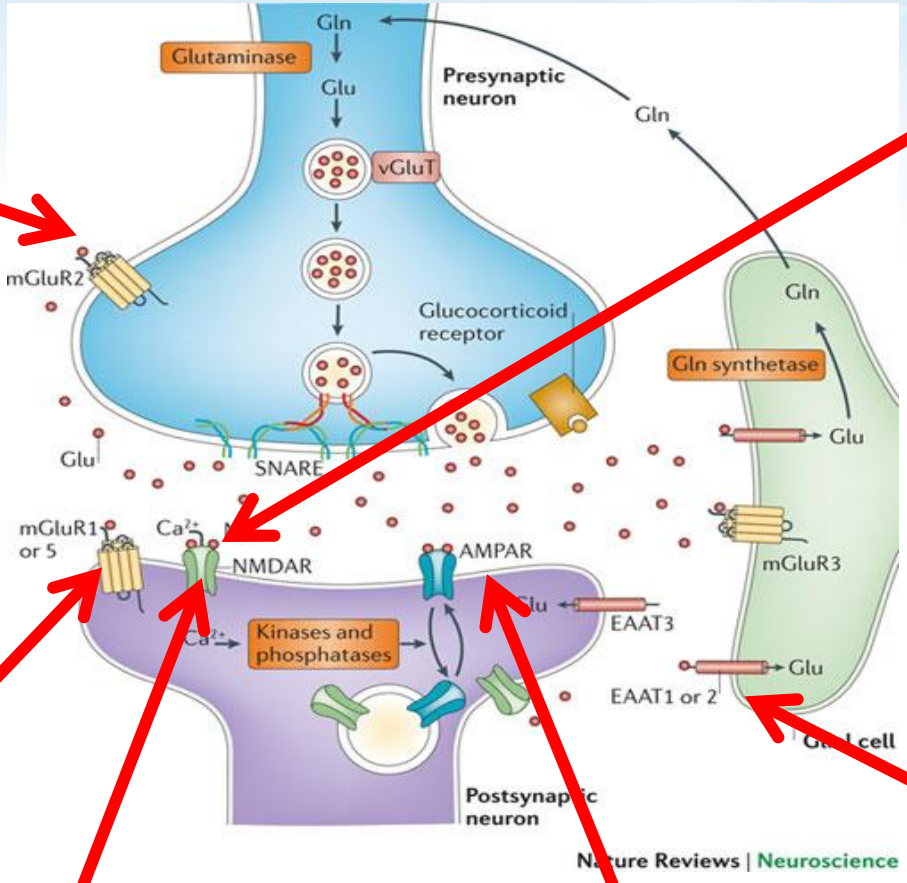
Na Channel
- Riluzole

mGluR2 PAM
- JNJ-40411813
- ADX41149

mGluR2/3 Antagonists
- MGS0039
- LY341495

mGluR2/3 NAMs
- R04491533
- R04499819

mGluR5 NAMs
- AZD2066
- STX-107
- R04917523
- RG7090 (Basimglurant)



GlyT-1 Inhibitors
- Sarcosine
- Bitopertin

Glycine Agonists
- D-serine

Glycine Partial Agonists
- Rapastinel (Glyx-13)
- NRX-1074

Glycine Antagonists
- D-cycloserine
- 4-Cl-KYN (AV-101)

EAAT2 Enhancers
- Ceftriaxone
- Diazoxide

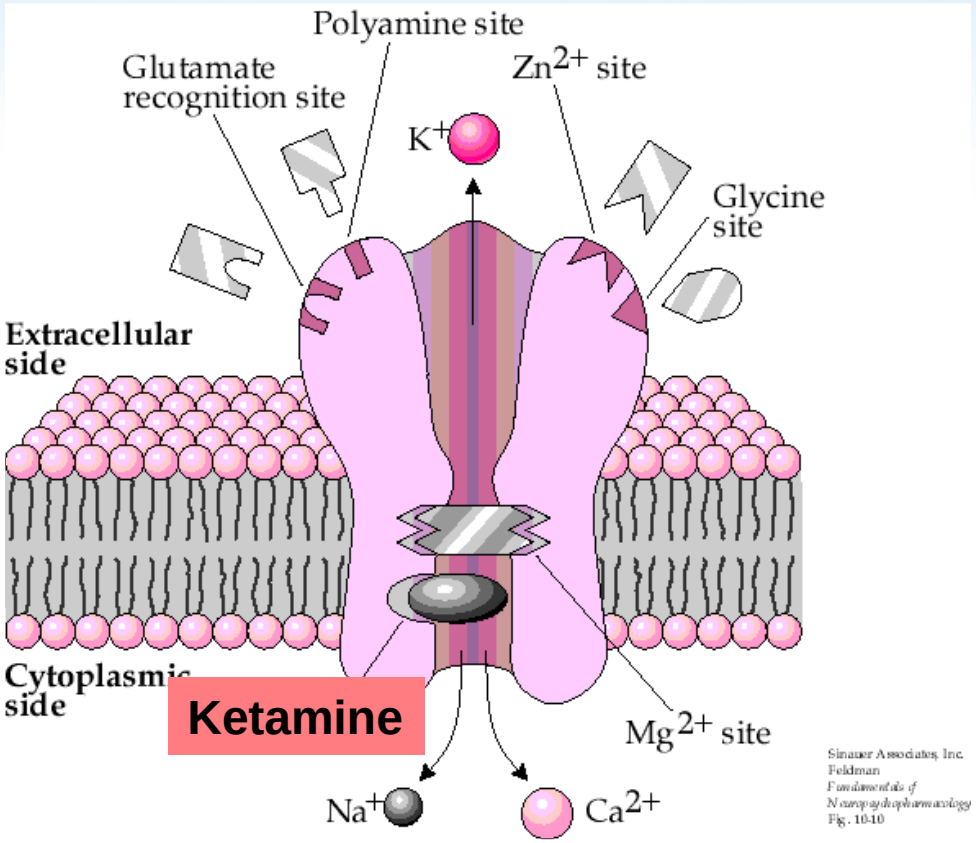
NMDA Complex Modulators

AMPA Potentiator
- ORG-26576

NMDA Complex Modulators

Broad NMDA antagonists

- Ketamine
- Memantine
- AZD6765
- DM/Q



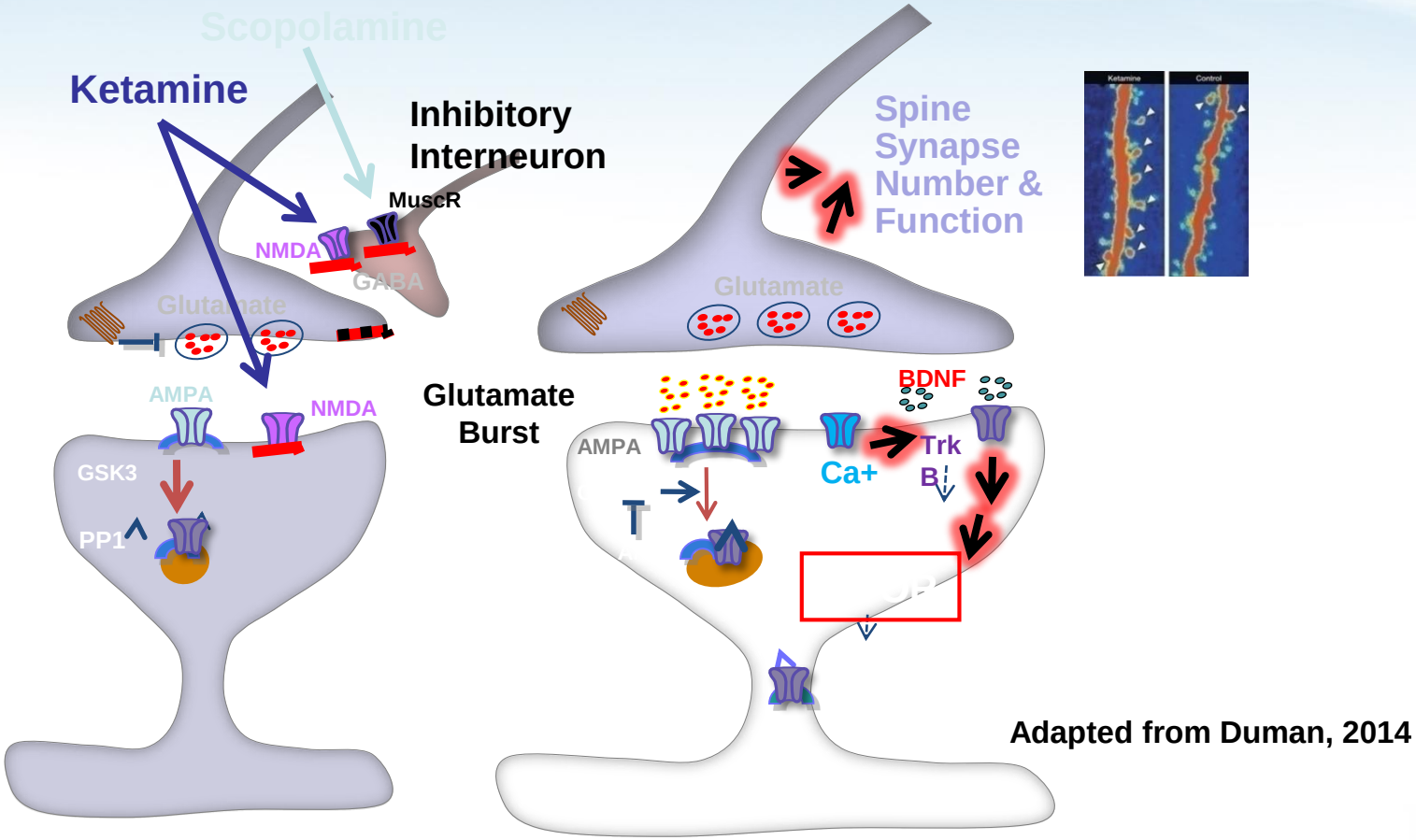
NR2B antagonists

- Ro 25-6981
- Ifenprodil
- Traxoprodil
- Evotec-101
- MK-0657*

Glycine site

- D-Serine
- D-cycloserine
- GLYX-13
- 4-Cl-KYN*

Is Glutamate Burst Critical to a Rapid Antidepressant Effect?

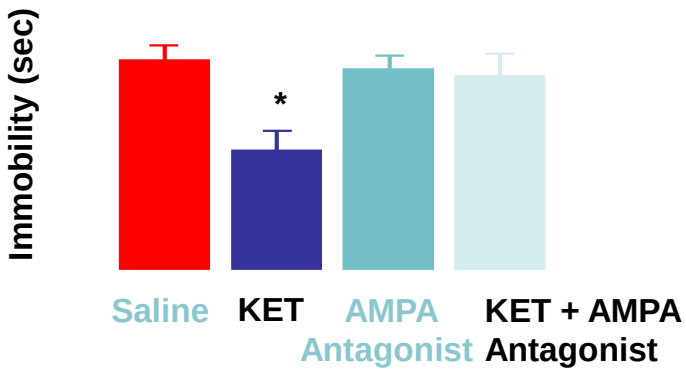


Adapted from Duman, 2014

Genes — Gene expression — Metabolome — Cellular — Neurochemical — Circuits — Rapid reversal of complex behavioral phenotype — RDoC

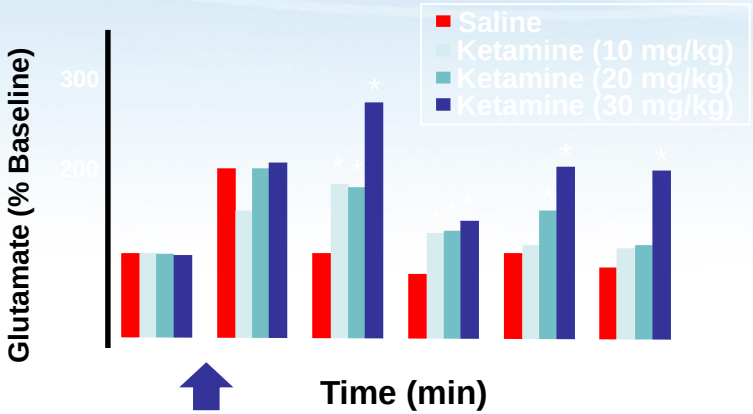
Ketamine Mechanism of Action: Pre-clinical Evidence

Ketamine produces a rapid surge in extracellular glutamate



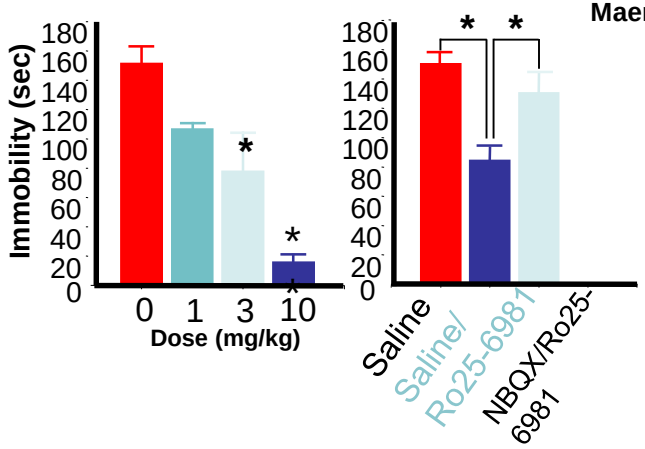
Maeng et al. Biol Psych 2008

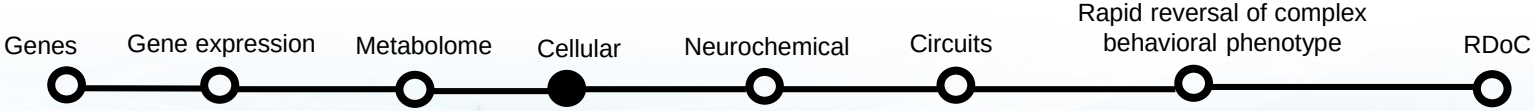
AMPA antagonism blocks the antidepressant effects of ketamine in animals in the forced swim test



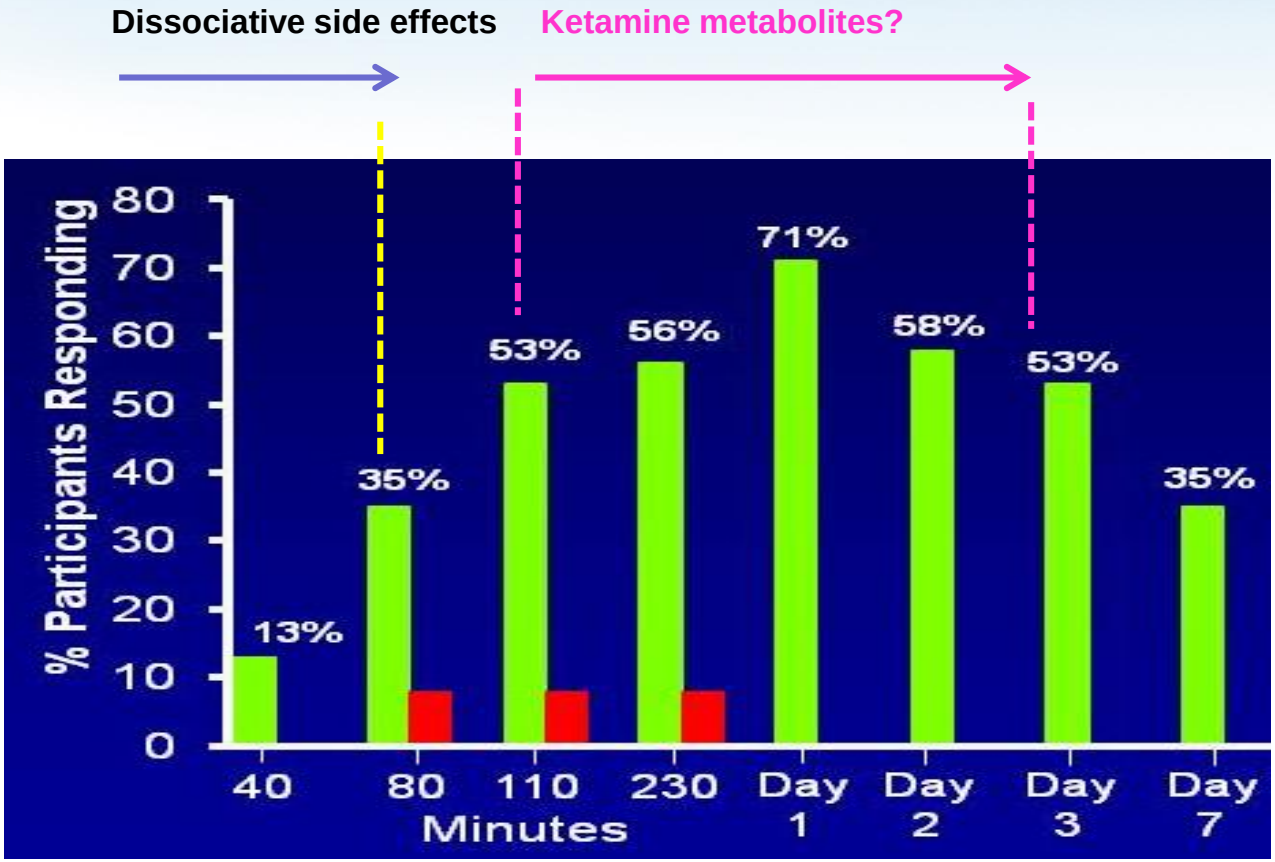
Moghaddam J Neurosci 1997

Maeng Biol Psych 2008



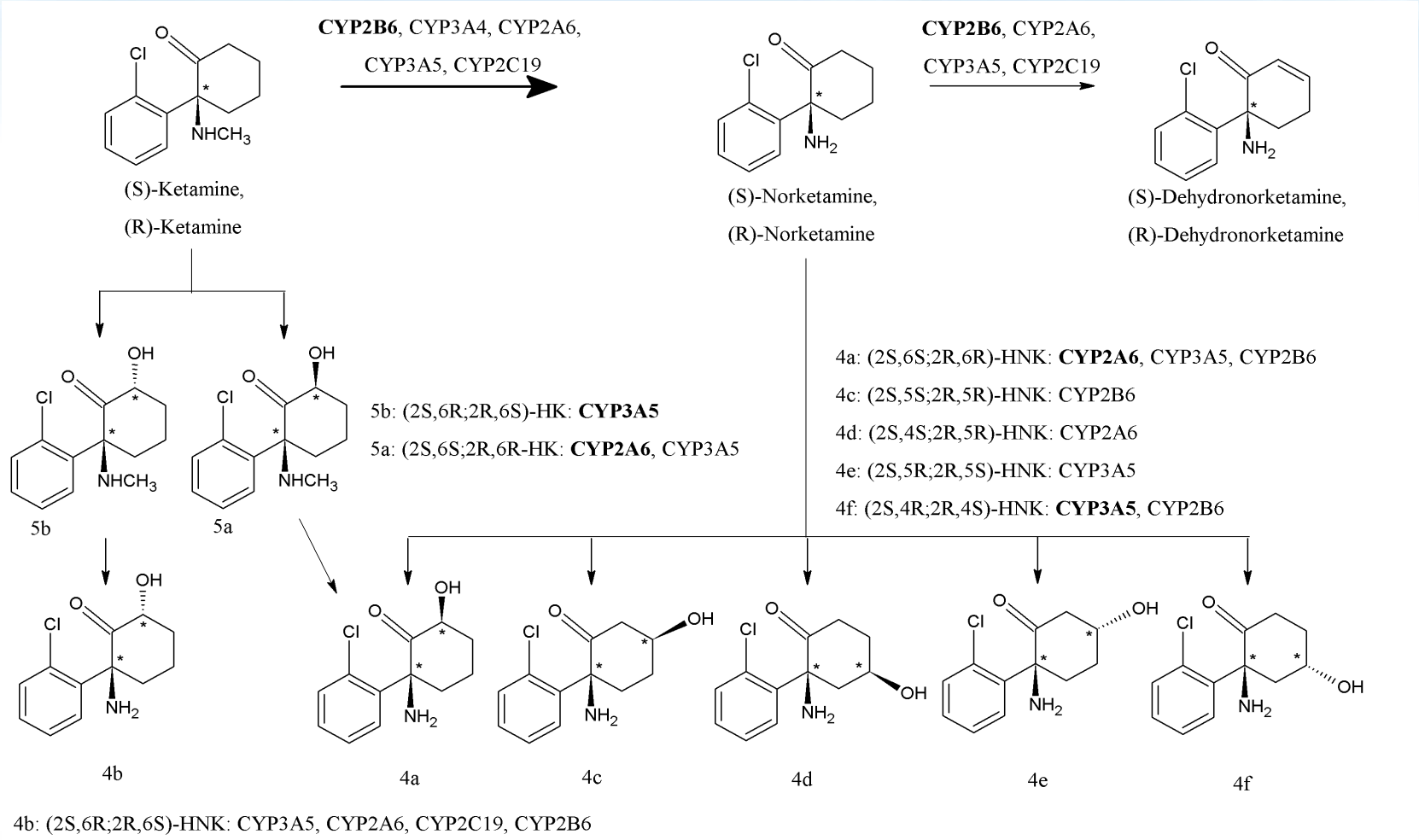


Temporal Development of Main Effects and Side Effects of Ketamine



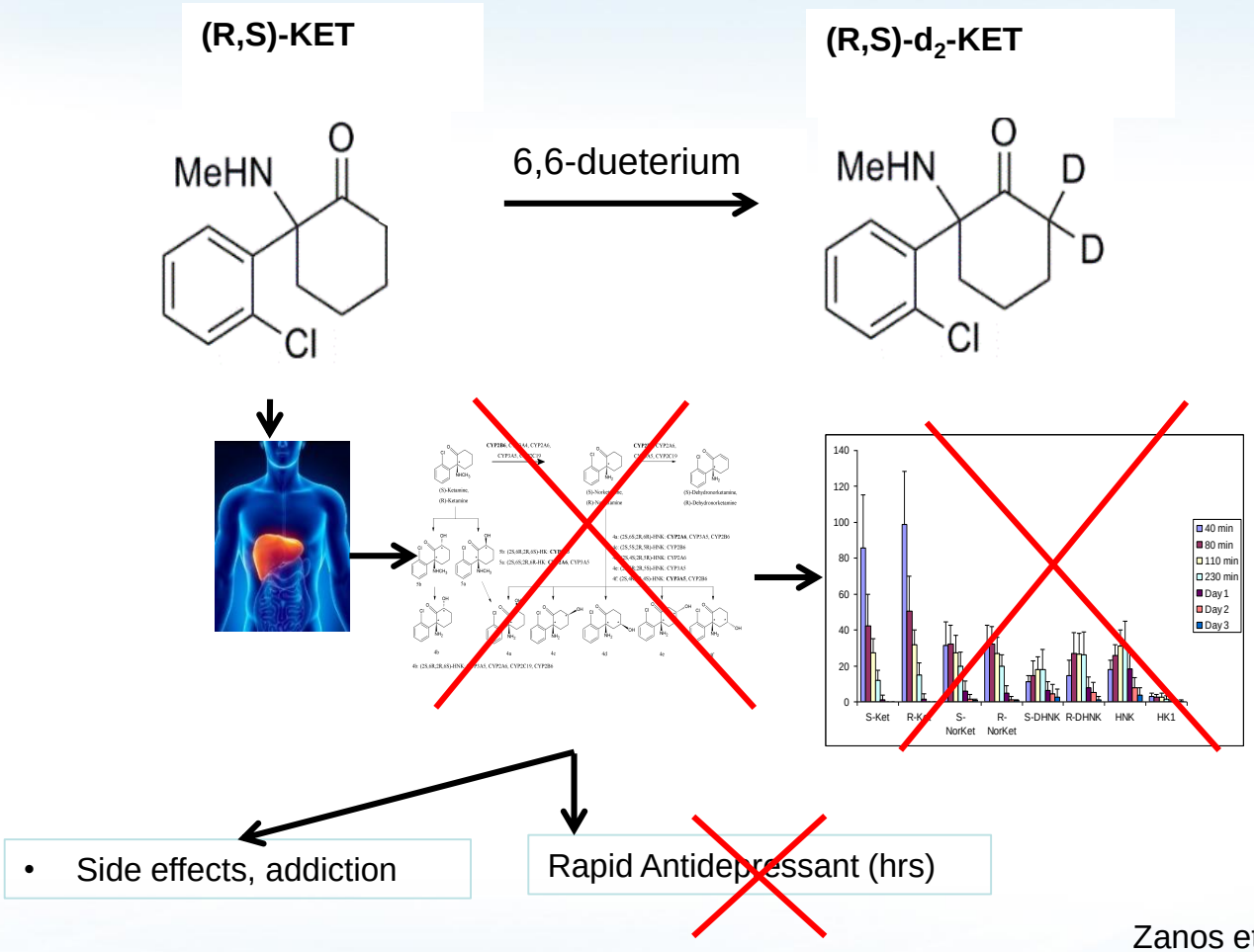
Zarate et al. Arch Gen Psych 2006; Zarate et al. Biol Psych 2012;

Ketamine Metabolites



Moaddel et al. Eur J Pharmacol 2013; Paul et al. Anesthesiol 2014

Blocking Ketamine Metabolism Abolishes Antidepressant Effect



Zanos et al. Nature 2016

NMDAR Inhibition-Independent Antidepressant Actions of Ketamine

- (R,S)-ketamine (single dose) exerts rapid and sustained antidepressant effects but associated with undesirable side effects
- Antidepressant action is blocked by blocking ketamine metabolism
- (2S,6S;2R,6R)-hydroxynorketamine (HNK) exerts behavioral, electroencephalographic, electrophysiological and cellular antidepressant actions in mice
- R enantiomer of HNK may have greater antidepressant effect
- R enantiomer of HNK does not appear to be related to side effects
- Antidepressant effects are blocked with AMPA antagonist

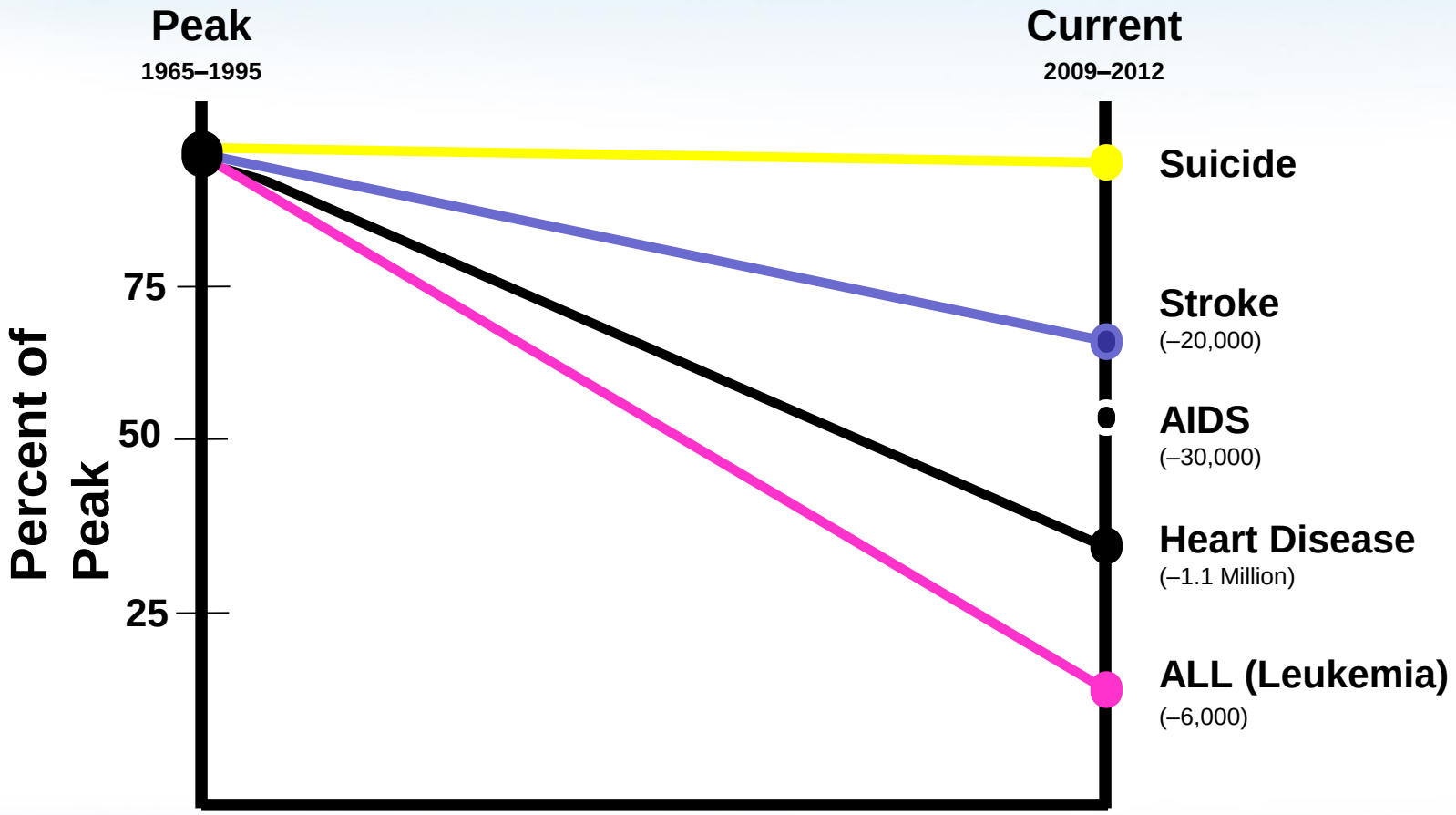
Zanos et al. Nature in press

Deaths per 100,000 population, age-adjusted

	2000	2013	2014
All causes	869.0	731.9	724.6
Heart disease	257.6	169.8	167.0
Cancer	199.6	163.2	161.2
Chronic lower resp.	44.2	42.1	40.5
Unintentional injuries	34.9	39.4	40.5
Stroke	60.9	36.2	36.5
Alzheimer's disease	18.1	23.5	25.4
Diabetes	25.0	21.2	20.9
Influenza/pneumonia	23.7	15.9	15.1
Kidney diseases	13.5	13.2	13.2
Suicide	10.4	12.6	13.0

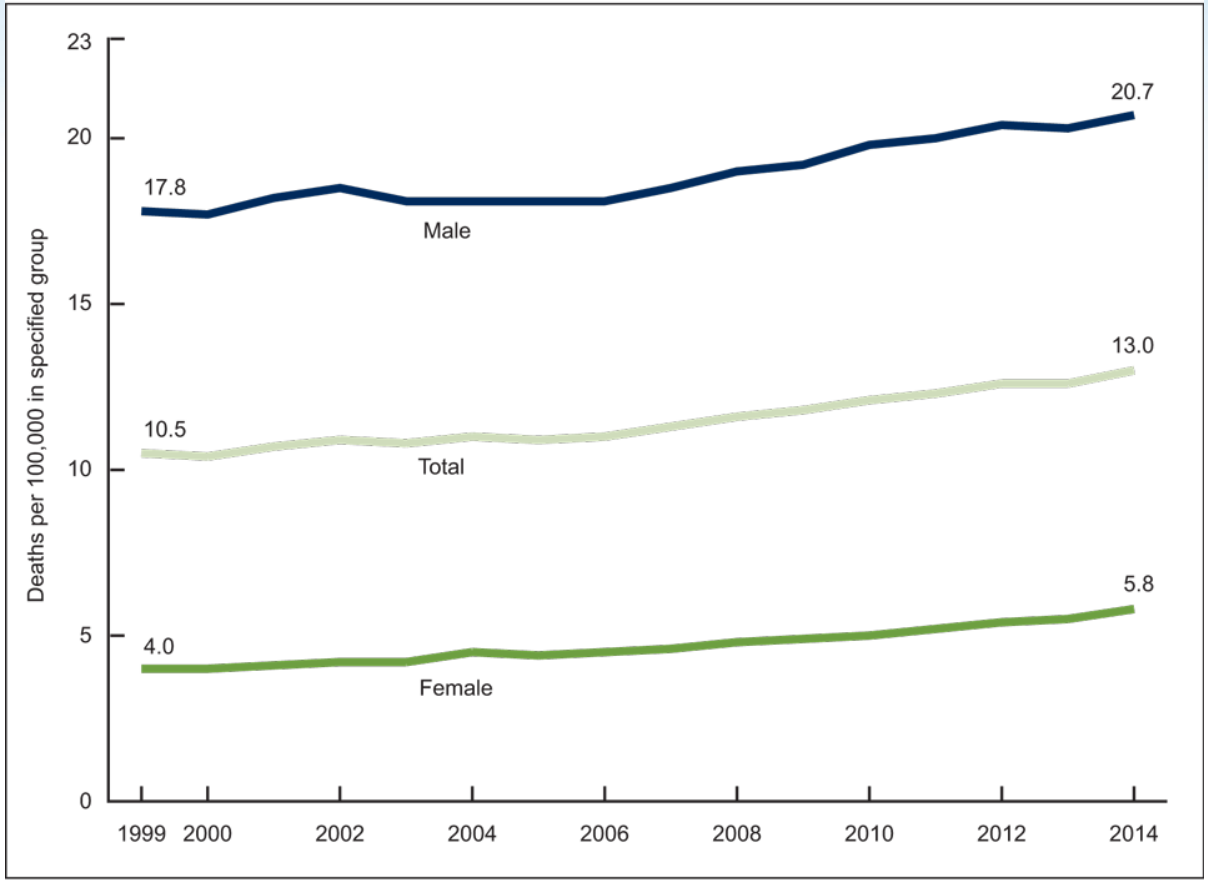
Health, United States, 2015, CDC

Mortality from Medical Causes



Suicide Remains a Significant Public Health Issue

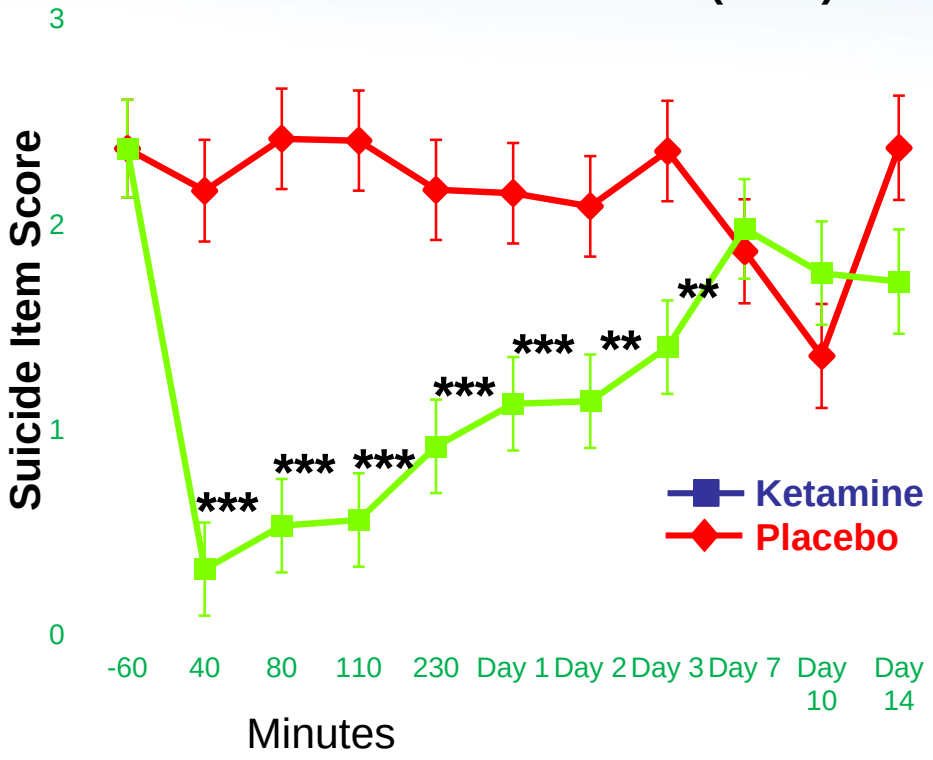
Figure 1. Age-adjusted suicide rates, by sex: United States, 1999–2014



NOTES: Suicide deaths are identified with codes U03, X60–X84, and Y87.0 from the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. Access data for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db241_table.pdf#1.
SOURCE: NCHS, National Vital Statistics System, Mortality.

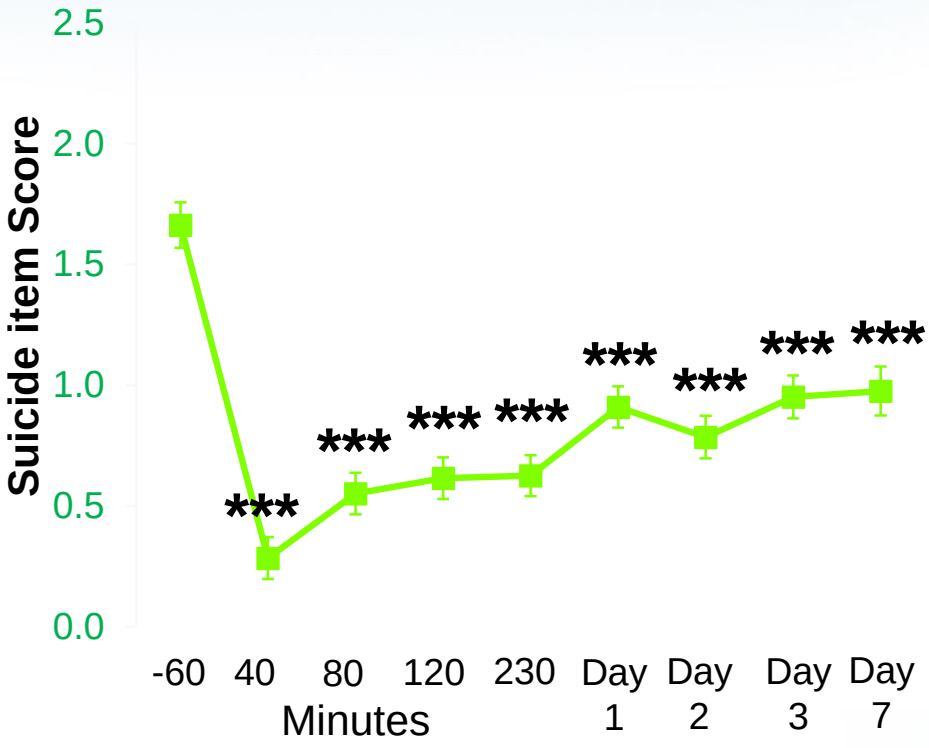
Rapid Decreases in Suicidal Ideation (SI) with Ketamine in MDD and BD

Treatment Resistant BD
MADRS Suicide Item (n=15)



***p<0.001, **p<0.01, *p<0.05

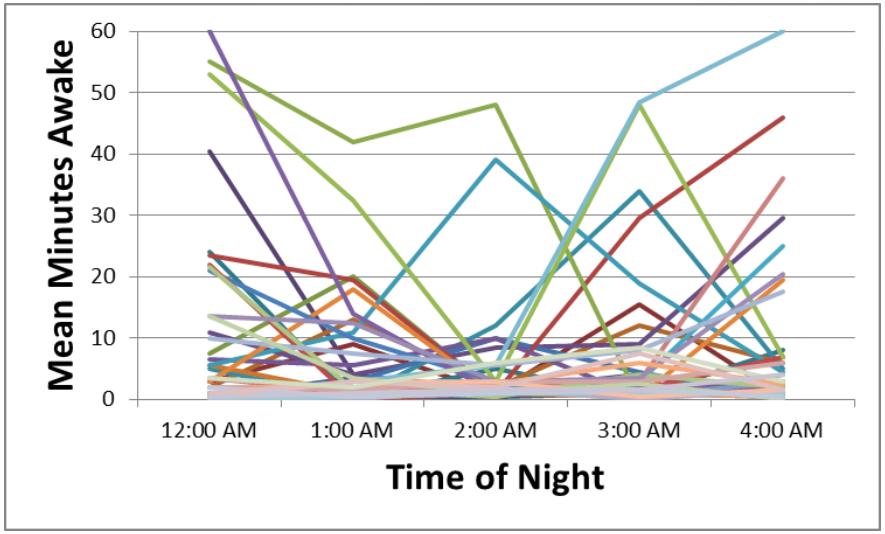
Combined MDD+BD
HAMD Suicide Item (n=66)



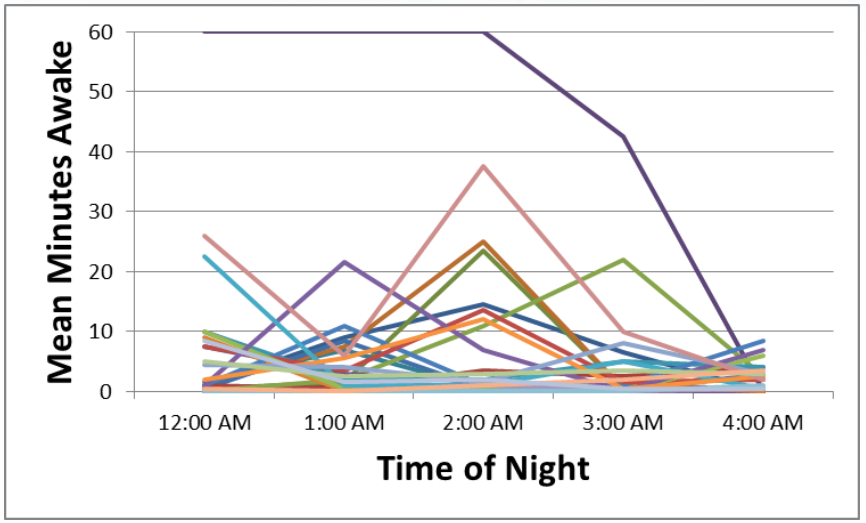
Diazgranados et al., Biol Psychiatr 2010

Wakefulness is Associated with Next-day Suicidal Ideation in Depressed Patients

Sleep Quality of Depressed Ideators



Sleep Quality of Depressed Non-Ideators



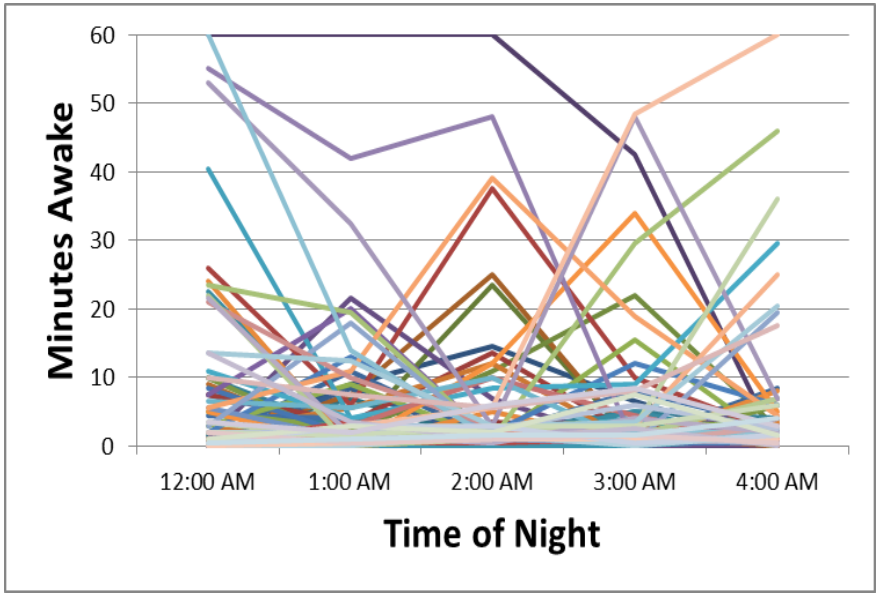
Significant time by ideation interaction for sleep between 12 and 4 am, p = .007

Time spent awake at 4 am predicted suicidal ideation the next day when controlling for depression severity, p = .008

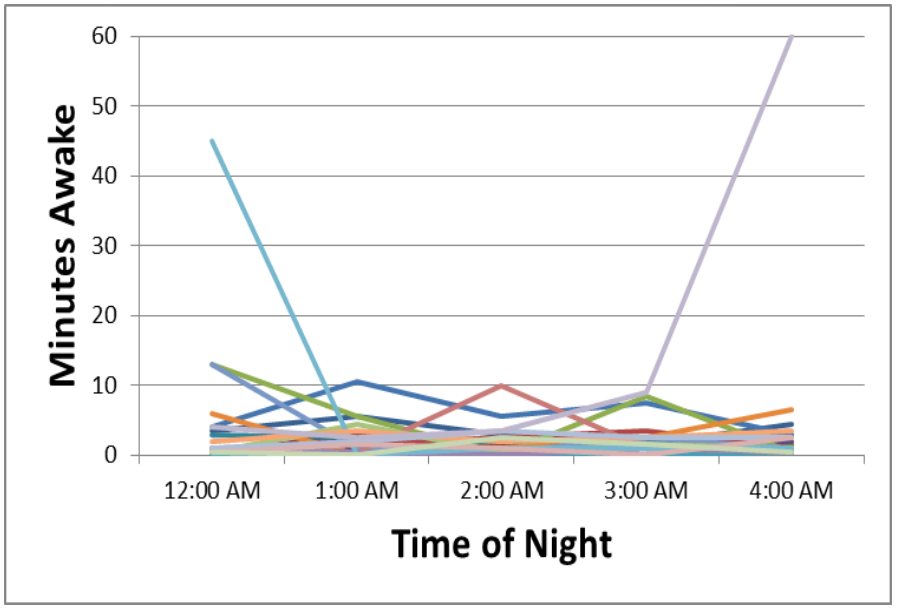
Ballard et al J Clin Psych, in press

Wakefulness in Depressed Patients and Healthy Controls

Wakefulness in Depressed Patients (n = 65)

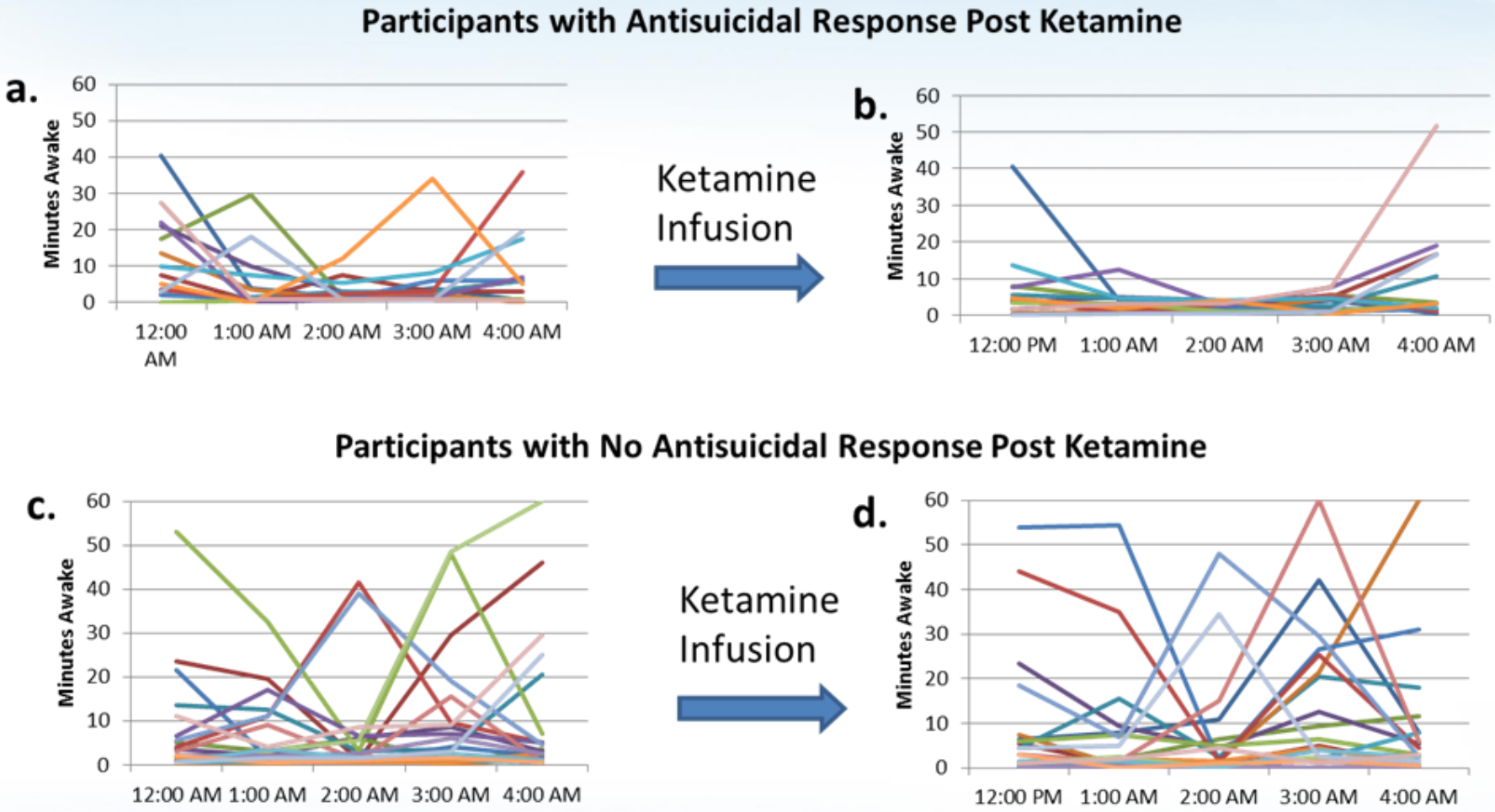


Wakefulness in Healthy Controls (n = 22)



Data collected using polysomnography

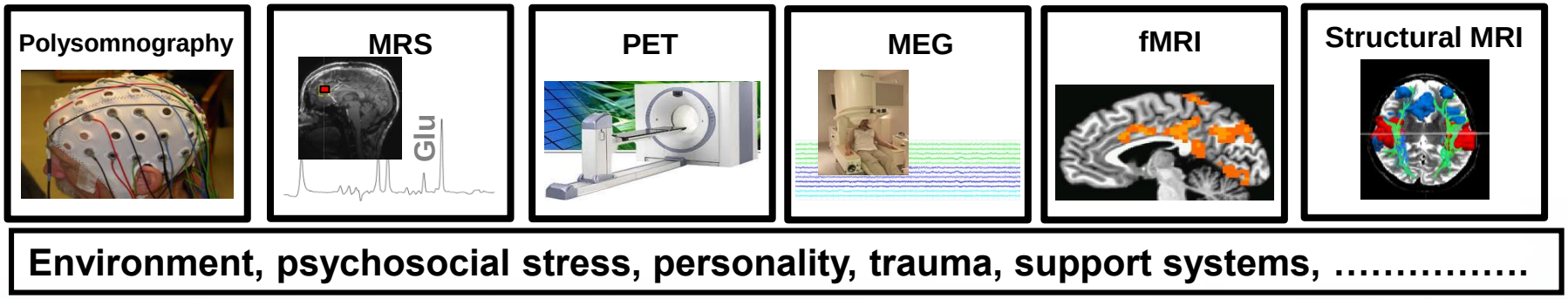
Relationship Between Wakefulness from 12:00 AM – 4:59 AM and Antisuicidal Response to Ketamine



Vandevoort, Ballard, Niciu in review

Neurobiology of Suicide Protocol: 15-M-0188

- Identify patients in current suicidal crisis
  - Suicide attempt or acute suicidal thoughts in last 2 weeks
  - Admission to inpatient unit– 7SE, CC, NIH
- Multimodal assessment to identify biomarkers of suicidal ideation
  - Dimensional perspective for suicidal thoughts/behaviors
- Replicate “rapid model paradigm” used for antidepressants treatments to develop rapid-acting anti-suicidal treatments
  - Evaluate ketamine and sleep deprivation in suicidal individuals
  - Identify neural correlates of antisuicidal response



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OP4, 7SW, MEG/MRI/MRS/PET/SSCC Cores, HSPU

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Brian Roth (University of North Carolina)

And especially Patients and their Families

Thank You

Contact:
lawrence.park@nih.gov

http://patientinfo.nimh.nih.gov/
1-877-MIND-NIH (1-877-646-3644)
moodresearch@mail.nih.gov

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infinite possibilities

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