

An Update on the Diagnosis, Treatment, and Research of Mood Disorders

NAMI
June 30, 2017

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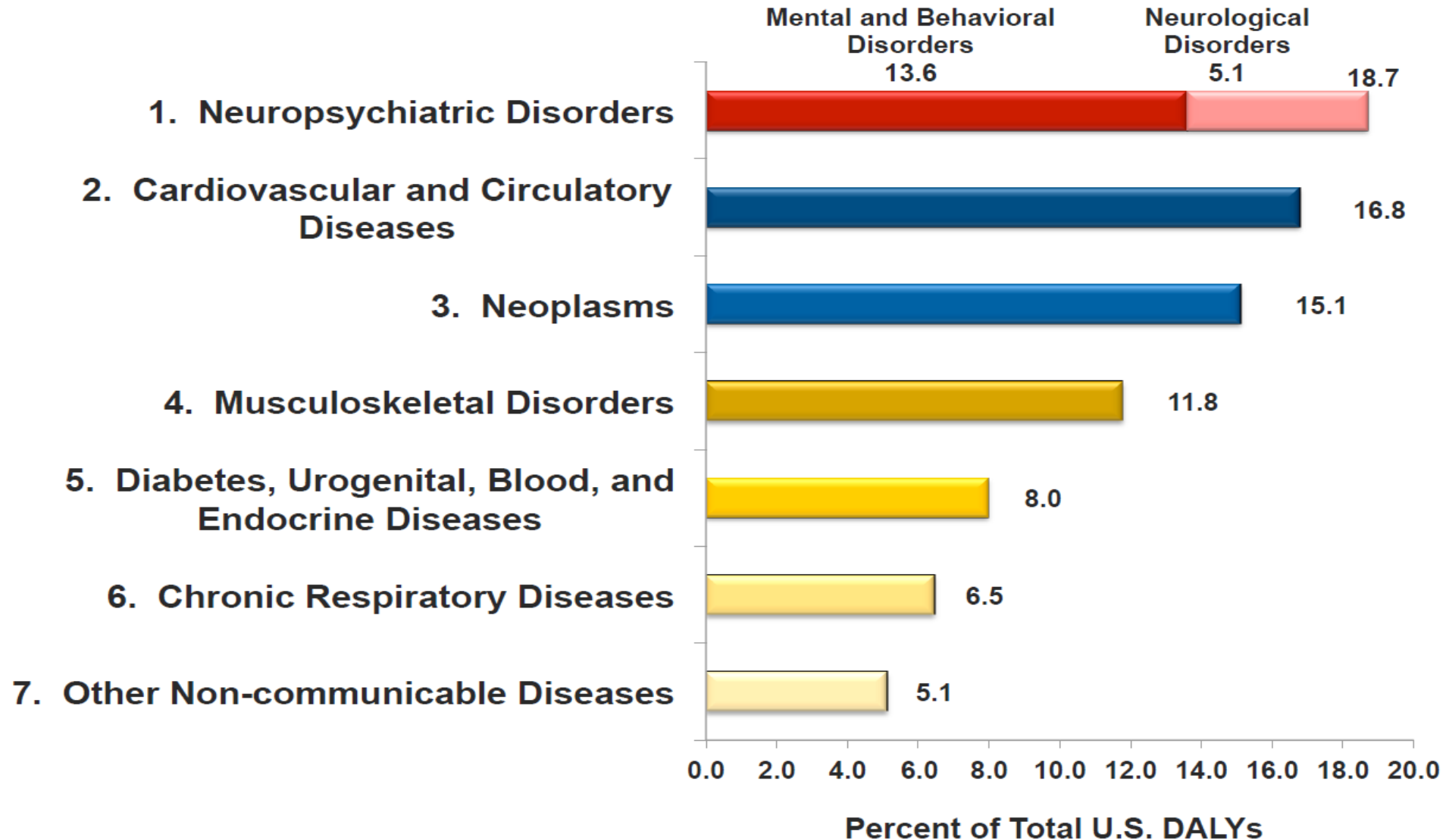
Overview

Major depressive disorders : a major cause of disability

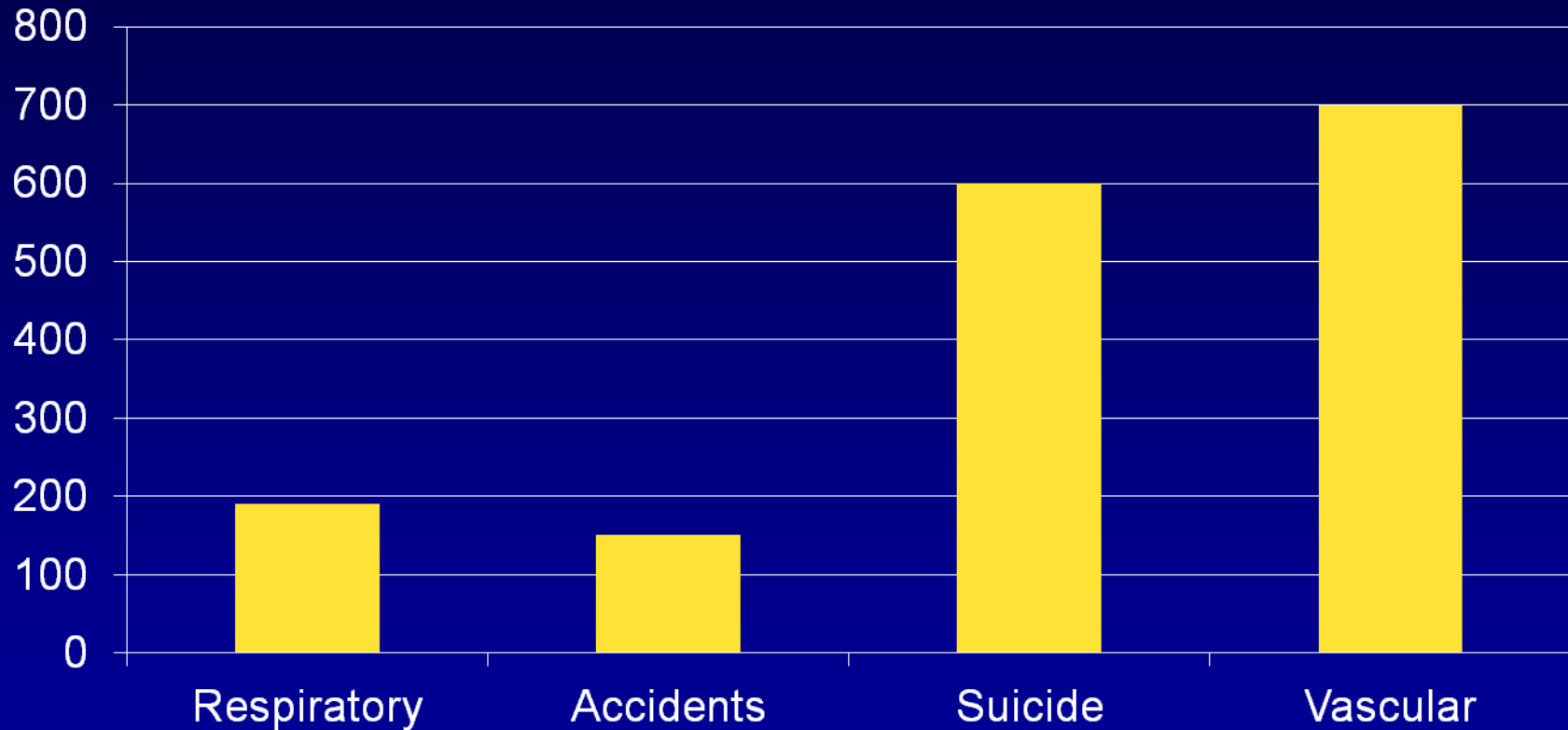
- **>10% of the American population suffer from a mood disorder each year**
- **Depression is one of THE leading causes of disability worldwide, ranking ahead of ischemic heart disease, cerebrovascular disease, cancers, infectious diseases, etc.**
- **An increase in the death rate at any age, independent of suicide, smoking, or other risk factors**
- **> 44,000 deaths from suicide/yr (cf ~ 18,000 homicides)**
- **Individuals with major depression sometimes describe an emotional pain much worse than any physical pain that they have experienced**

U.S. Burden of Diseases: 291 diseases and injuries

Leading Categories of DALYs 2010

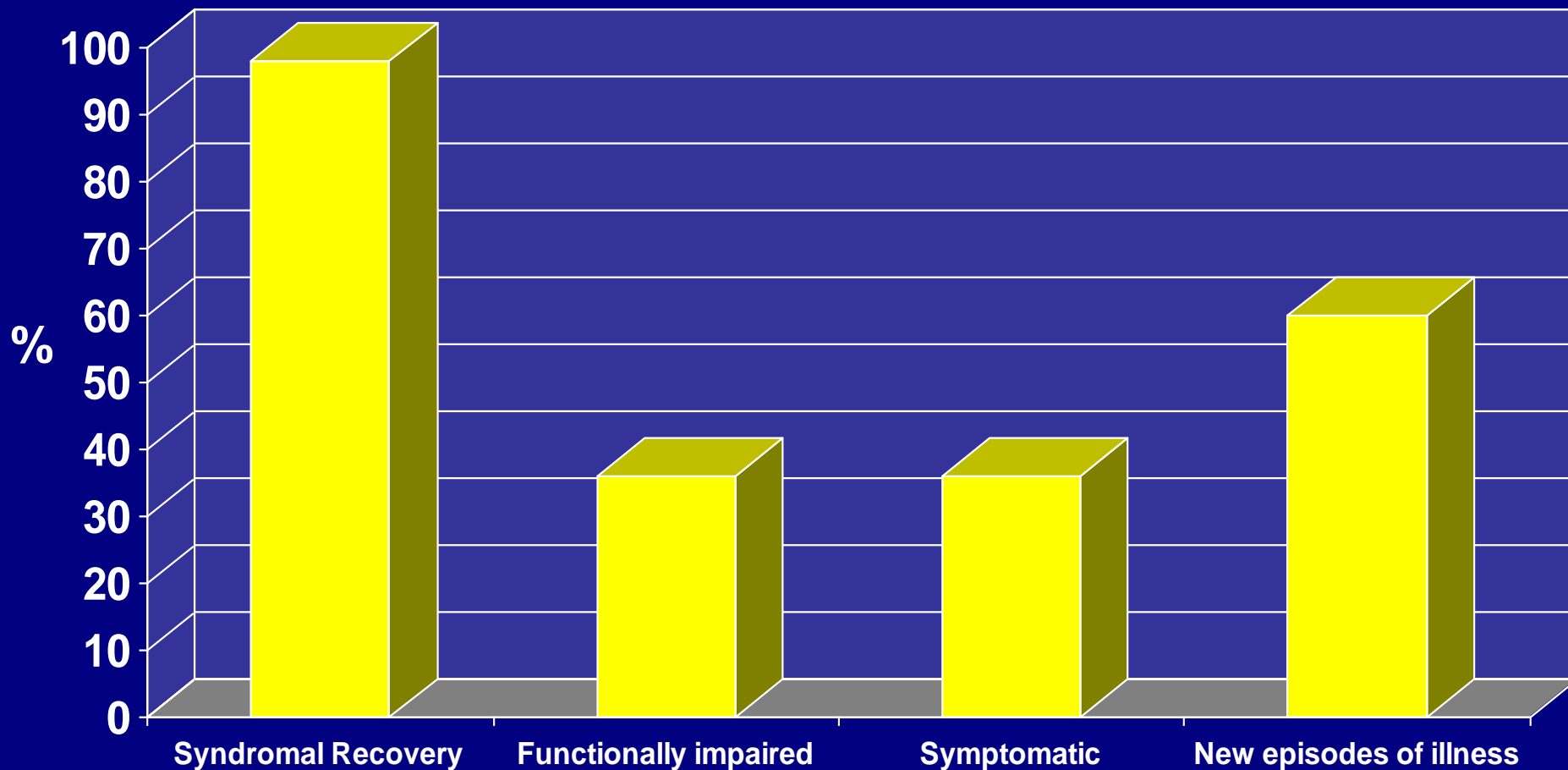


Excess deaths in bipolar disorder

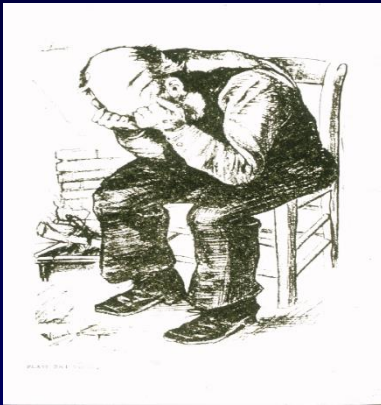


Osby et al. Arch Gen Psych 2001

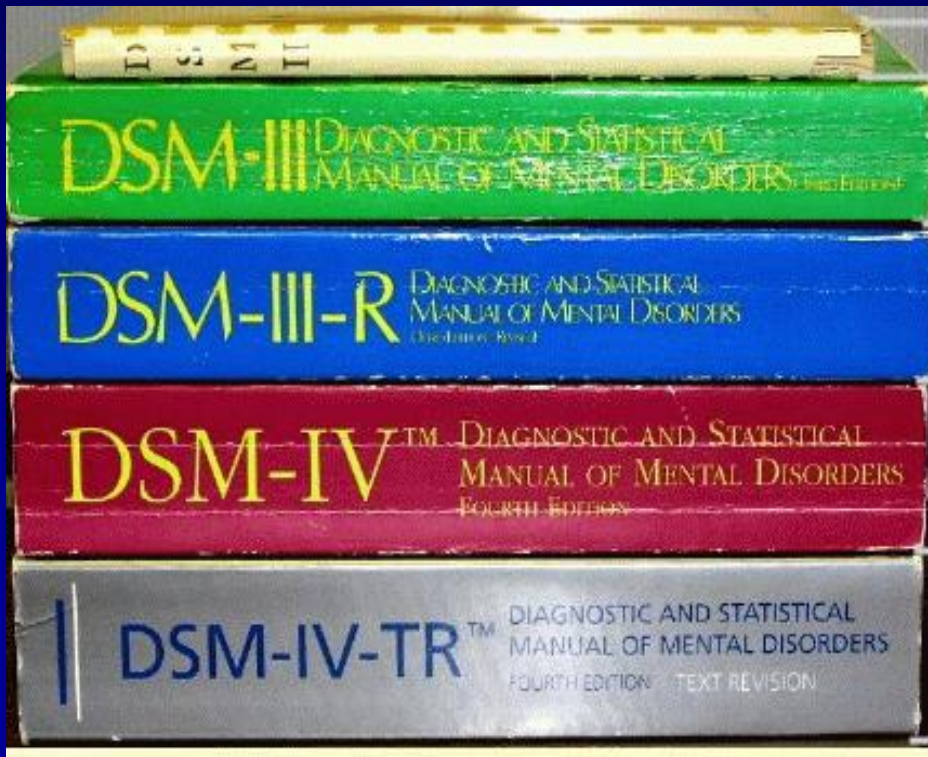
The McLean-Harvard First-Episode Mania Study: Prediction of Recovery and First Recurrence at 24-Months (N=166)



Diagnosis



DSM5



DIAGNOSTIC AND STATISTICAL
MANUAL OF
MENTAL DISORDERS

FIFTH EDITION

DSM-5

AMERICAN PSYCHIATRIC ASSOCIATION

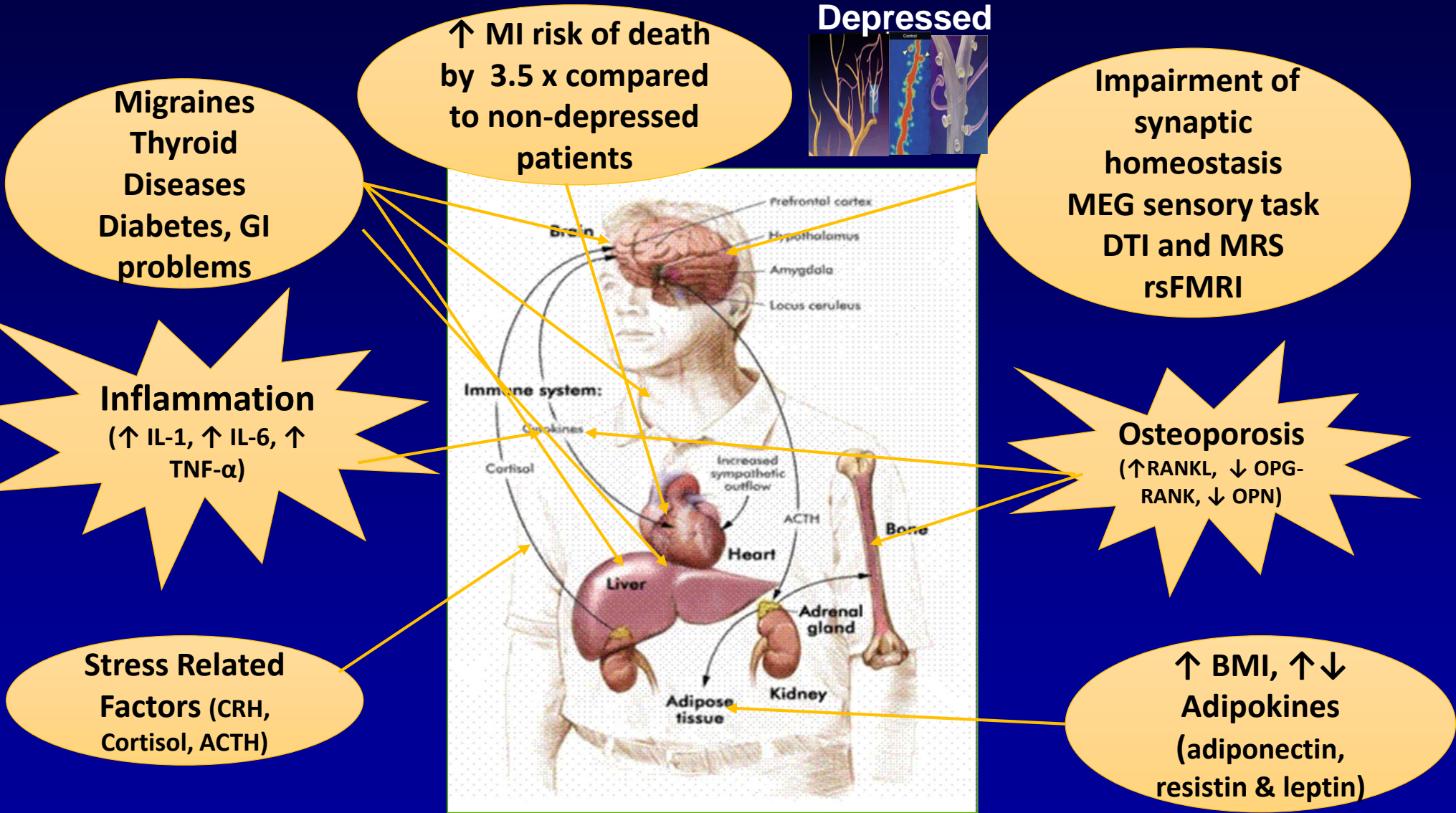
Depressive Disorders

- ❖ Disruptive Mood Dysregulation Disorder (<12 Yrs)
- ❖ Major Depressive Disorder
- ❖ Persistent Depressive Disorder (Dysthymia)
- ❖ Premenstrual Dysphoric Disorder
- ❖ Substance/Medication Induced Depressive Disorder
- ❖ Depressive Disorder Due to Another Medical Condition
- ❖ Other Specified or Unspecified

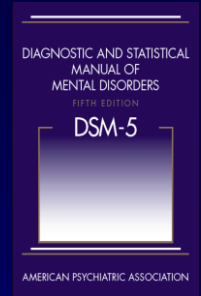
Major Depressive Disorder

- ✓ A. Five of the 9 SXS of depression with either depressed mood or anhedonia as one of the SXS, for a 2 week period most of the day nearly everyday.
 - ❑ Depressed mood
 - ❑ Anhedonia
 - ❑ Weight (5% in one month) or appetite changes
 - ❑ Sleep changes
 - ❑ Psychomotor changes (observable by others, not just subjective)
 - ❑ Fatigue or energy loss
 - ❑ Worthlessness/inappropriate guilt
 - ❑ Diminished ability to concentrate/ think / make decisions
 - ❑ Recurrent thoughts of death or dying/ suicidality
- ✓ B. Significant distress or impairment in functioning
- ✓ C. Not due to substance or another medical condition
- ✓ D. Not better explained by another psychotic disorder
- ✓ E. There has never been a manic or hypomanic episode

Depression: A Brain and Systemic Medical Illness



Diagnostic Statistical Manual (DSM) & Research Domain Criteria (RDoC)

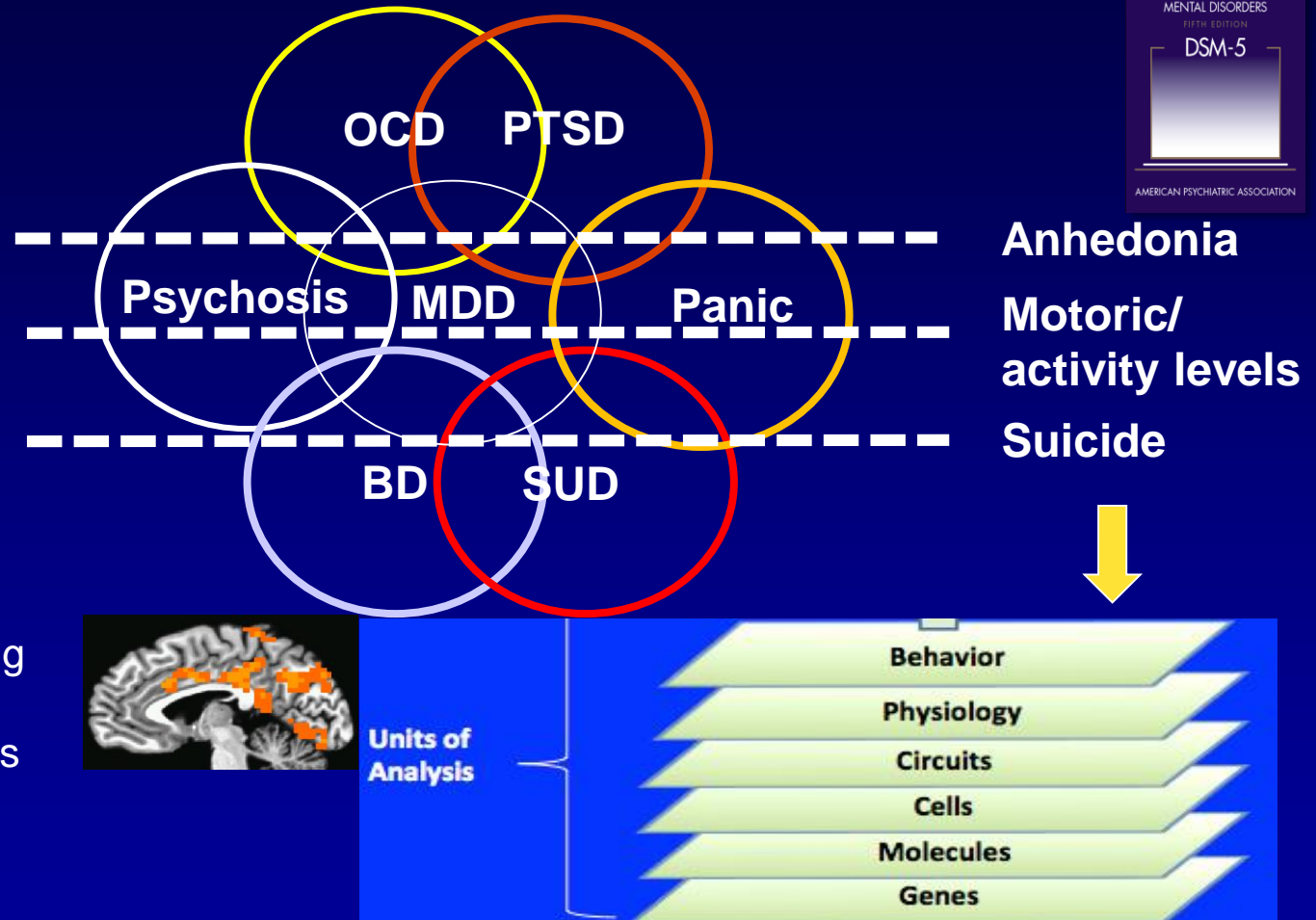


DSM diagnosis

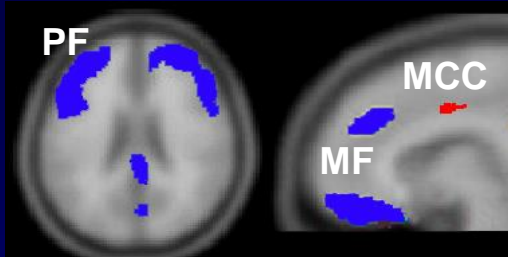
- Common language for describing psychopathology
- Significant overlap in symptoms across disorders
- Symptoms do not overlap with pathophysiology

RDoc

- Focus is on understanding pathophysiology, e.g., neural circuitry, with levels of analysis

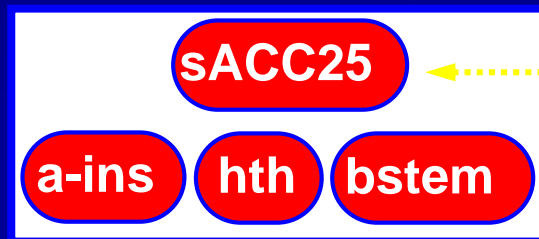
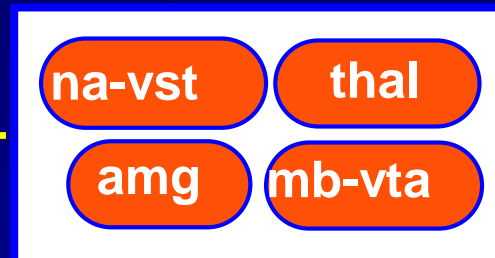
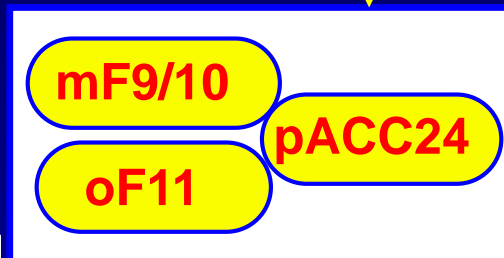
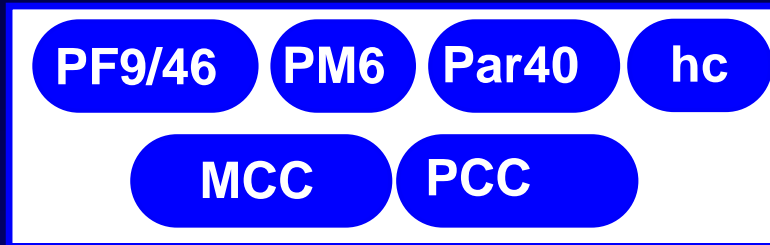


Defining Depression Circuits Response Pathways



CBT

Cognition
(attention-appraisal-action)

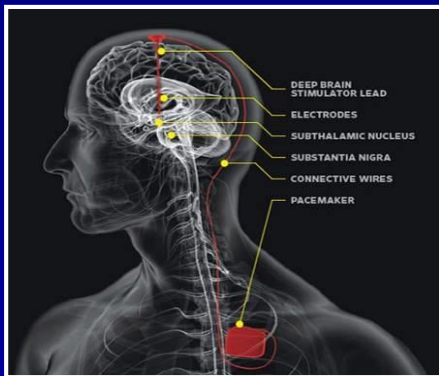


Interoception
(drive-autonomic-circadian)

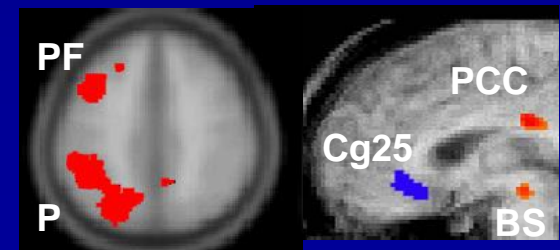
Mood state

MEDS

Self-awareness insight



Br Med Bul 65:193-207, 2003
Arch Gen Psych 61:34-41-2004

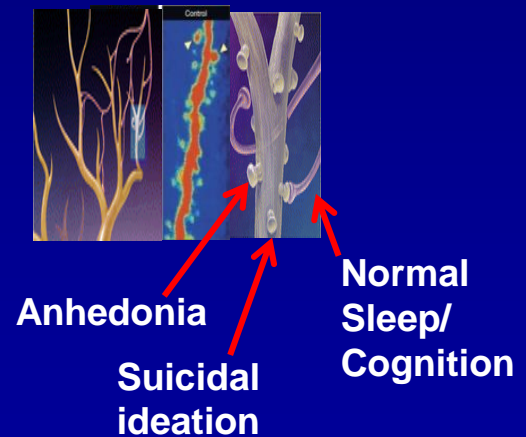
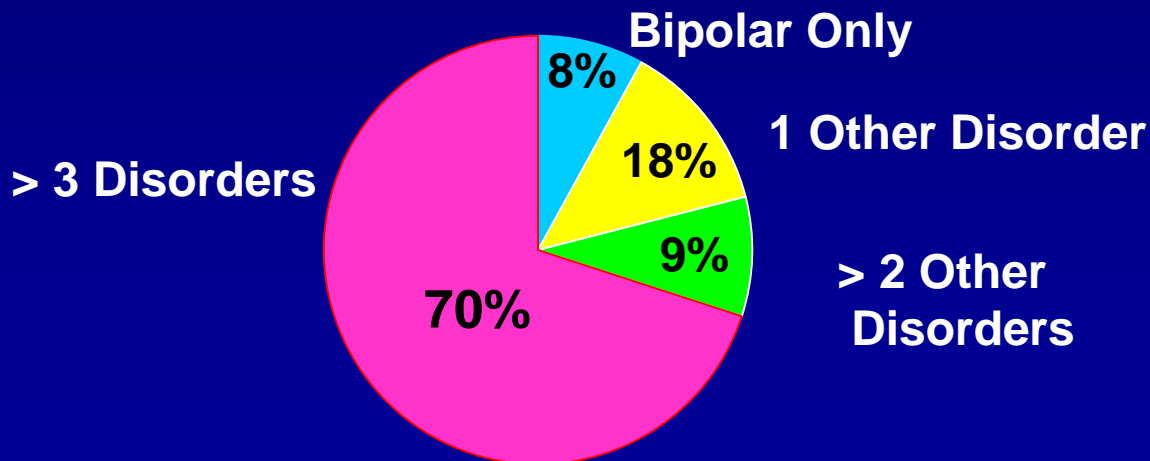
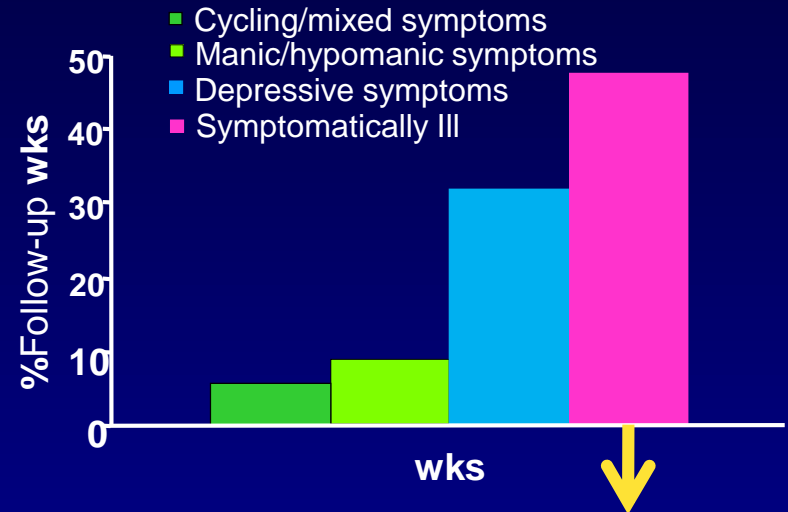


Course of Illness

Bipolar Disorder: Course of illness, Comorbidity, Life Impact, Disability, and Neurobiological Insights

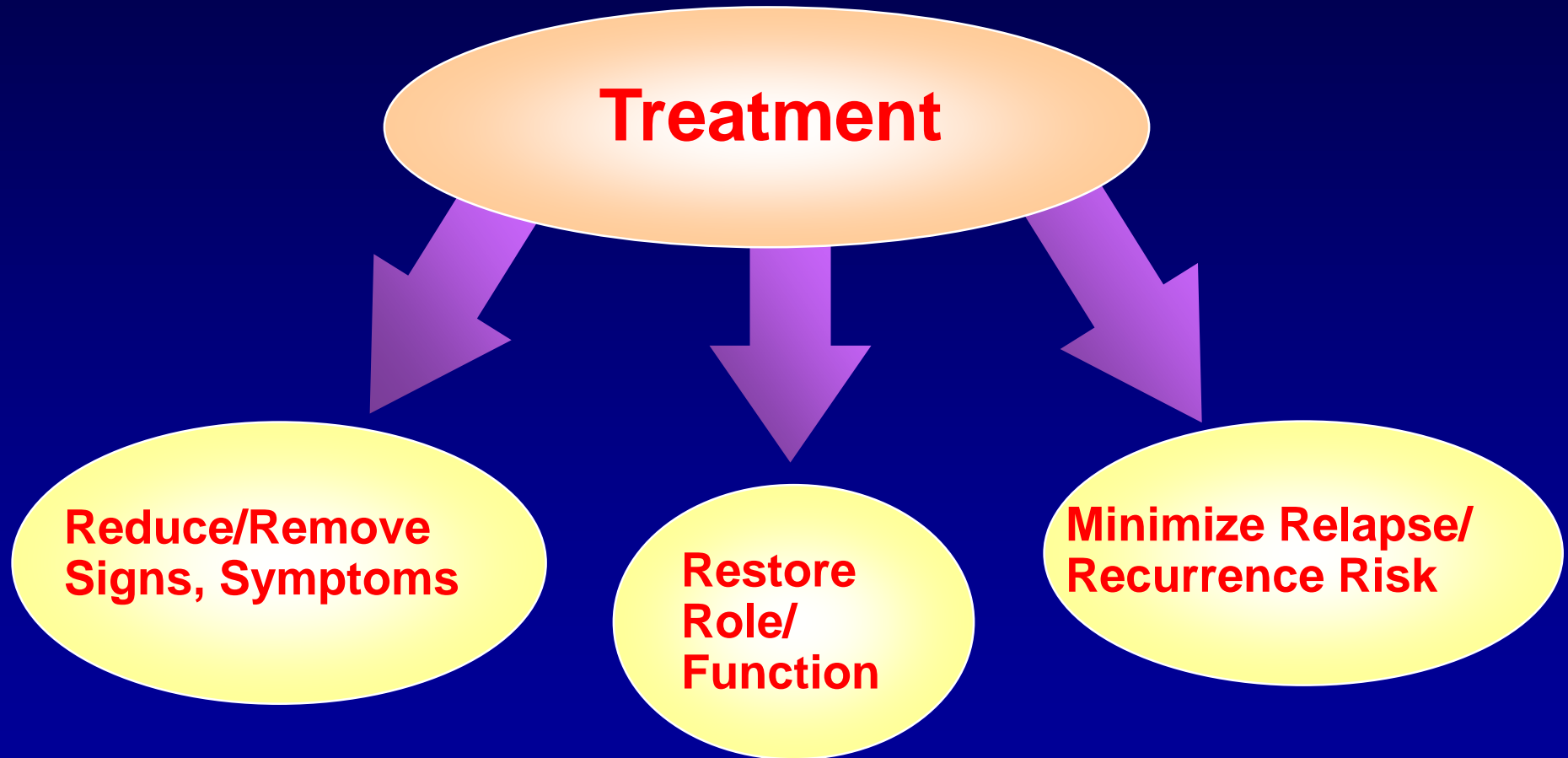


- Disruption to:
 - Personal life
 - Familial life
 - Occupation
 - Social life
 - economic well-being
- Risk for suicidal behavior



Treatment

Depressive Disorders: Treatment Goals



Indications for Formal Psychotherapy as Monotherapy

Psychotherapy only if

- **Mild disorder**
- **Psychotic or melancholic features are absent**
- **History of chronic psychosocial problems**

Antidepressants

SSRIs

- Fluoxetine (Prozac)
- Citalopram (Celexa)
- Fluvoxamine (Luvox)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Escitalopram (Lexapro)

SNRIs

- Venlafaxine (Effexor)
- Duloxetine (Cymbalta)

Tricyclics/ Tetracyclics

- Nortriptyline (Pamelor)
- Amitriptyline (Elavil)
- Desipramine (Norpramin)
- Imipramine (Tofranil)
- Doxepin (Sinequan)
- Protriptyline (Vivactil)
- Trimipramine (Surmontil)
- Maprotiline
- Clomipramine
- Amoxapine
- Dothiepin

DNRI

- Bupropion (Wellbutrin)

MAOIs

- Phenzelzine (Nardil)
- Tranylcypromine (Parnate)
- Selegiline transd (EMSAM)

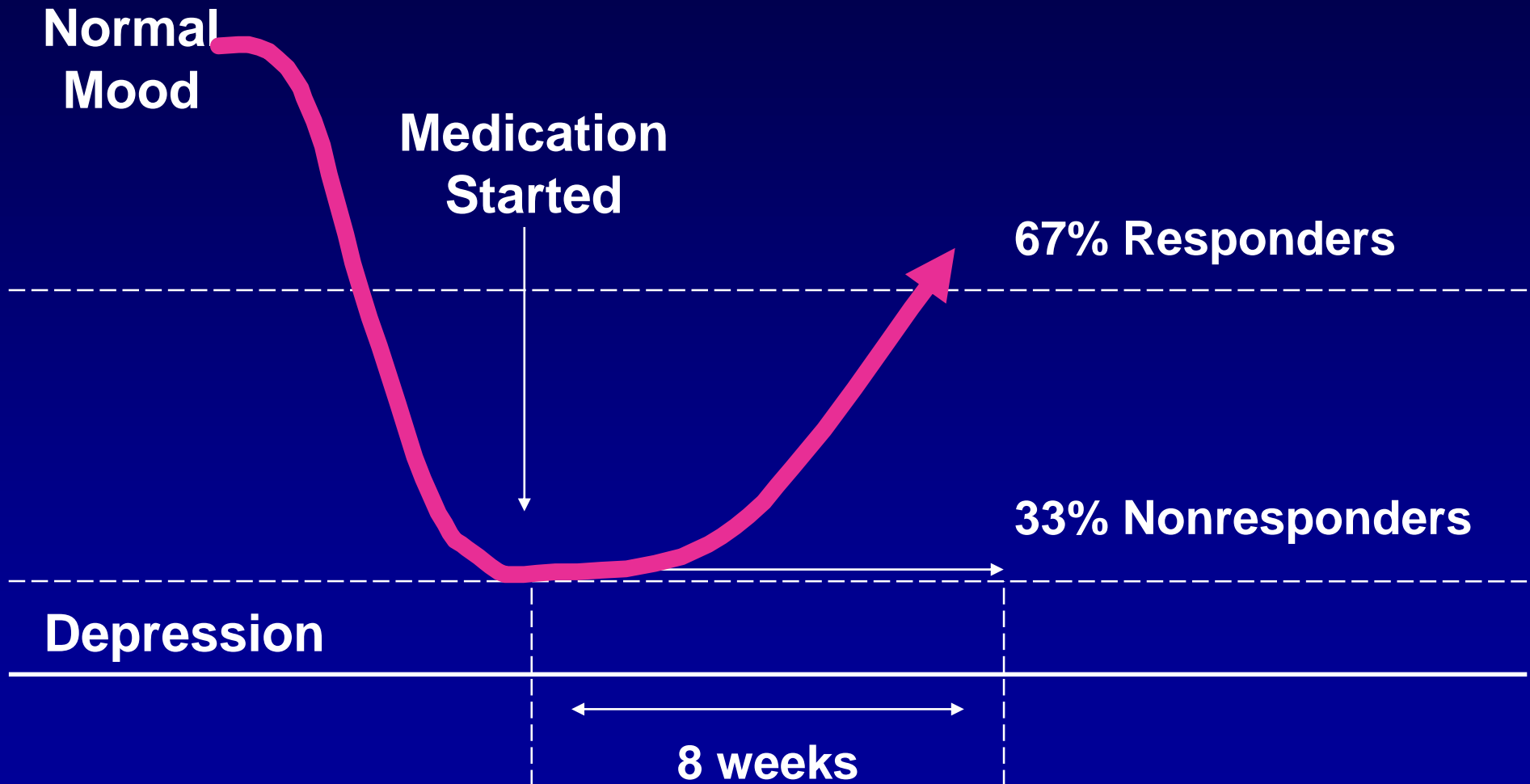
Newer

- Vortioxetine (Brintellix)
- Vilazadone (Viibryd)
- Levomilnacipran transd (Fetzima)

All Antidepressants Are Efficacious

- 70 - 80% efficacy with any marketed antidepressant
- **SRI's or Bupropion are excellent first line choices**
- TCA's may be superior for some "severe" depressions
- **MAO-I's may be preferred for some atypical depressions**

Response Rate After Pharmacologic Treatment Of Depression



Diagnostic Challenges:

1. Specific Depressive Subtypes may suggest specific treatment modifications
 - A. Depression with anxiety or Anxious Depression (PTSD, Social anxiety disorder, GAD, panic disorder, OCD)
 - B. Depression with psychotic features
 - C. Atypical depression
 - D. Depression with substance abuse
 - E. Bipolar depression
 - F. Depression with personality disorder

Pharmacotherapy of Treatment Resistant Depression: Next Step

- Optimize
- High Dose Therapy
- Switch
- Augment/Co-prescribe
- Neuromodulation (eg., ECT, TMS)
- Psychotherapy

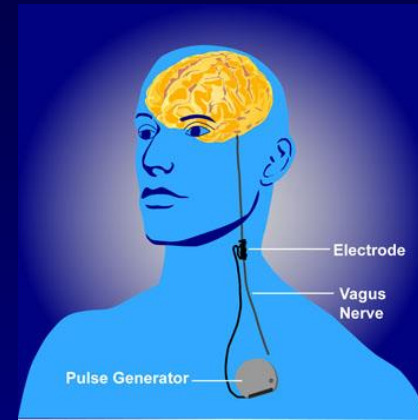
Antidepressant “Augmenters”

- Augmenters with established effectiveness:
 - **Lithium carbonate**
 - Triiodothyronine
- **Co-prescribing strategies:**
 - SSRI + TCA
 - **Antidepressant + Bupropion**
 - Antidepressant + Mirtazapine
- With possible effectiveness
 - **Stimulants**
 - Dopaminergic agonists
 - **Pindolol**
 - Buspirone
 - **Atypical antipsychotic**
- Other proposed augmentations strategies
 - **Modafinil (Provigil)**
 - Estrogen
 - **Testosterone**
 - Lamotrigine
 - **Folate**
 - Dexamethasone
 - **Ketoconazole**
 - Inositol

Neuromodulation: Devices for Depression



Electroconvulsive Therapy (ECT)



Vagus Nerve Stimulation (VNS)



**Repetitive Transcranial
Magnetic Stimulation (rTMS)**



**Transcranial Electrical
Stimulation (tES)**

Electroconvulsive Therapy (ECT)

- Developed in 1930s
- **FDA- Approved Device in 1979 (grand-fathered)**
- Brief electrical pulse passed through scalp
- **Patient under anesthesia**
- Produce seizure on EEG
- **Muscle paralysis prevents convulsive movement**
- Bilateral or unilateral
- **6 - 12 treatments**
- **2 - 3 treatments per week**



Limitations:

Headache, muscle aches

Cognitive Side Effects: Memory

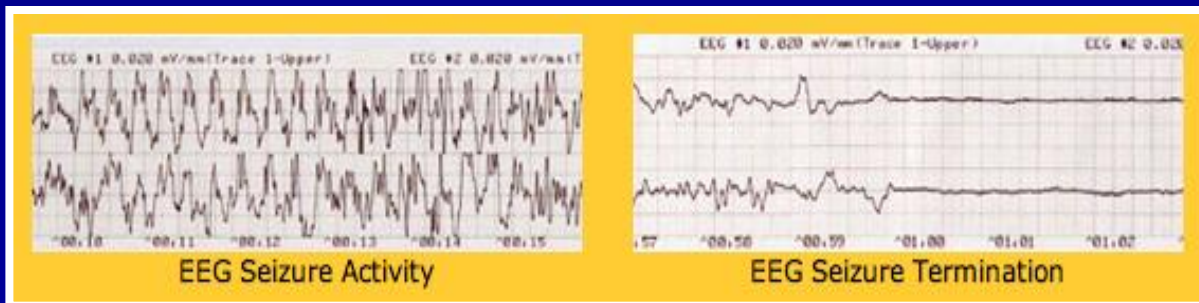
Access: Hospital, Often Inpatient

Stigma

Anesthesia Risks

Cost

Maintenance: ECT v. meds



Repetitive Transcranial Magnetic Stimulation (rTMS)

Non-invasive technique

USA: Approved (NeuroStar TMS Therapy®)

Approved: Canada and Israel

Strong, pulsed magnetic fields pass through skull

Coil placed on head in awake patient

**Induces electrical current in cortex which
depolarizes neurons**

Control over site and intensity of stimulation



Limitations:

Need more controlled trials for efficacy/maintenance data

Higher intensity stimulation leads to higher risk of motor convulsion

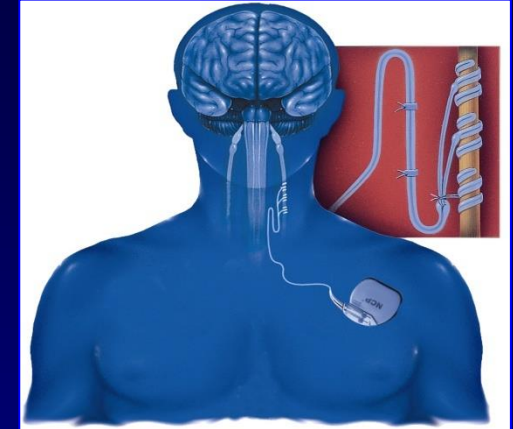
Best stimulation parameters not known

Noisy; high-freq clicking

Neuronal depolarization only extends 2 cm below scalp - effects limited to cortex

Vagus Nerve Stimulation (VNS)

- FDA approved for epilepsy; FDA approved for TRD 2005
- **Implanted in over 30,000 patients worldwide**
- Pulse generator implanted in left chest wall area, connected to leads attached to left vagus nerve
- **Mild electrical pulses applied to CN X for transmission to the brain**



Limitations

Efficacy data from nonrandomized study

Surgical procedure

Limited acute antidepressant effect

MRI contraindication

Battery Life (3- 8 yrs)

Side effects: cough, site infection, hoarseness, trouble swallowing, shortness of breath

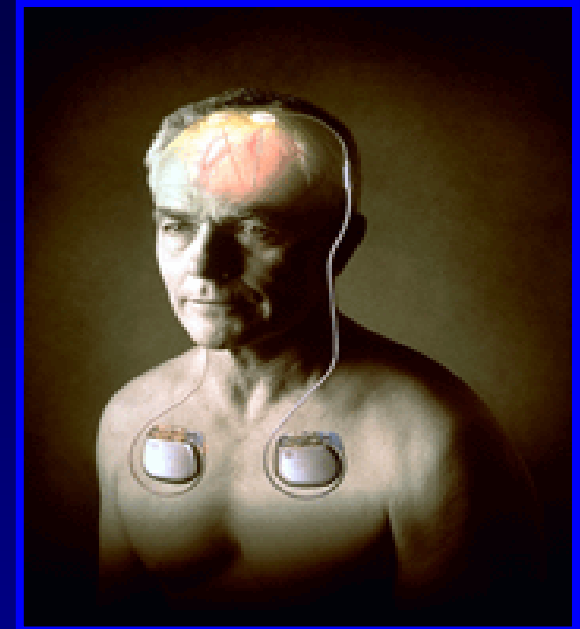


Deep Brain Stimulation (DBS)

- FDA Approved for Parkinson's and Tremor
- **Investigational for OCD, TRD**
- Stereotactic Target from MRI
- **Two chest-wall Internal Pulse Generators**
- Burr holes in skull for electrode placement
- **Stimulation parameters programmed by computer**

Limitations

- **Limited, short-term, open-label data in psychiatry**
- Considerable Surgical Risk
- **Targets and stimulation parameters not established**
- MRI contraindication
- **Battery Life**



This information concerns a use that has not been approved by the U.S Food and Drug Administration

Low Field Magnetic Stimulation



- **Initial Observation**

- BP depressed SS undergoing EP-MRSI had immediate relief

- **Early POC trial**

- **Animal study (FST)**

- **^{18}F FDG PET healthy volunteer study**

- **Prototype Development**

- **20 minute session**

- **Positive Scale**

- interested*
- excited
- strong
- enthusiastic*
- proud*
- alert*
- inspired*
- determined
- attentive*
- active

- **Negative Scale**

- distressed*
- upset*
- guilty
- scared
- hostile
- irritable
- ashamed
- nervous
- jittery
- afraid

Transcranial Electrical Stimulation

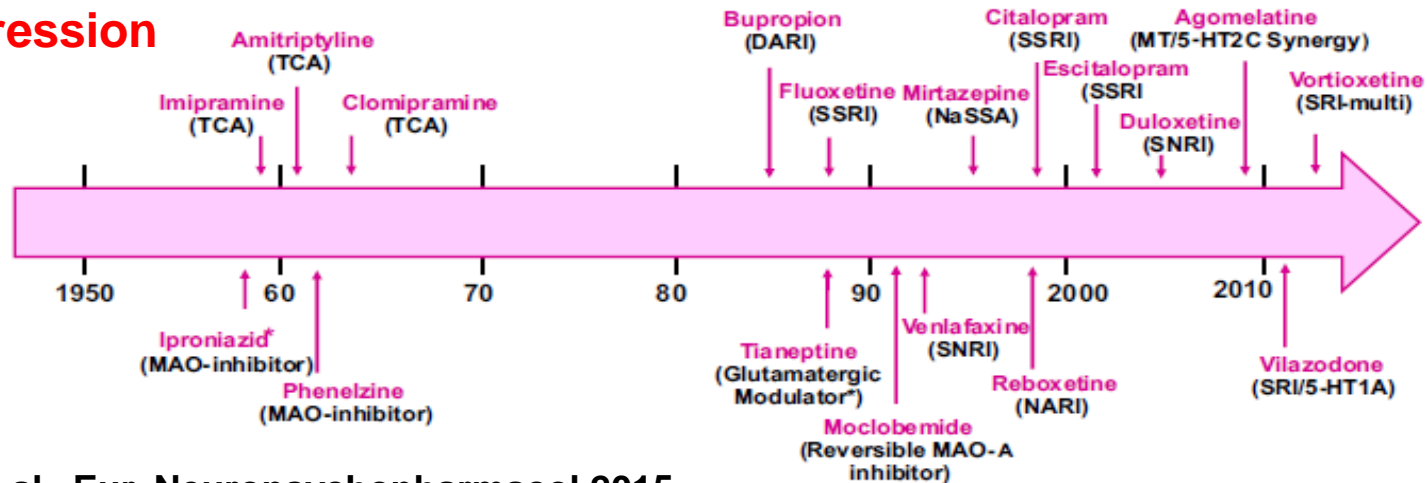


- **tDCS: direct current**
- **tACS: alternating current**
- **tRNS: random noise**
- **tPCS: pulsed current**



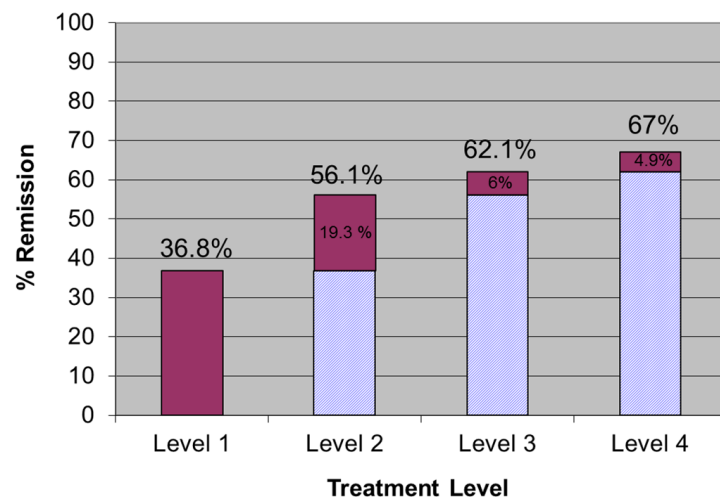
Chronology for Antidepressants for Mood Disorders

Major depression



Milan et al., Eur. Neuropsychopharmacol 2015

STAR*D Remission Rates



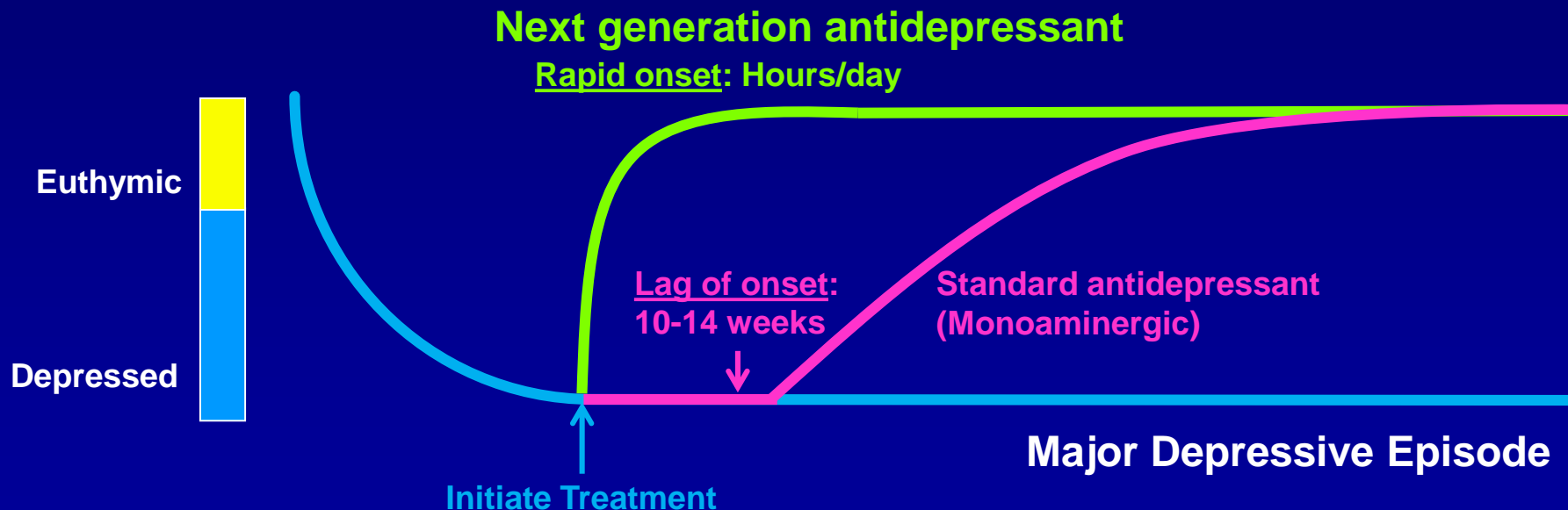
Available Treatments for Mood Disorders are less than Optimal

- Low remission rates
- Delay of onset (weeks to months)
- Personal and social problems (job, marriage, kids)
- Increase risk of suicidal behavior (mostly 1st 30 days of an AD)

Depression: The Need for Improved Treatments

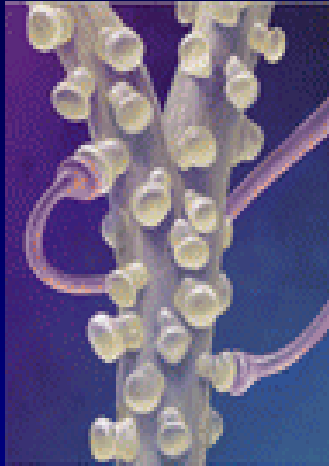
Problems with Current Antidepressants:

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

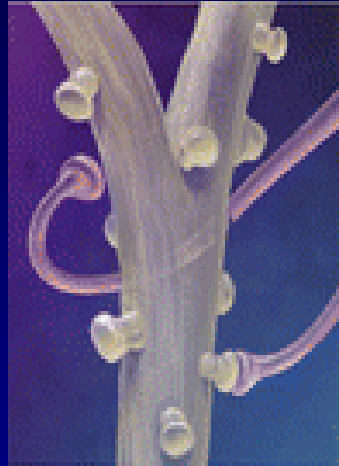


Neuroimaging & Postmortem Findings in Severe Recurrent Mood Disorders

Non mood disorder

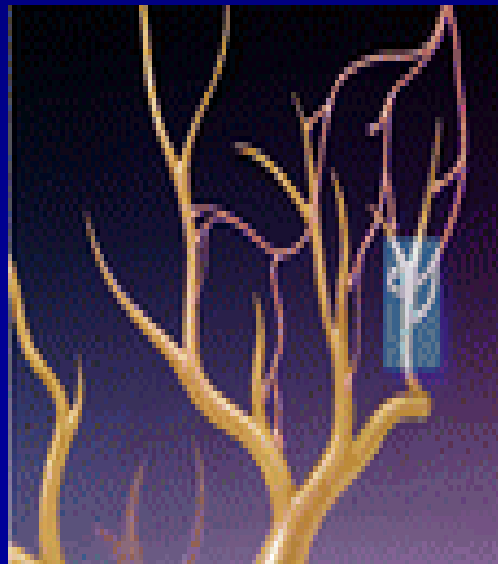


Severe recurrent Mood Disorders



↓ Volume of specific areas

↓ Neuron -- mainly atrophy (neuropil reduction)



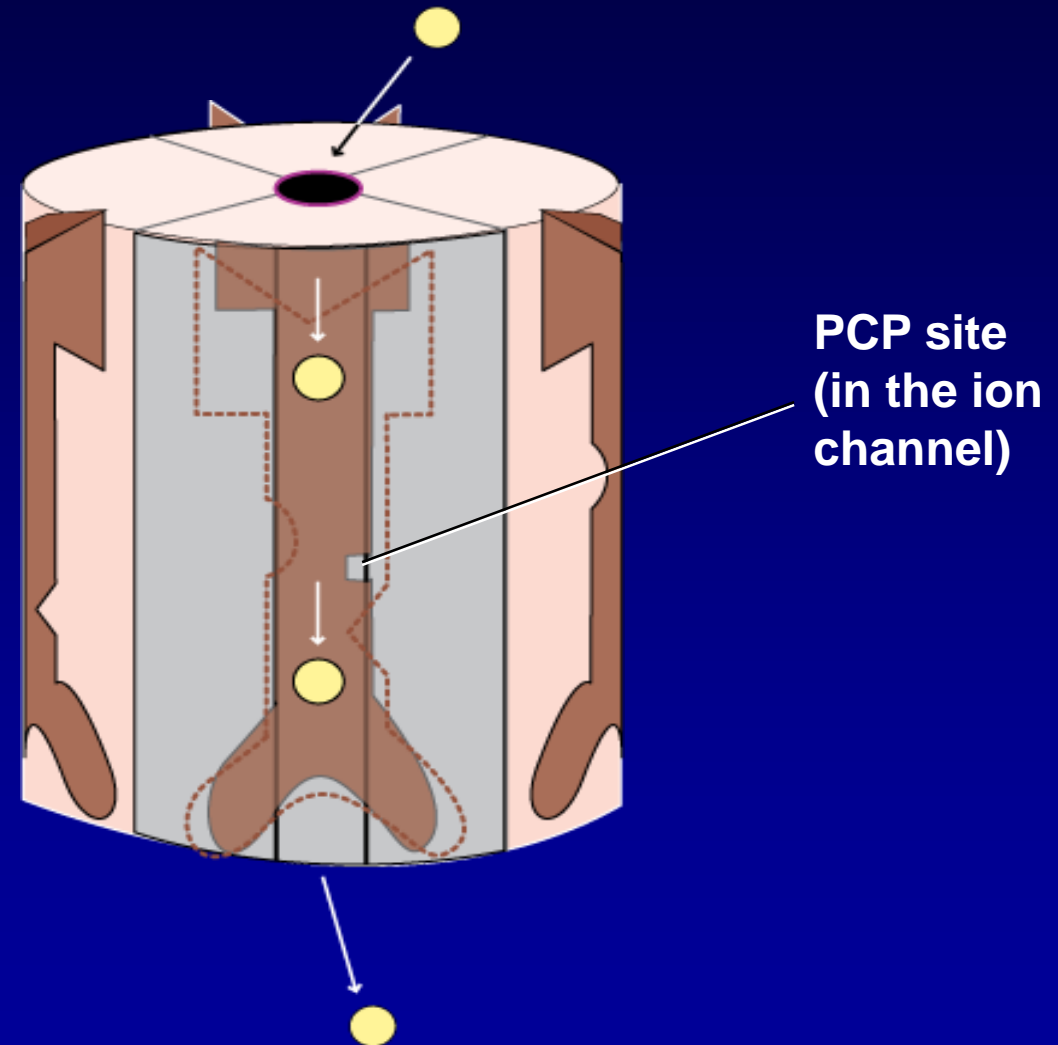
Anhedonia

Suicidal
ideation

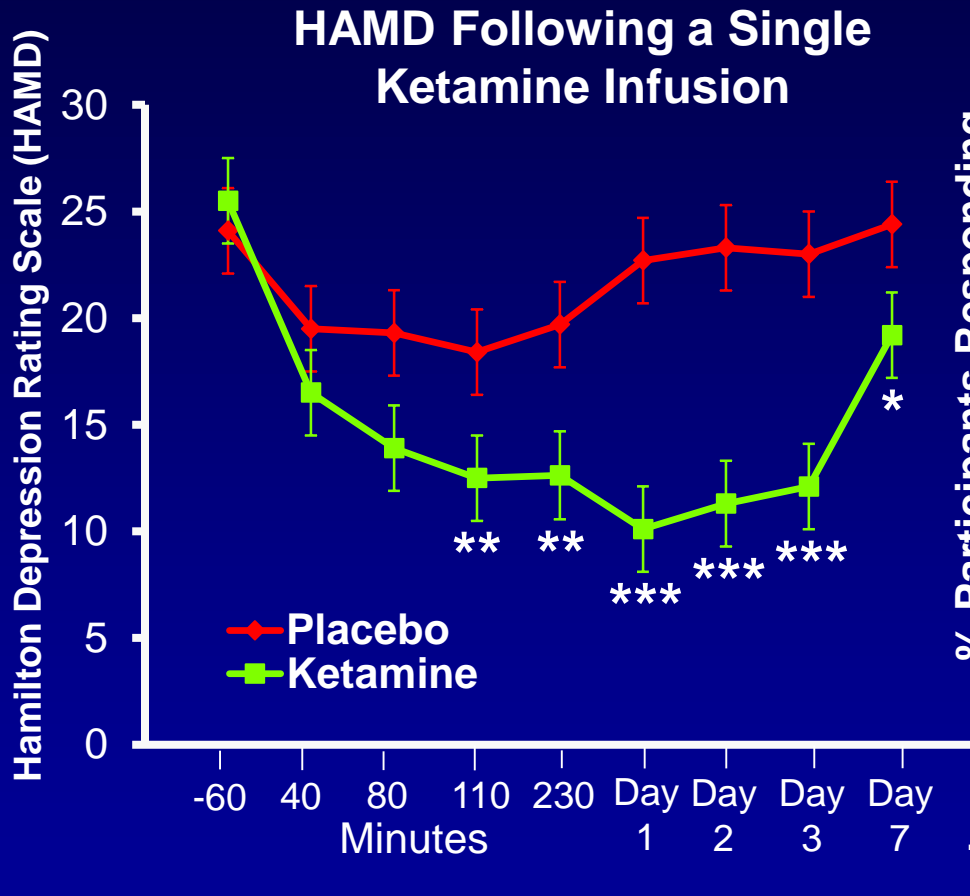
Normal
Sleep/
Cognition

Site of Action of Ketamine: Binds to Open Channel at PCP Site to Block NMDA Receptor

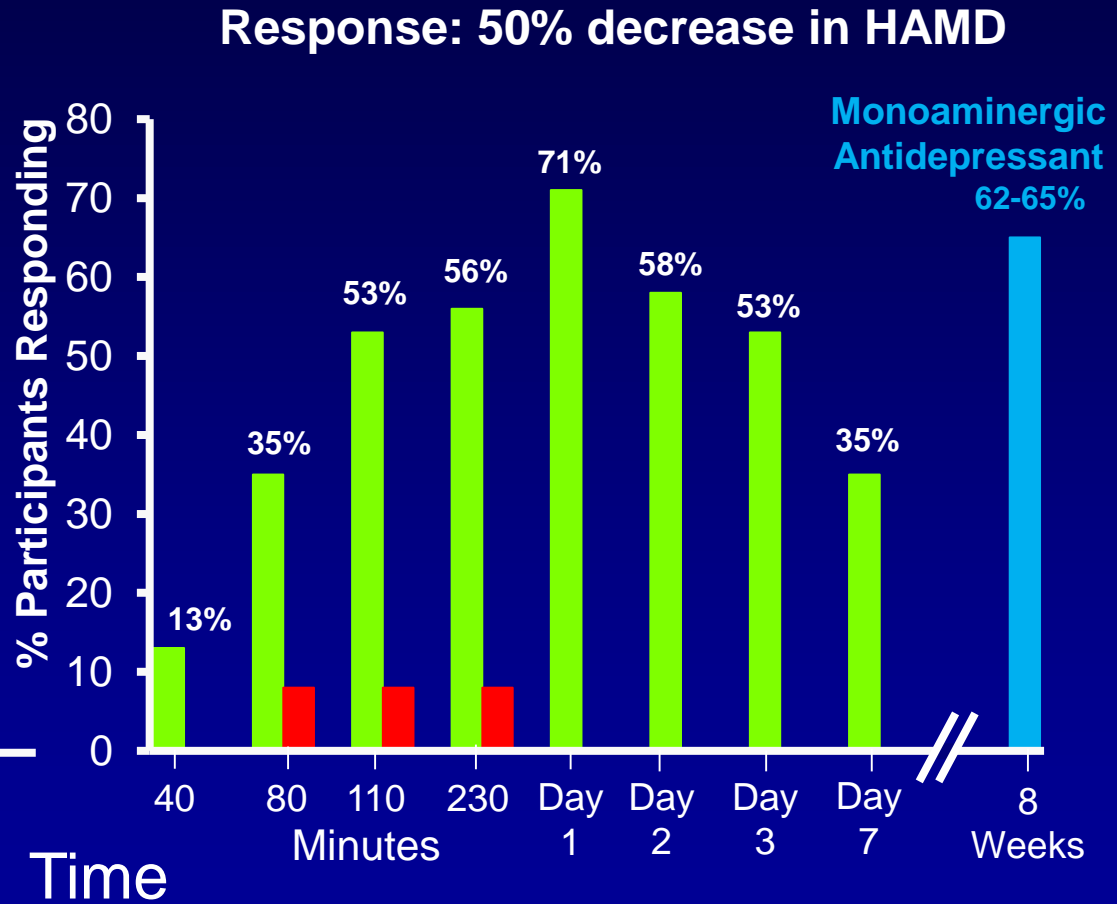
- Synonyms: Ketalar®, K, Special K, Vitamin K, Lady K,
- Source: Available by prescription only
- Drug Class: Dissociative anesthetic
- Medical and Recreational Uses:
 - In veterinary as a tranquilizer
 - Diagnostic and surgical procedures
 - Recreationally used
- Bioavailability
 - Intravenous: 100%
 - Intramuscular: 93%
 - Intranasal: 25-50%
 - Oral: 20%
 - Half-life Ket 2 hs, Norket 3-5 hs



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

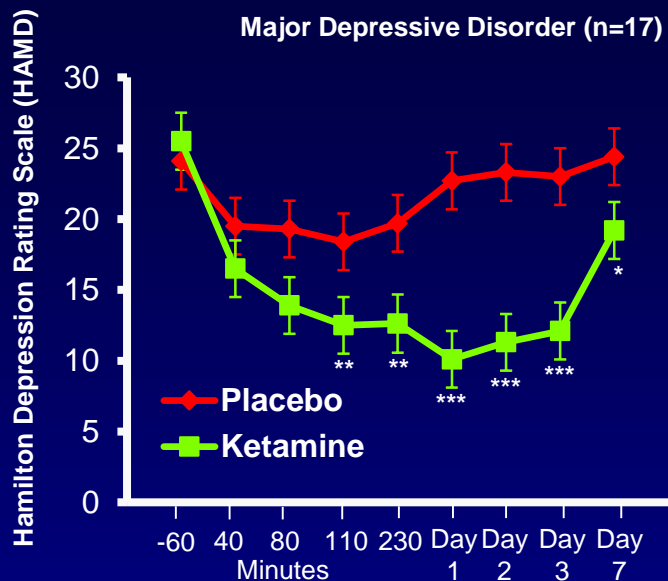


Zarate et al. Arch Gen Psychiatry 2006

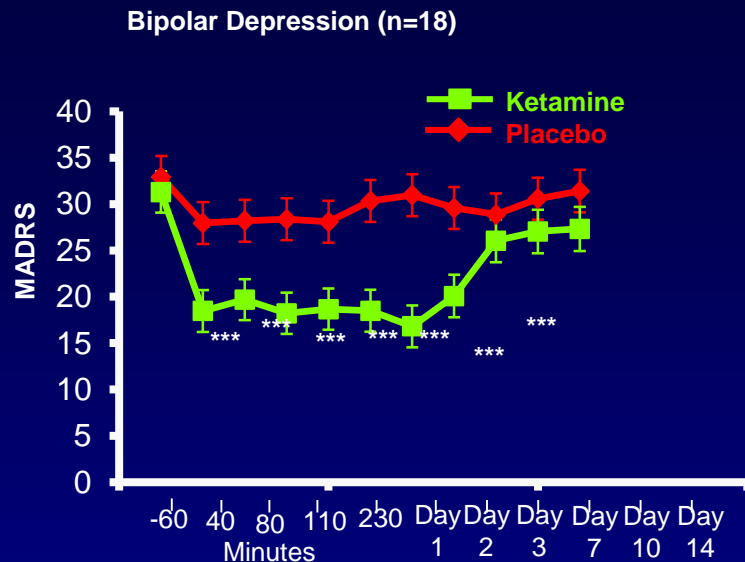


***p<0.001, **p<0.01, *p<0.05

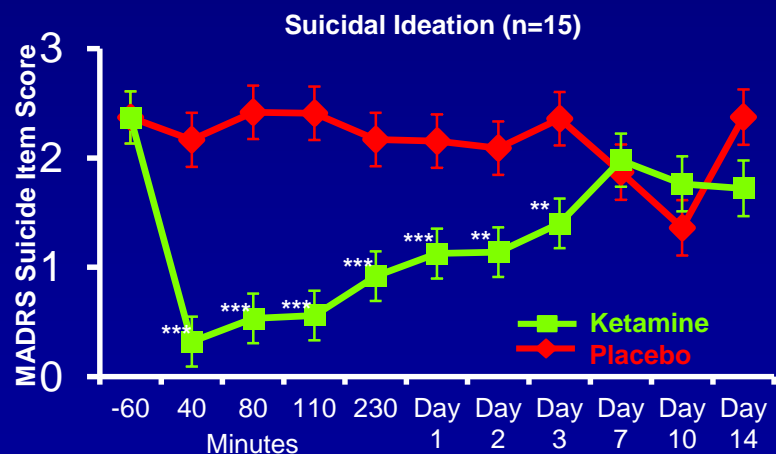
Rapid antidepressant, antisuicidal, and antianhedonic effects of Ketamine in Treatment Resistant Depression



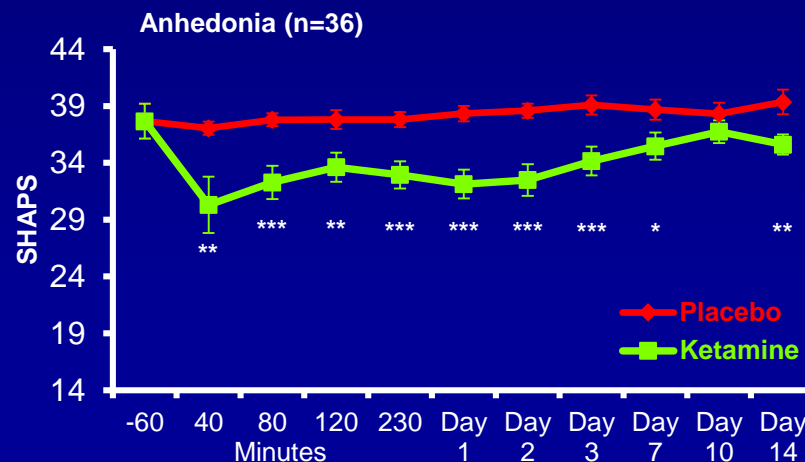
Zarate et al. Arch Gen Psychiatry 2006



Diazgranados et al. Arch Gen Psych 2010

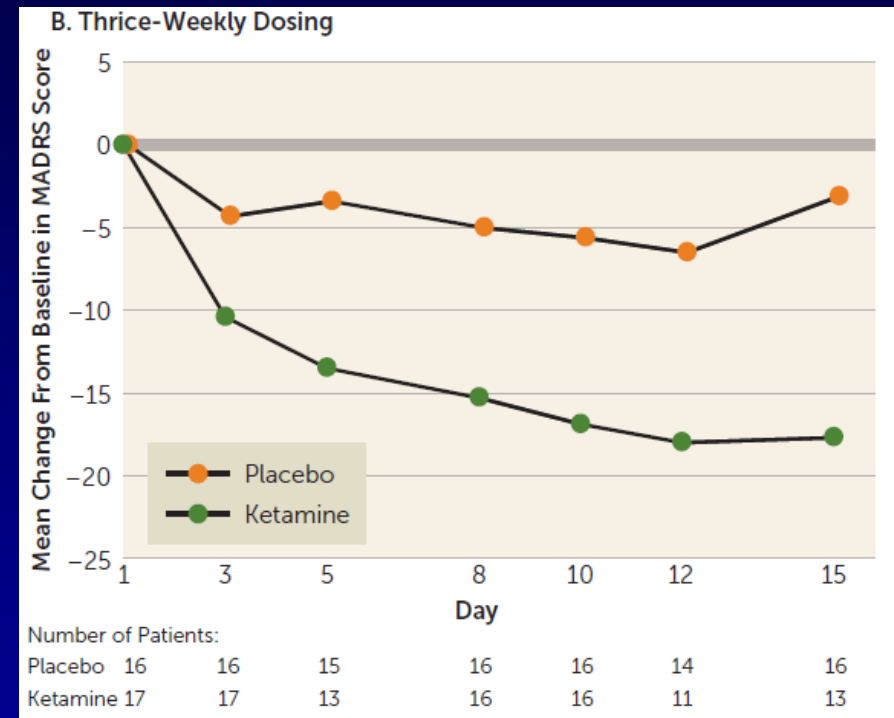
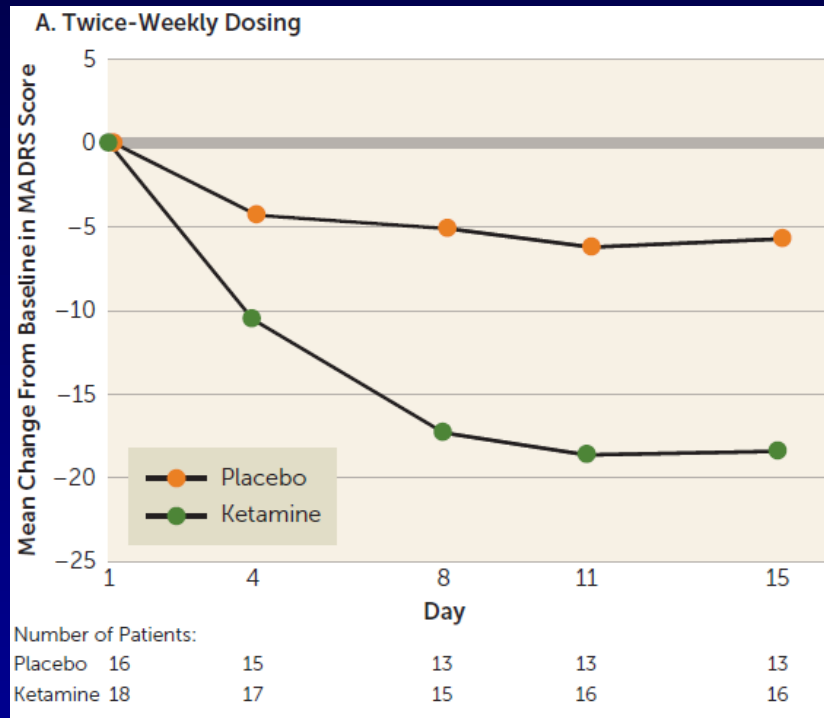


Zarate et al., Biological Psychiatry 2012



Lally et al., Translational Psychi 2014

Change in MADRS Score, by Dose Frequency, From Baseline Through Day 15 of the Double-Blind Phase in Study of I.V. Ketamine in TRD



Singh et al. Am J Psych 2016

What is Suicide?

Suicide in the News



From April 11, 2016:

Canadian First Nation Declares State Of Emergency Over Suicide Attempts

“The CBC reports that about 2,000 people live in the community. **On Saturday night, according to Chief Bruce Shisheesh, 11 people attempted suicide....**”



The Washington Post

November 5, 2015:

A group of middle-aged whites in the U.S. is dying at a startling rate

“The mortality rate for white men and women ages 45-54 with less than a college education increased markedly between 1999 and 2013, most likely because of problems with **legal and illegal drugs, alcohol and suicide**, the researchers concluded. Before then, death rates for that group dropped steadily, and at a faster pace.

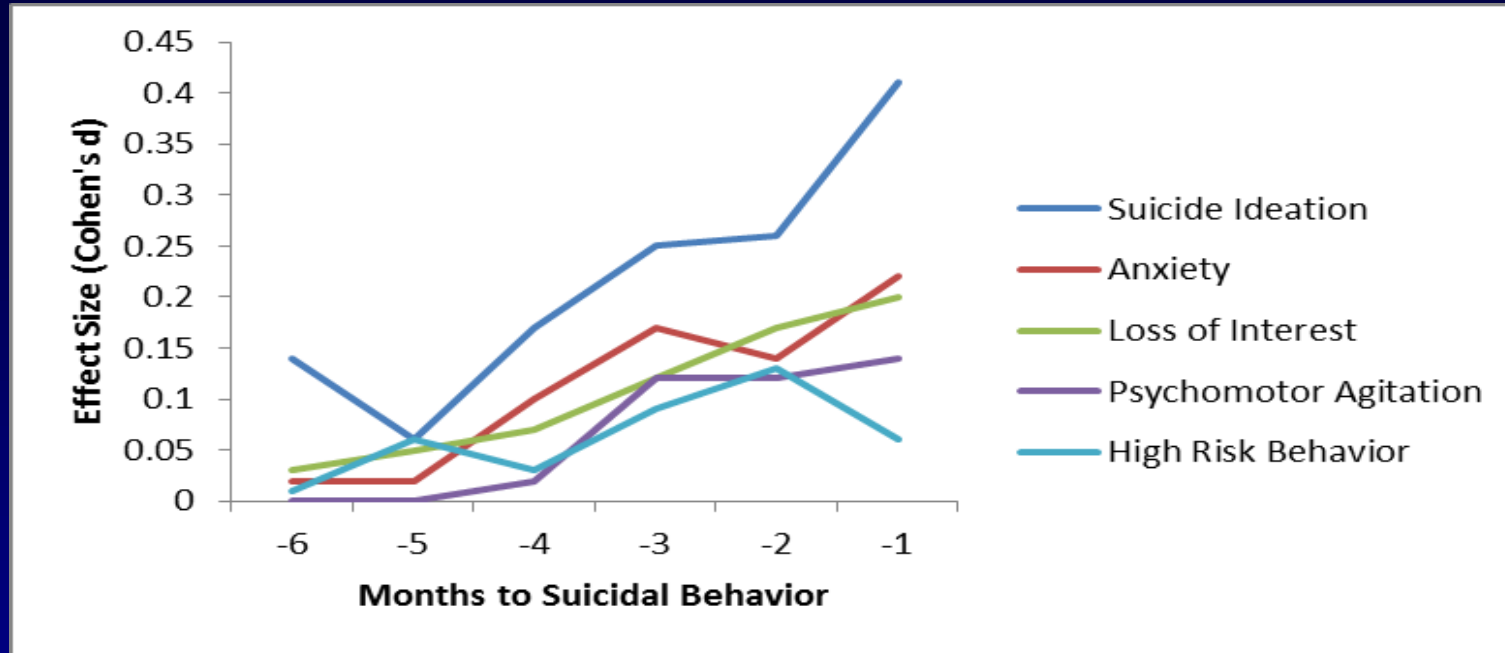
An increase in the mortality rate for any large demographic group in an advanced nation has been virtually unheard of in recent decades, with the exception of Russian men after the collapse of the Soviet Union.”

Risk factors for suicide

Multifactorial

- Previous suicide attempts
- **Major depression or bipolar disorders**
- Comorbid abuse of alcohol or drugs
- **Multiple comorbidity**
- Losses, deaths, shame, poverty, disability
- **Social isolation, unmarried**
- Lack of access to clinical care
- **Access to firearms, toxins, medicines**

Acute Risk Factors Before Suicide Attempt or Death



- Patients who attempted or died by suicide in STEP BD
- Suicidal ideation and loss of interest significantly increased in severity in months before suicidal behavior. Anxiety may be similarly elevated
- No change in agitation or high risk behavior

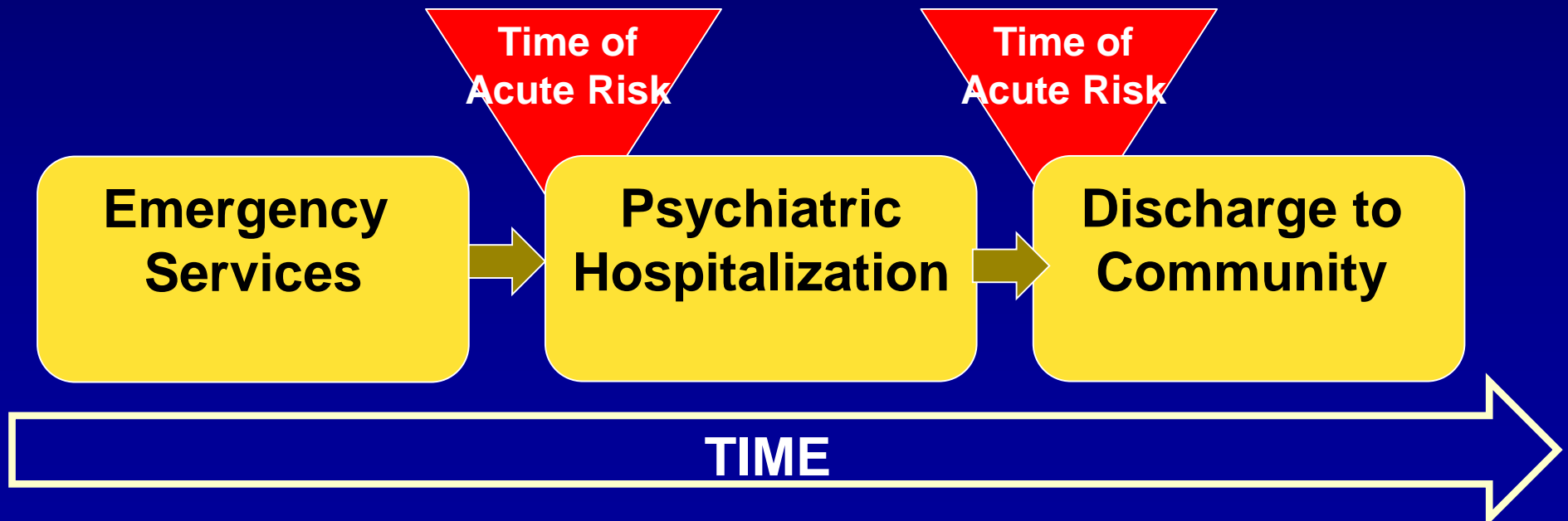
Current Treatments

- Only FDA approved medication for suicidal behavior: clozapine for patients with schizophrenia
- **No FDA approved medication for suicidal thoughts**
- Lithium not FDA approved but evidence of reducing suicidal behaviors
- **Black box warning on SSRIs may have led to decreased depression treatment in adolescents and adults**

Ting et al., 2012; Deisenhammer et al. J Clin Psychiatry 2009; Larkin et al. Crisis 2008; Janofsky J Am Acad Psychiatry Law 2009; Jick et al. JAMA 2004; Diazgranados et al. J Clin Psych 2010; Lu et al., 2014

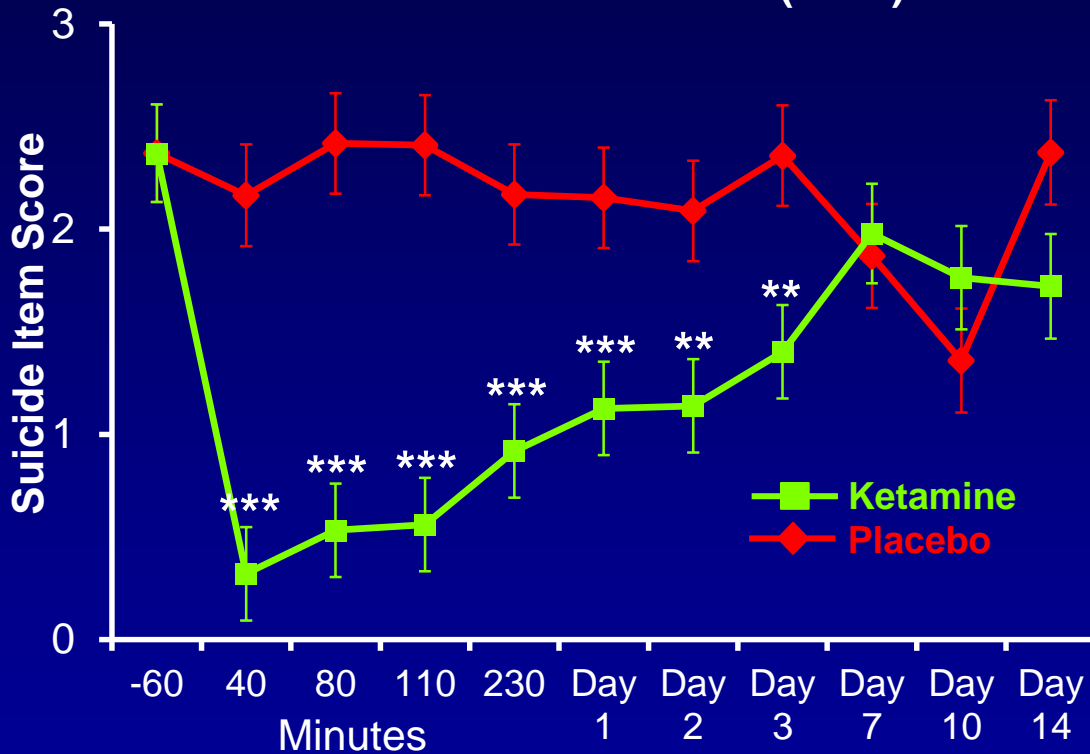
Critical Windows of Suicide Risk

- Wk after psychiatric admission and wk after psychiatric discharge
- **First 9 days of starting an antidepressant**
- Provide treatment across “critical window” from emergency/inpatient treatment to outpatient follow-up
- Reduction in risk can allow time to connect patient to long-term resources (i.e. medication management, psychotherapy)

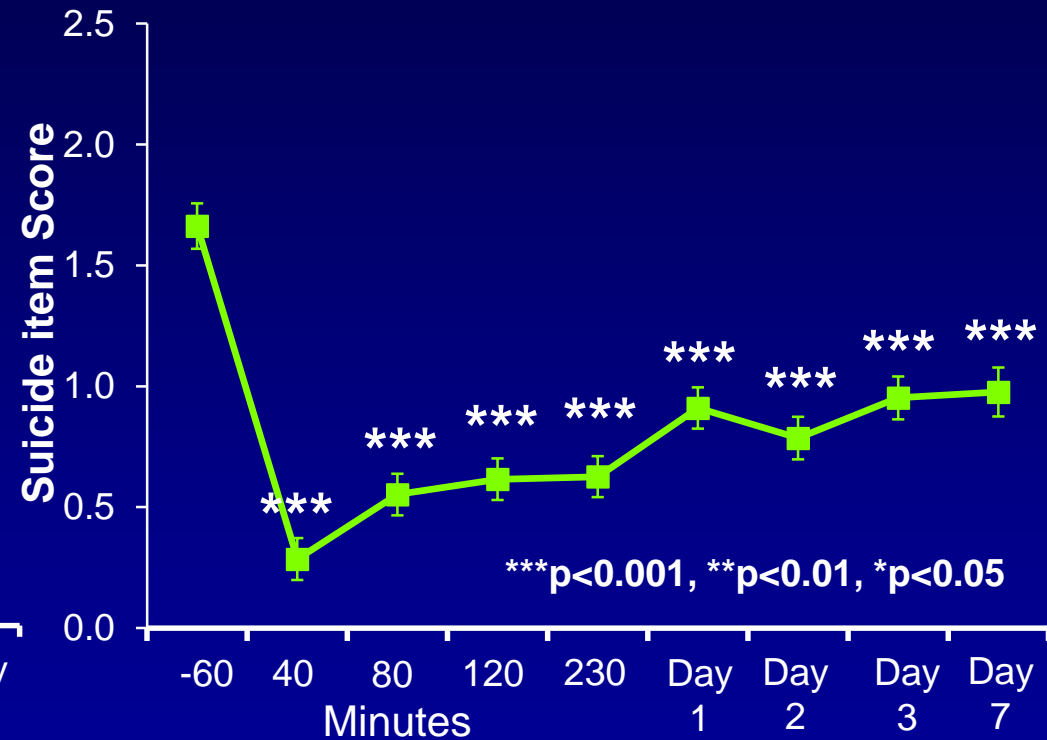


Rapid Decreases in Suicidal Ideation (SI) with Ketamine in MDD and BD

Treatment Resistant BD
MADRS Suicide Item (n=15)



Combined MDD+BD
HAM-D Suicide Item (n=66)

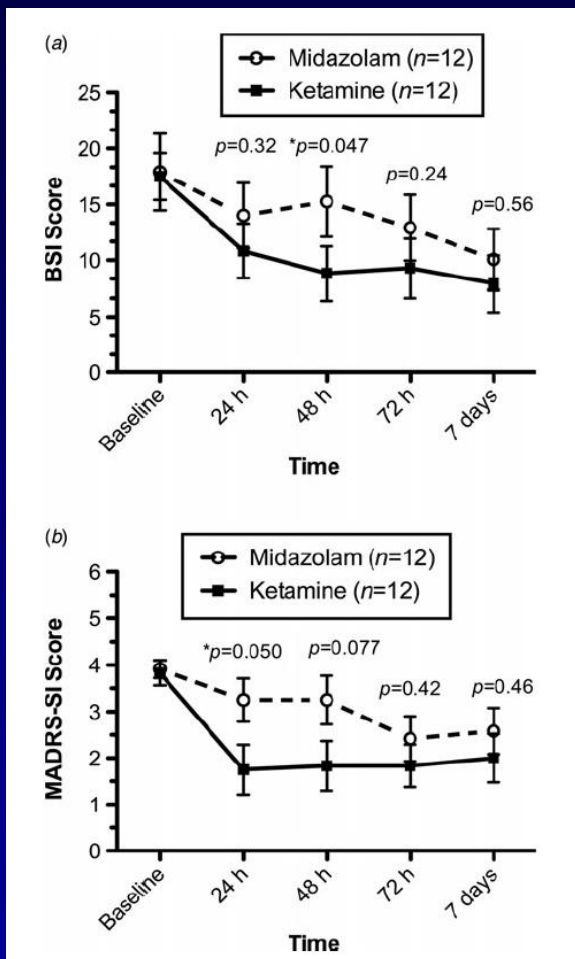


Zarate et al., Biological Psychiatry 2012

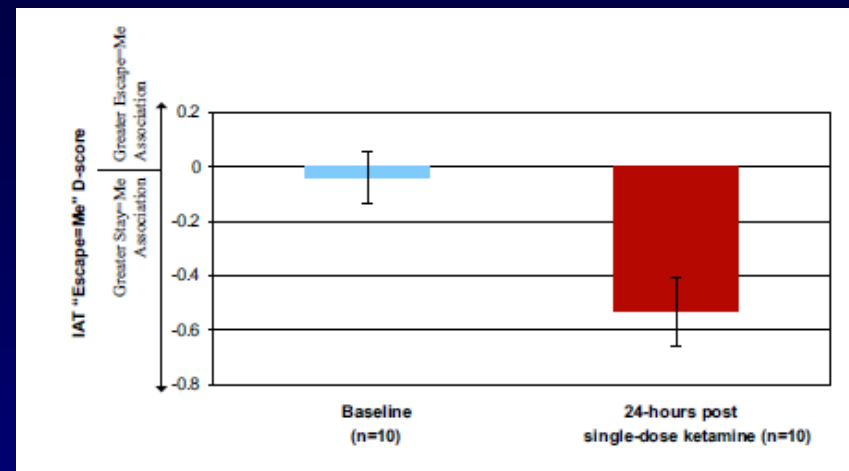
Potential to revolutionize management of acute suicidality



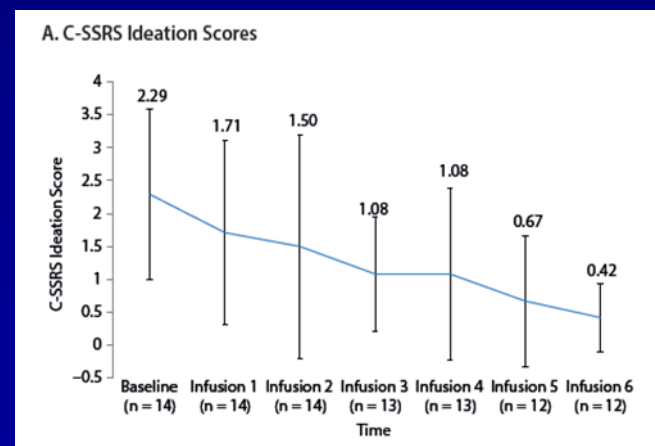
Literature on Suicide and Ketamine



Murrough 2015; RCT of ketamine vs midazolam in actively suicidal pts

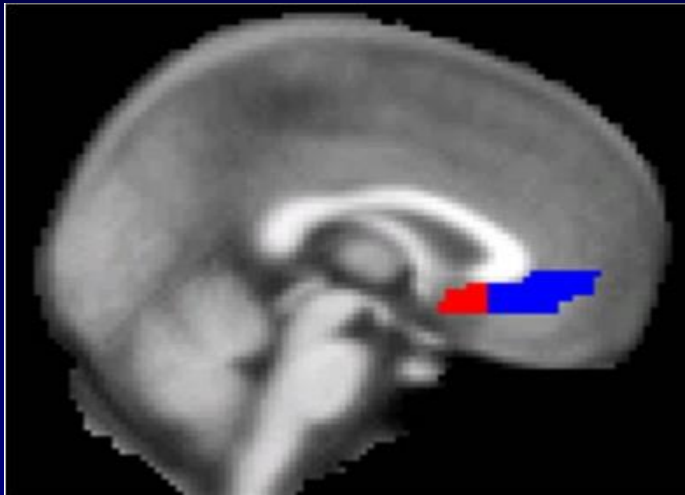


Price 2009, 2014; Changes on suicide implicit association test (IAT)

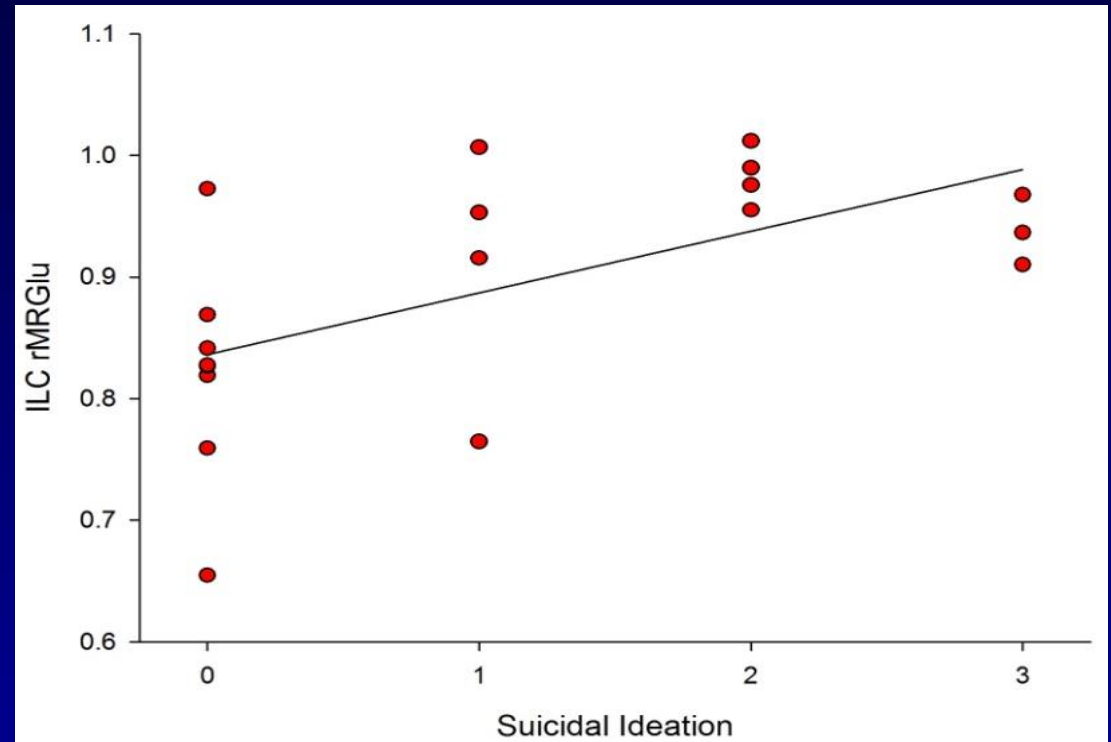


Ionescu 2016; Repeat dose open-label ketamine

rMRGlu in infralimbic cortex associated with suicidal ideation and its reduction in MDD



Regional placement of the infralimbic cortex (red) and subgenual cingulate cortex (blue)



Significant correlation between baseline suicidal ideation and rMRGlu in the infralimbic cortex ($r = .59$, $p = .007$), but not depression ($p = .79$).

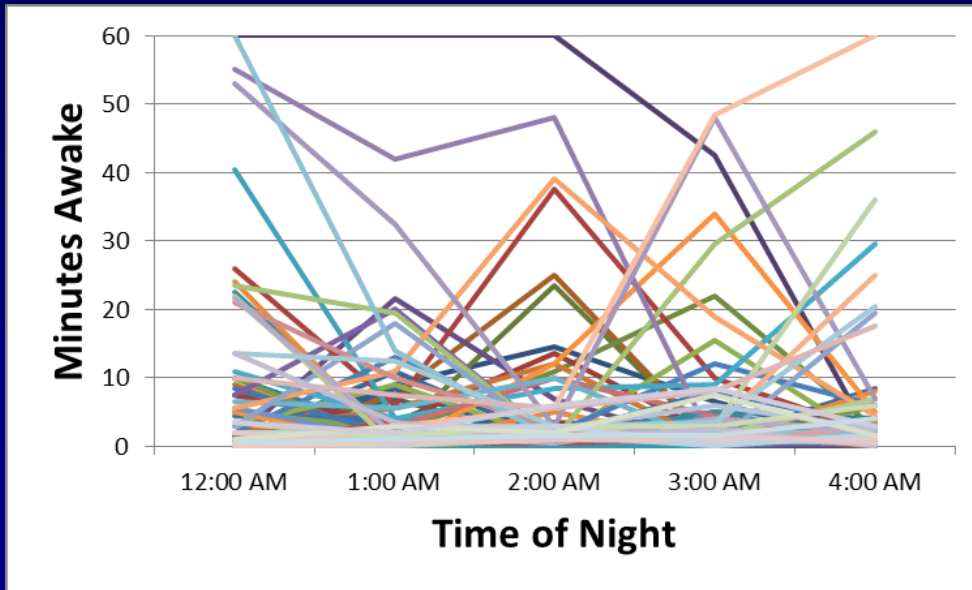
Significant association between reduction in suicidal ideation and decreased rMRGlu in the infralimbic cortex after ketamine ($r = .54$, $p = .02$), but not depression ($p = .69$)

Suicide Ideation and Sleep

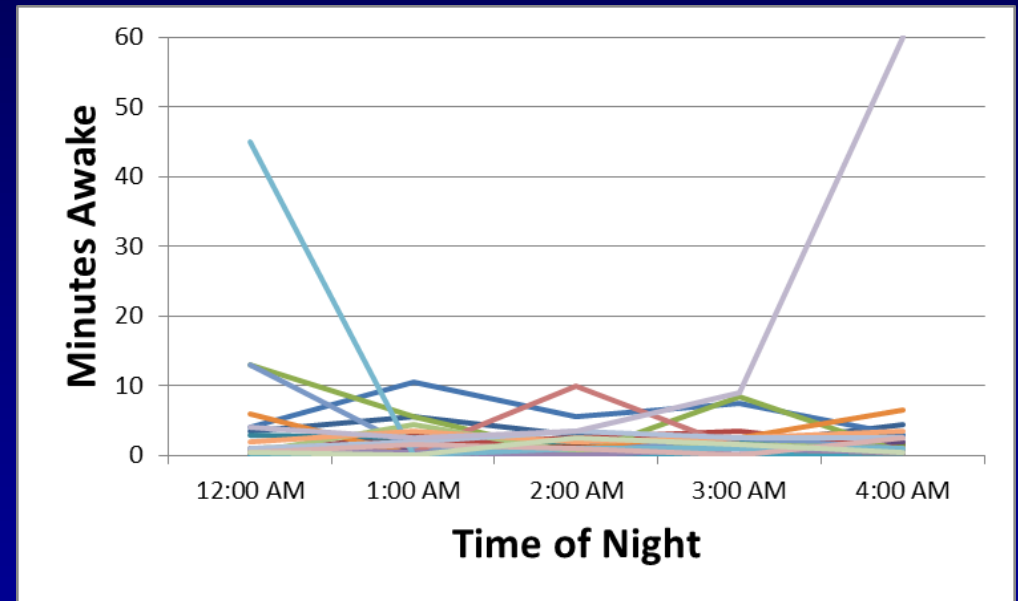
- Difficulties with sleep is associated with later suicide risk
- Sleep represents an important, potential modifiable acute risk factor for suicide
- Time period of 12-4:59 am may be a particularly high-risk time for suicide

Wakefulness in Depressed Patients and Healthy Controls

Wakefulness in Depressed Patients (n = 65)



Wakefulness in Healthy Controls (n = 22)

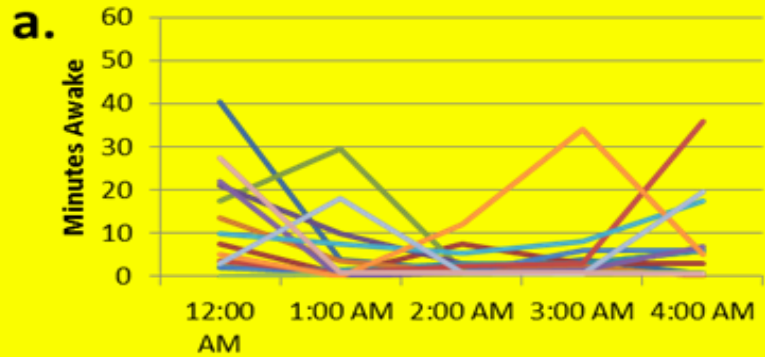


Data collected using polysomnography

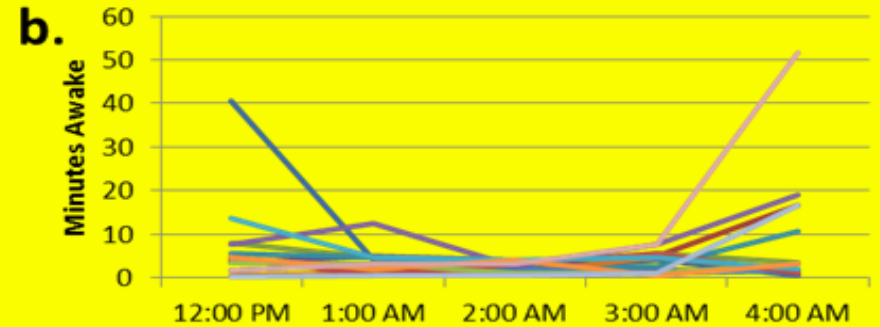
Time period of 12-4:59 am may be a particularly high-risk time for suicide (Perlis, 2014).

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

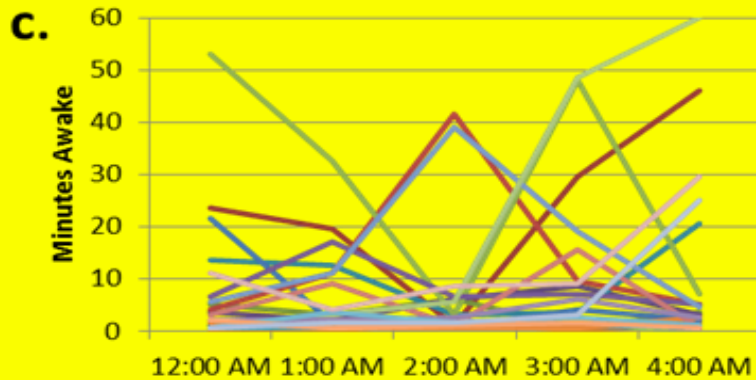
Participants with Antisuicidal Response Post Ketamine



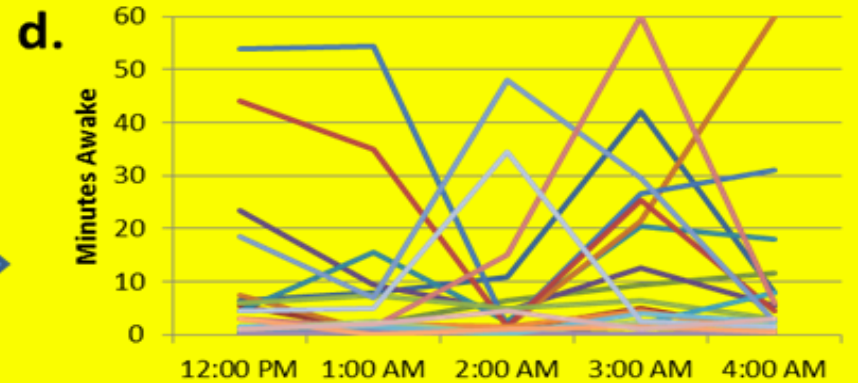
Ketamine
Infusion



Participants with No Antisuicidal Response Post Ketamine



Ketamine
Infusion



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 antisuicidal treatments**
 - Evaluate ketamine and sleep deprivation in suicidal individuals
 - Identify neural correlates of antisuicidal response



Environment, psychosocial stress, personality, trauma, support systems,

Mark O. Hatfield Clinical Research Center

Intramural Research Program/NIMH



Research staff
7SE Unit staff
OP4
7SW sleep lab
Section on Neuroimaging
Affective Pathophysiology Lab
NCF staff
Intramural research pgm
Office of the Clinical Director/NIMH
MEG CORE facility
Anesthesia
Patient and their families

Research studies:

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