

# Clinical Use of Ketamine in Psychiatry

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## Disclosure Information

- I have no financial relationships to disclose.
- I will discuss the off label use of ketamine in this presentation.

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## Mental health disorders impact the population worldwide.

1.5 billion people

64 Million Americans

1.1 Million Minnesotans

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Depression is the leading cause of disability worldwide.

400 million people  
\$210 billion  
\$12 billion in lost workdays

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Psychiatrists face 3 epidemics:

Depression  
Suicide  
Opioid Epidemic

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Psychiatrists face 3 epidemics:

Depression  
Suicide  
**Ketamine**  
Opioid Epidemic

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## Outline

- Historical overview of antidepressant development and treatment-resistant depression
- Review of research on ketamine for depression
- Ketamine mechanism(s) of action → new developments on safety
- Future directions

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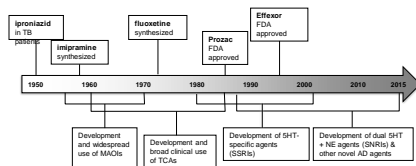
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## All antidepressant pharmacotherapies target the monoaminergic system.




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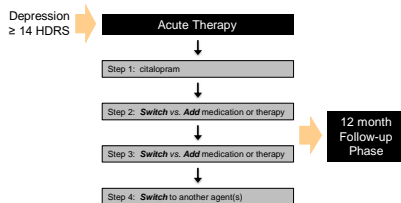
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## STAR\*D Study Design (Sequenced Treatment Alternatives to Relieve Depression)




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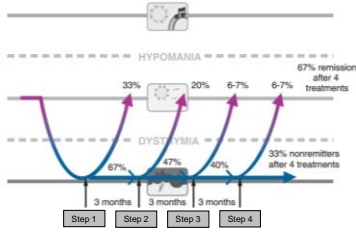
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STAR\*D Results




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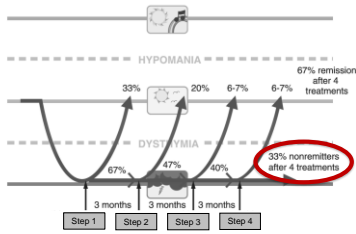
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STAR\*D Results




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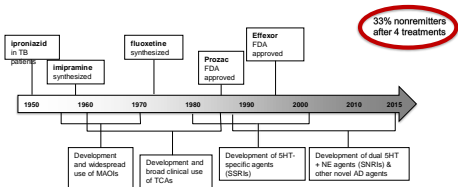
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All antidepressant pharmacotherapies target the monoaminergic system.




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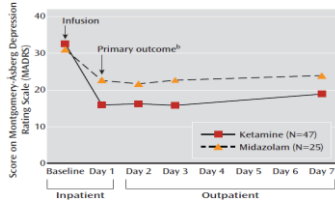
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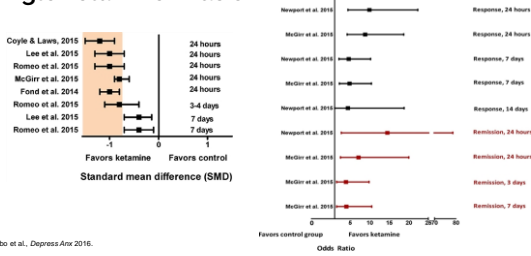


### Single Ketamine Infusion



Murrough et al., Am J Psychiatry 2013

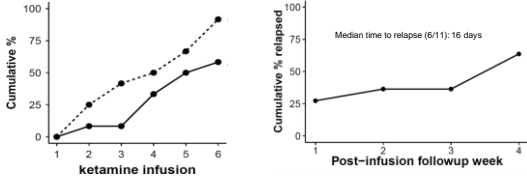
### Comparison of outcomes in meta-analyses of single ketamine infusions



Bobo et al., Depress Anx 2016.

### Repeated-infusion studies of ketamine

### Repeated infusions increase response & durability.



Shiroma et al., *J Affect Disord* 2014

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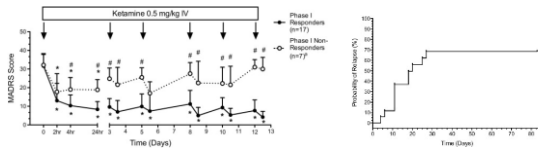
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### Repeated infusions increase response & durability.



Munough et al., *Biol Psychiatry* 2013.

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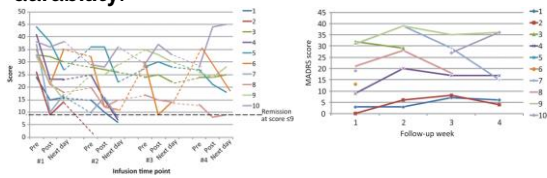
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### Repeated infusions increase response & durability.



Rasmussen et al., *J Pharmacol* 2013.

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## Ketamine for Suicidal Ideation

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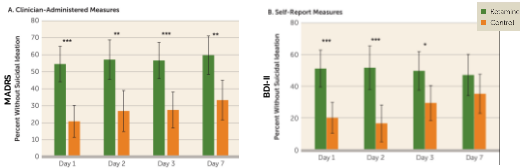
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A greater proportion of patients who received ketamine were without suicidal ideation compared to placebo.



Wilkinson ST, et al. *Am J Psychiatry*. 2017.

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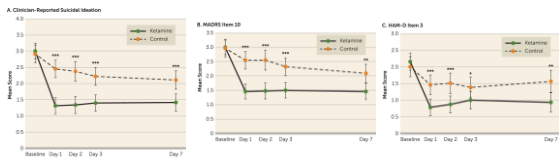
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Effect of a single infusion of ketamine on suicidal ideation per clinician administered scales.



Wilkinson ST, et al. *Am J Psychiatry*. 2017.

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### Effect of a single infusion of ketamine on suicidal ideation per self-reported scales.



Wilkinson ST, et al. *Am J Journal Psychiatry*, 2017.

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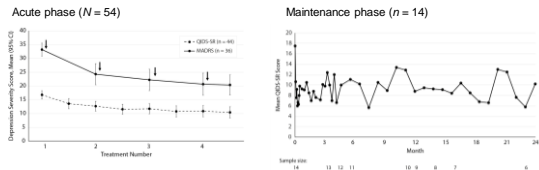
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### Continuation & Maintenance

#### Longer-term outcomes in patients receiving maintenance ketamine infusions.



Wilkinson ST, et al. *J Clin Psychiatry*, 2018.

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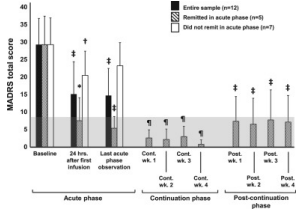
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**Acute + continuation ketamine infusions prolong depression remission.**



Vande Voort, et al. J Affective Disorders, 2016.

**Acute + continuation ketamine infusions prolong depression remission.**

Patient	Age, y	Sex	Unipolar or Bipolar	No. Maintenance Treatments	No. Total Treatments	Total Length of Treatment, wk	Baseline HDR-II	Postacute Treatment HDR-II	Maintenance HDR-II (range)	Final HDR-II	Outcome
A	56	F	Unipolar	8	16	49	32	18 (13-24)	17	Continuing ketamine at end of study	
B	50	F	Unipolar	6	12	38	8	34 (29-38)	23	Continuing ketamine at end of study	
C	55	F	Unipolar	13	21	19	37	24 (22-30)	29	Continuing ketamine at end of study; transitioned to intranasal ketamine	
D	69	M	Unipolar	38	25	49	23	12 (10-18)	11	Continuing ketamine at end of study	
E	61	F	Unipolar	4	10	8	30	25 (24-28)	28	Discontinued ketamine due to loss of effect; discontinued	
F	60	F	Unipolar	2	10	6	27	20 (17-22)	22	Discontinued ketamine due to loss of effect; discontinued	
G	35	F	Bipolar	14	24	28	45	15 (13-20)	27	Discontinued ketamine due to loss of effect	
H	60	F	Unipolar	8	16	10	38	22 (20-45)	34	Discontinued ketamine due to loss of effect	
I	31	F	Bipolar	45	51	36	38	26 (19-38)	35	Discontinued ketamine due to perceived side effects	
J	46	F	Bipolar	3	11	23	37	29 (26-29)	25	Discontinued ketamine for unclear reasons	
N	41	F	Unipolar	12	20	38	58	47 (36-45)	34	Discontinued ketamine for unclear reasons	

Baseline HDR-II is the HDR-II score before the first acute ketamine treatment. Postacute Treatment HDR-II is the score after the initial acute course of 4 or 8 infusions. Maintenance HDR-II is median score throughout maintenance treatments, along with the range in HDR-II. The Final HDR-II is the HDR-II score before the last infusion received by the patient before discontinuing ketamine or the last documented score for those continuing.

Archer, et al. J Clin Psychopharm, 2018.

**Summary of reports describing maintenance ketamine infusions.**

	Wilkinson (2017)	Archer (2018)	Messer (unpublished)
Subjects	14	11	45
Mean No. Maintenance Treatments (SD)	25 (10.5)	12	8.6 (8.0)
Length between treatments (weeks)	3.2	1.95	2.8
Baseline score	17 (QIDS)	38.2 (BDI-II)	Not available
Final score	10.5 (QIDS)	26.8 (BDI-II)	Not available

### Ketamine Mechanism of Action

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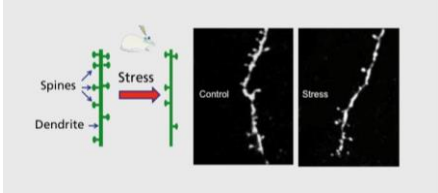
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Chronic stress causes neuronal atrophy in the rodent prefrontal cortex.



Duman RS. Dialogues CNS. 2014 Mar; 16(1): 11-27.

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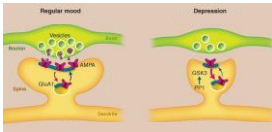
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Synaptogenic model of depression as a form of chronic stress.



Duman RS. Science 2012;338:68-72

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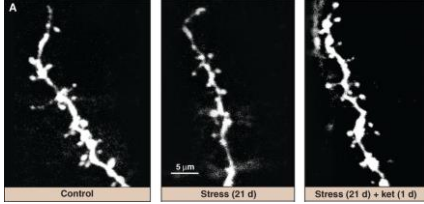
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**Ketamine rapidly reverses the effects of chronic stress.**



Duman RS. Science 2012;338:68-72

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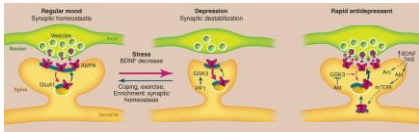
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**Synaptogenic Model of Chronic Stress and Treatment Response**



Duman RS. Science 2012;338:68-72

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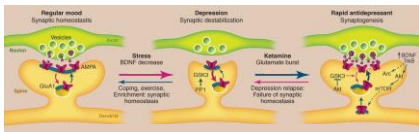
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**Depression, as a syndrome of chronic stress, is treated by ketamine.**



Duman RS. Science 2012;338:68-72

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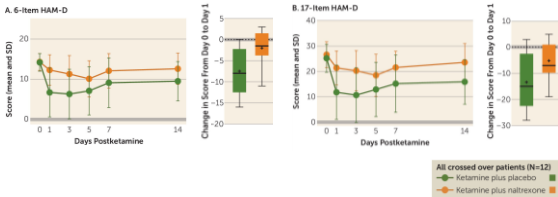
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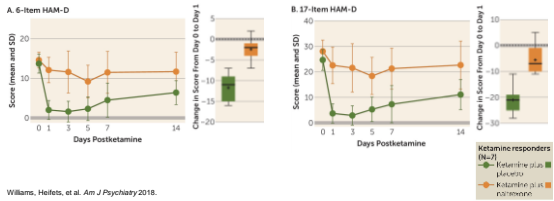
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### Naltrexone reduces antidepressant effects of ketamine compared to placebo. (N = 12)



Williams NR, Helfrich BD, et al. *Am J Psychiatry* 2018.

### Naltrexone blocks antidepressant effects in ketamine-responders. (n = 7)



Williams, Helfrich, et al. *Am J Psychiatry* 2018.

Where are we now?



**APA recommends 7 components for evaluating appropriateness of ketamine treatment.**

- Comprehensive diagnostic evaluation
- Objective measurement of baseline symptoms
- Thorough history of antidepressant treatment
- Review of medical systems
- Physical exam and laboratory screening
- Careful review of past medical and psychiatric records
- Informed consent process

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**MN Ketamine Task Force**

- Registry
- Development of a state-wide community standard of practice
- Creation of an evidence-based treatment algorithm
- Informed recommendations on dose titration, monitoring, transitioning to alternative treatment modalities

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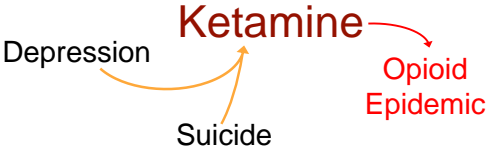
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**Psychiatrists face 3 epidemics:**




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Thank you.

Please email me if you are interested in joining MN Ketamine Task Force:

albot002@umn.edu

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