Treatment of Major Depression and Unmet Needs

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Matthew Macaluso, D.O. has conducted clinical trials research as principal investigator for the following pharmaceutical companies over the last twelve months:

Acadia, Allergan, Alkermes, AssureRx/Myriad, Boehringer-Ingelheim, Eisai, Lundbeck, Liva Nova, Janssen, Neurim, Otsuka, SAGE pharmaceuticals, Suven

All clinical trial and study contracts were with and payments made to the the University of Alabama at Birmingham.

From April 2019 to June of 2020, Dr Macaluso was a member of the speaker bureau for Janssen
pharmaceuticals (Spravato/esketamine).

Dr Macaluso has also received royalties from Springer Nature for his work as co-editor of the textbook titled Antidepressants: From Biogenic Amines to New Mechanisms of Action. This book was published in May of 2019.

Pre-Lecture Exam Question 1

Limitations of the STAR*D trial include

a. Lack of a placebo group
b. Patients had the option of not participating in a randomization
c. Lack of inclusion of common augmenting agents such as antipsychotics
d. All of the above

3

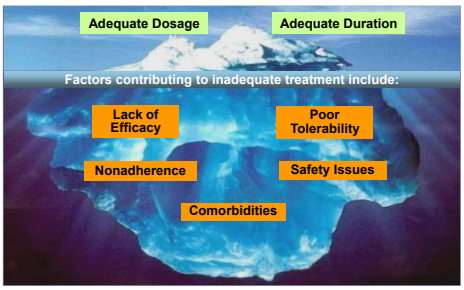
Question 2

Compared to medication augmentation in the STAR*D trial, the addition of cognitive therapy was

a. significantly less effective
b. significantly more effective
c. about equally effective
d. not studied

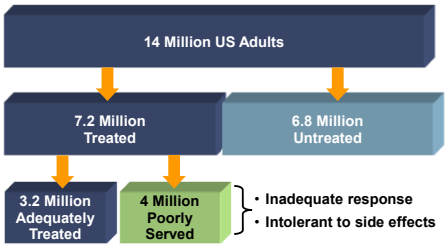
4

In MDD, "Adequate" Treatment Is Difficult to Achieve[1-3]



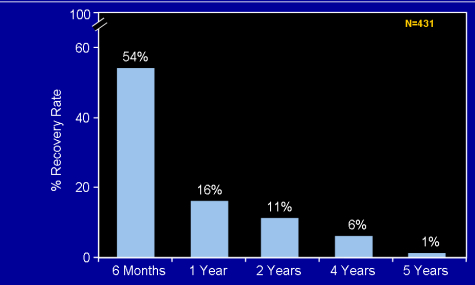
1. Nemeroff CB. *Depress Anxiety*. 1996/1997;4(4):169-181; 2. Oquendo MA et al. *J Clin Psychiatry*. 2003;64(7):825-833; 3. Oquendo MA et al. *Am J Psychiatry*. 1999;156(2):190-194.

A Significant Percentage of Patients With MDD Remain Poorly Served



Kessler RC et al. *JAMA*. 2003;289(23):3095-3105.

Rates of recovery diminish with duration of major depressive episode

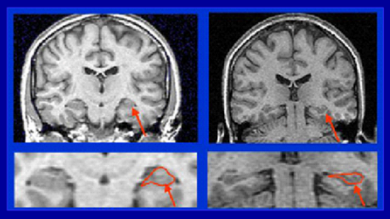


Recovery=8 weeks of Psychiatric Status Rating (PSR) 1 or 2.
Recovery=sustained remission.

Keller MB, et al. *Arch Gen Psychiatry*. 1992;49(10):809-816.

Brain atrophy in depression?

Atrophy of the Hippocampus in Depression



Bremner JD, et al. *Am J Psychiatry*. 2000;157(1):115-118.

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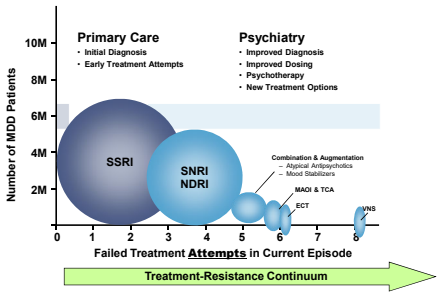
Current Treatment Practices in MDD



Kessler RC et al. *Arch Gen Psychiatry*. 2005;62(6):617-627; Kessler RC et al. *JAMA*. 2003;289(23):3095-3105; Herrmann RC et al. *Am J Psychiatry*. 1995;152(6):869-875.

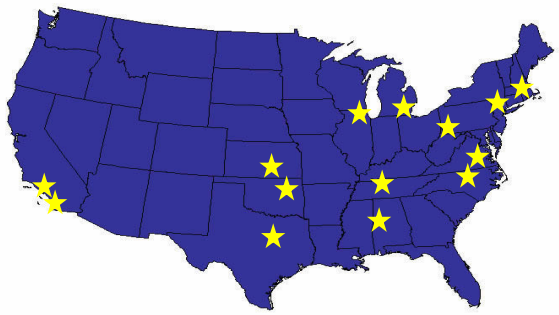
Sequenced Treatment Alternatives To Relieve Depression

STAR*D

National Institute of Mental Health

http://www.edc.gsph.pitt.edu/stard

STAR*D Regional Centers



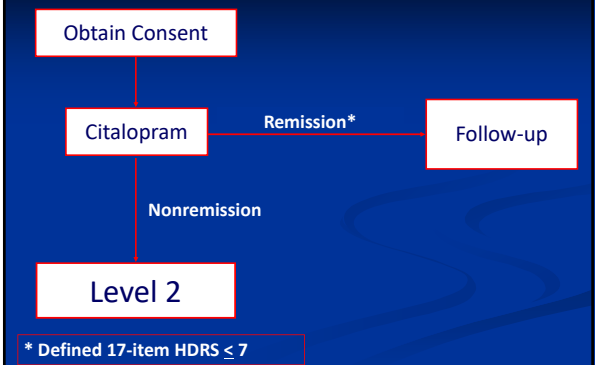
STAR*D: Patient Participants

- N = 4,000
- MDD, nonpsychotic
- Specialty and primary care
- Almost all co-morbidities

Treatment Duration:

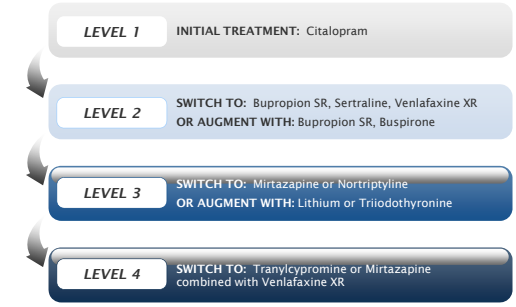
- 12 weeks at each level at highest recommended dose
- 1 year follow up after a satisfactory therapeutic response

Level 1

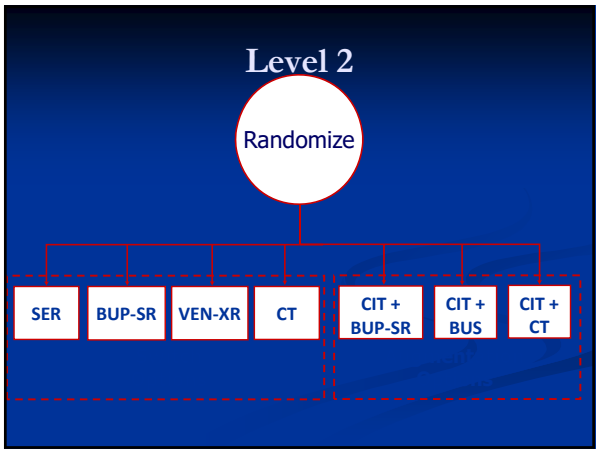


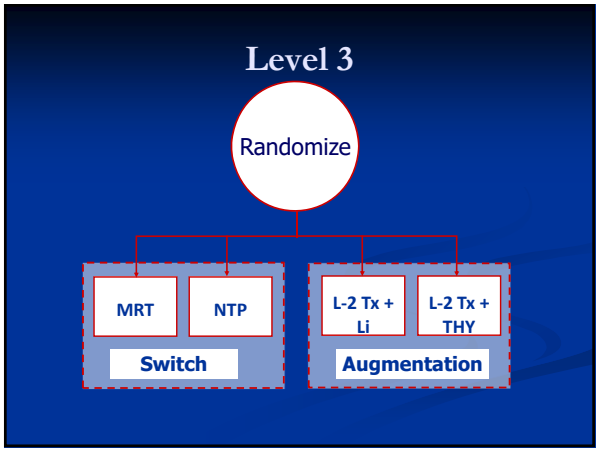
* Defined 17-item HDRS ≤ 7

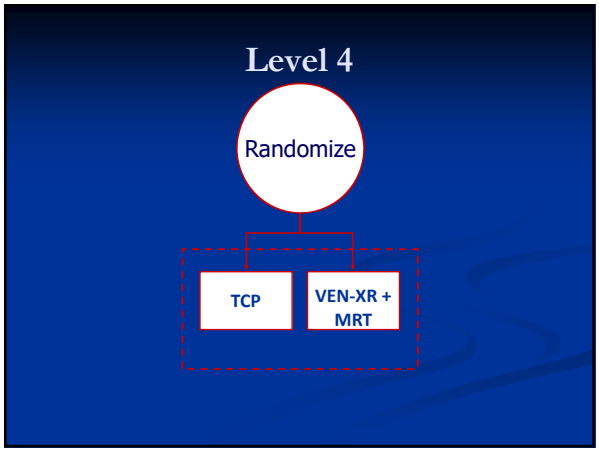
STAR*D Study Design Overview



Rush, 2006


Level 2
Randomize
SER
BUP-SR
VEN-XR
CT
CIT + BUP-SR
CIT + BUS
CIT + CT


Level 3
Randomize
MRT
NTP
Switch
L-2 Tx + Li
L-2 Tx + THY
Augmentation


Level 4
Randomize
TCP
VEN-XR + MRT

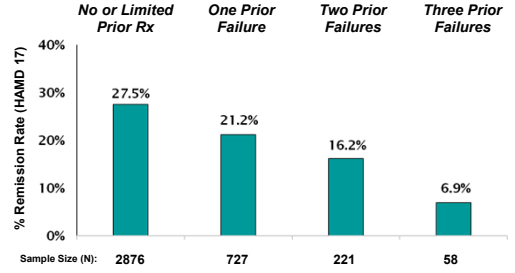
Remission Rates (RR)* in STAR*D by Treatment Level

Level	RR Range	% Average RR	% Original Population Still Symptomatic**
1	28	28	72
2	18-30	25	54
3	12-25	18	44
4	7-14	11	39

* Remission = a score of ≤7 on a 17-item Hamilton Depression Rating Scale.

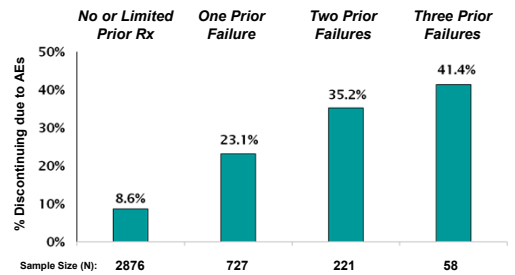
** Assumes every nonremitter went through the next treatment level rather than dropping out.

Acute Outcome Worsens with Increasing Number of Prior Treatment Failures



Trivedi et al. (Am J Psychiatry, 2006); Rush et al. (NEJM, 2006);
Fava et al (Am J Psychiatry, 2006); McGrath et al (Am J Psychiatry, 2006)

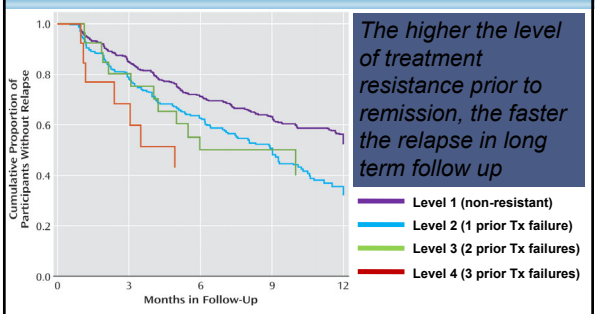
Discontinuation due to AEs Accelerates with Increasing Treatment Resistance



Trivedi et al. (Am J Psychiatry, 2006); Rush et al. (NEJM, 2006);
Fava et al (Am J Psychiatry, 2006); McGrath et al (Am J Psychiatry, 2006)

Relapse During Long-Term Follow-Up

STAR*D Study Results



The higher the level of treatment resistance prior to remission, the faster the relapse in long term follow up

- Level 1 (non-resistant)
- Level 2 (1 prior Tx failure)
- Level 3 (2 prior Tx failures)
- Level 4 (3 prior Tx failures)

Rush, (2006)

Currently Marketed Antidepressant Medications

Unmet needs

Limited and significant overlap in efficacy with small gain to switching between existing biogenic amine based antidepressants .

All Slow onset of action.

Newer drugs (SSRIs/SNRIs vs TCAs/MAOIs) have better tolerability and safety but not better efficacy.

Glutamate as a target neurotransmitter system

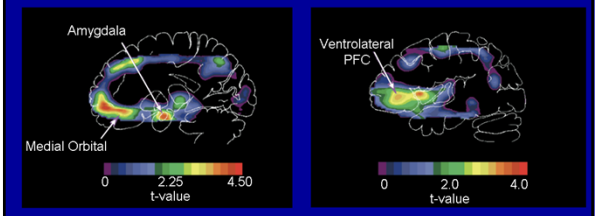
Major excitatory neurotranmitter in the brain:
"The Ying to the Yang of GABA"

Like GABA, found at 50% of all synapses in the brain.

Is circuits implicated in the pathophysiology of major depression

Regional blood flow abnormalities in patients with depression

Comparison of Patients With Depression With Positive Family History (n=13) and Healthy Controls (n=33)

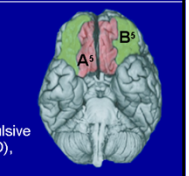


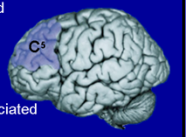
- Patients with depression had increased blood flow in amygdala and left medial and lateral orbital cortex, extending to ventrolateral PFC

Drevets WC, et al. *J Neurosci*. 1992;12(9):3628-3641.

Key brain areas involved in regulation of mood

- (A) Ventromedial prefrontal cortex (VMPFC)[1]
  - Modulates pain and aggression, and sexual and eating behaviors[2]
  - Regulates autonomic and neuroendocrine response
- (B) Lateral orbital prefrontal cortex (LOPFC)[3]
  - Activity is increased in depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), and panic disorder
  - Corrects and inhibits maladaptive, perseverative, and emotional responses
- (C) Dorsolateral prefrontal cortex (DLPFC)[4]
  - Cognitive control, solving complex tasks, and manipulation of information in working memory
  - Hypoactivity of DLPFC in depression has been associated with neuropsychological manifestation of depression

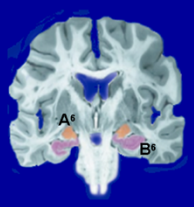




1. Öngür D, Price JL. *Cereb Cortex*. 2000;10(3):206-219.
2. Swanson LW. In: Björklund A, Hökfelt T, eds. *Handbook of Chemical Neuroanatomy*. 1983;1:124.
3. Drevets WC. *Annu Rev Med*. 1998;49:341-361.
4. MacDonald AW III, et al. *Science*. 2000;288(5472):1835-1838.
5. Davidson RJ, et al. *Annu Rev Psychol*. 2002;53:545-574.

Key brain areas involved in regulation of mood (cont.)

- (A) Amygdala: regulates cortical arousal and neuroendocrine response to surprising and ambiguous stimuli[1]
  - Role in emotional learning and memory
  - Activation of amygdala correlates with degree of depression[2]
  - Implicated in tendency to ruminate on negative memories[2]
- (B) Hippocampus: has a role in episodic, contextual learning and memory[3,4]
  - Rich in corticosteroid receptors[5]
  - Regulatory feedback to hypothalamic-pituitary-adrenal axis
  - Hippocampal dysfunction may be responsible for inappropriate emotional responses



1. Davidson RJ. *Psychophysiology*. 2003;40(5):655-665.
2. Drevets WC. *Curr Opin Neurobiol*. 2001;11(2):240-249.
3. Squire LR, Knowlton BJ. In: Gazzaniga MS, ed. *The New Cognitive Neurosciences*; 2000:765-779.
4. Fanselow MS. *Behav Brain Res*. 2000;110(1-2):73-81.
5. Reul JM, De Kloet ER. *J Steroid Biochem*. 1986;24(1):269-272.
6. Davidson RJ, et al. *Annu Rev Psychol*. 2002;53:545-574.

Hippocampus: The "weak link"?

- 5-HT and NE influence the balance between excitatory (glutaminergic) and inhibitory (GABAergic) activity in the prefrontal cortex and limbic system[1]
- Excitatory (glutaminergic) neurons from the prefrontal cortex have regulatory influence on the locus coeruleus (LC-NE) and the dorsal nuclei raphe (DNR-5-HT)[1]
- A combination of excessive excitatory input from the VMPFC and increased levels of glucocorticoids may have a "toxic" effect on the hippocampus[2]
- Hippocampal dysfunction may contribute to cognitive impairment and emotional and neuroendocrine dysregulation observed in MDD[2]

1. Paul IA, Skolnick P. *Ann N Y Acad Sci*. 2003;1003:250-272.
2. Sheline YI. *Biol Psychiatry*. 2000;48(8):791-800.

Antidepressant Effects of the CP-101,606 (NR2B NMDA Antagonist) versus Placebo

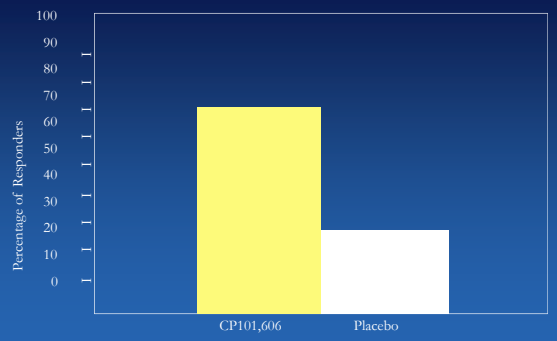
employed a double-blind, parallel group design in a small number (n = 30) of patients with treatment resistant major depression,

used an IV dose of CP-101,606 that did not produce dissociative symptoms,

evaluated response at prespecified 96 hours after CP-101,606 administration,

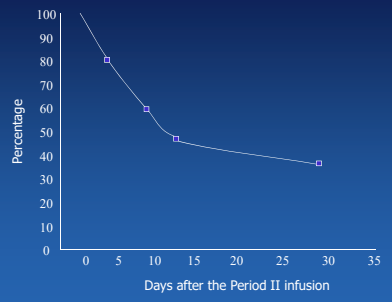
found robust antidepressant response which was sustained up to 30 days after a single administration.

Antidepressant Effects of CP-101,606 versus Placebo



Preskorn, S., et al. J Clin Psychopharmacol 28(6):1-7, 2008.

Percentage of CP-101,606 treated responders continuing to meet response criteria (i.e., ≥ 50% reduction in HDRS score) at subsequent Period II visits.



Preskorn, S., et al. J Clin Psychopharmacol 28(6):1-7, 2008.

Antidepressant Effects of the NR2B NMDA Antagonist, CP-101,606 versus Placebo

Further replication is needed in a larger scale study.

Development plan should address:

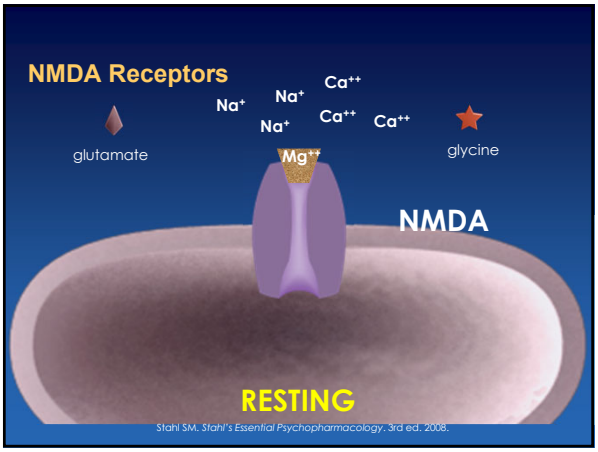
Can an oral drug be developed capable of producing a comparable antidepressant response?

Is the effect sustained with repeated administration?

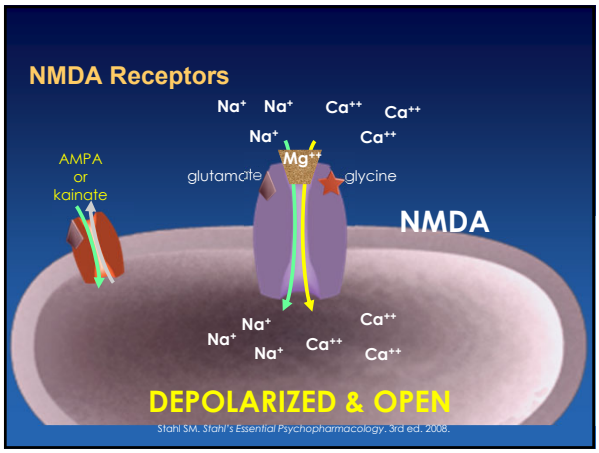
If so, how frequently must the drug be administered?

Is efficacy limited to patients with treatment resistant depression?

What is the risk:benefit ratio (i.e., where do such drugs fit within relative to existing antidepressants)?



Stahl SM. *Stahl's Essential Psychopharmacology*. 3rd ed. 2008.


NMDA Receptors
Na+ Na+ Ca++ Ca++
Na+ Ca++
AMPA
or
kainate
glutamate
Mg++
glycine
NMDA
Na+ Na+ Na+ Ca++ Ca++ Ca++
DEPOLARIZED & OPEN
Stahl SM. Stahl's Essential Psychopharmacology. 3rd ed. 2008.


The End.
Thank You.