

What is depression?

- **Everybody feels sad, disappointed, frustrated.**
- **Imagine every day was the worst day of your life:**
 - Can't get out of bed. *Anxious, No energy.*
 - Can't get out of your head. *Consumed by negative ruminations.*
 - Can't take care of yourself: *Can't sleep, no appetite, no hope, no motivation.*
 - Can't function. *Can't think or make decisions*
 - Overcome by apathy or wrapped in despair
- **What might you do?**
 - Lose your job, marriage, friendships
 - Drink alcohol or smoke cannabis to sleep
 - Cut yourself to “feel something”
 - Suicide
- **Medical consequences?**
 - Cardiac, cancer, stroke, diabetes, other morbidity, mortality
 - Shorten productive life: 13 years
 - Shorten life by 5 years

How did you get there?

- **Maybe you had risk factors?**
 - Family history
 - Early childhood stress
 - Substance abuse history
- **Maybe you were under stress?**
 - Chronic stress
 - Major disruption or stress in social relationships (loss, divorce, fired,...)
 - Traumatic stress
- **Medical illnesses or medications**
 - Illness with high inflammation (cardiac disease, etc.)
 - Proinflammatory medications (interferon, etc.)

What helped? *What didn't help?*

- **Many forms of treatment:**
 - *Behavior:* psychotherapy (CBT, IPT, psychoanalysis)
 - *Circuits:* neurostimulation (ECT, TMS, tDCS, DBS)
 - *Molecules:* antidepressants
- **Treatments not specific to depression or particular depressed patients**
- **Antidepressants – a qualified success:**
 - 30% remission to initial treatment (STAR*D): average 2 months
 - 30% “treatment resistant” after 4 “standard” trials in 1 year (STAR*D)
 - Heterogeneity in antidepressant response:
 - 25% of depressed patients worse on SSRI than placebo
 - Relapse rate reduced by only 13% over 6 months
 - Augmentation (medication, psychotherapy) more helpful than switching
 - Precision medicine at very early stage

New hope: new treatments

- **Ketamine**

- <24 hours after a single dose (not months)
- 50-75% response for treatment-resistant (not 10-30%)
 - Suicidal ideation
 - Bipolar, PTSD, OCD, etc.
- Dosed weekly-monthly (not daily)
- Risks: transient dissociative symptoms, abuse liability

- **Novel mechanisms of action:**

- Activates cortical networks implicated in mood (AMPA-R) –converge with DBS?
- Transiently raises BDNF-downstream signaling (Akt/mTOR)
- Inhibition of downregulation of synaptic efficacy (eEIF2)
- Associated with rapid increase in synaptic efficacy and synaptic proliferation
- Implicates many potential novel targets/MOA



YALE-NEW

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Psychiatric

Depression: Access Gap

- One-third of depressed patients:
 - Diagnosed
 - Referred for treatment
 - Adhere to follow-up
 - Received diagnosis before mental health presentation
- One-tenth of depressed patients:
 - Treated by a psychiatrist