

# What is depression?

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- **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?

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- **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?*

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- **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

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- **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



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Psychiatric

# Depression: Access Gap

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- 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