Esketamine: A Game Changer in Depression Treatment?

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Objectives

- By the end of this presentation you should:
  - Know the definition of treatment resistant depression
  - Know the risks and benefits of esketamine
  - Understand barriers and challenges involved in using esketamine in clinical practice

Disclosures

- I have received honorarium from Aifred, an AI company for participating in a clinical trial
  - There is no relationship with this session
- I will be discussing off-label treatments

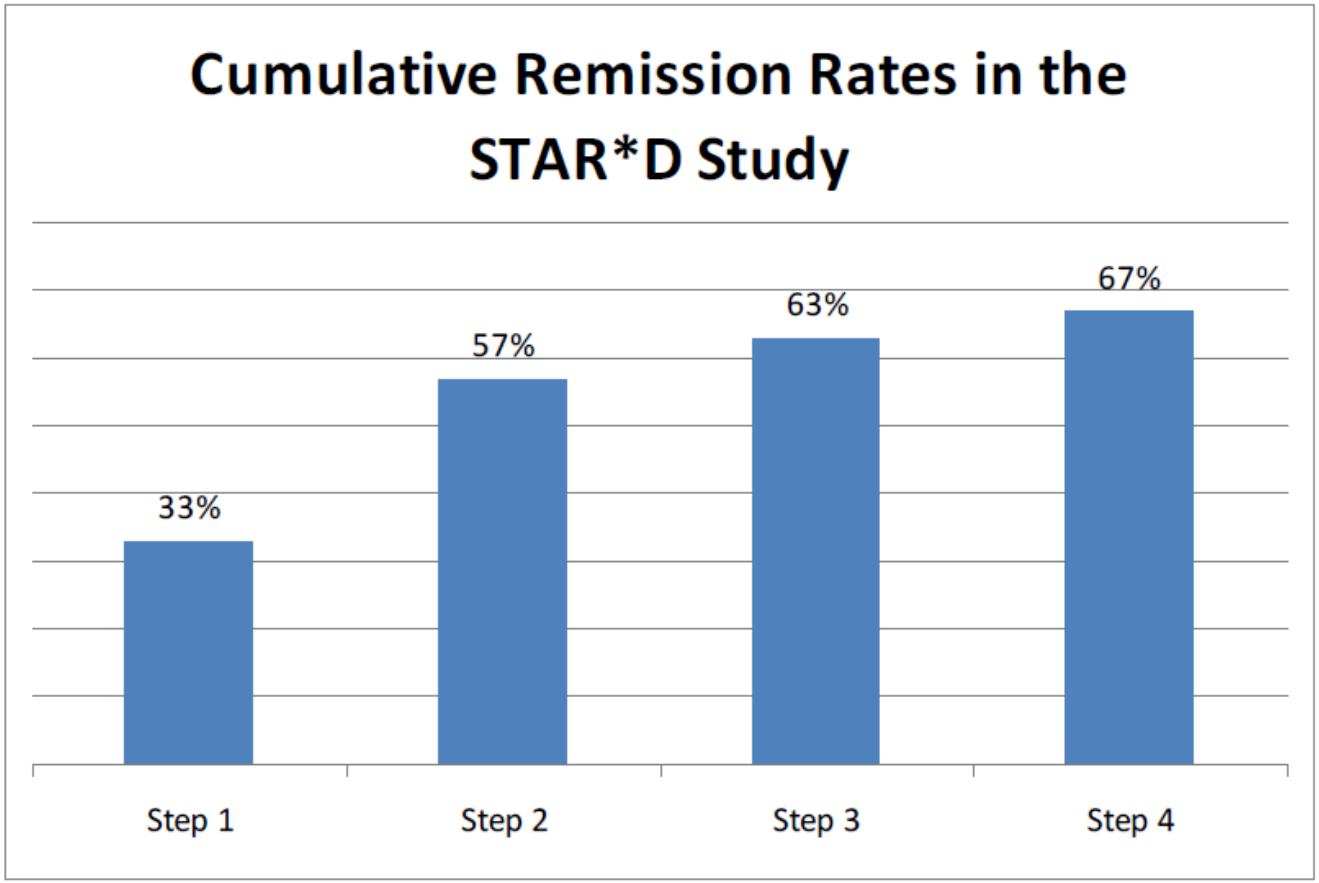
Burden of depression

- Lifetime prevalence
  - MDD 17-18% in developed countries
  - PDD 3%

- 12-month prevalence
  - MDD 6%
  - PDD 2%

Treatment resistant depression (TRD)

- 67% do not remit after 1st ADM
- 43% do not remit after 2 ADM
- Diminishing returns after 2 treatments



Israel, J. Pharmaceuticals 2010, 3, 2426-2440

Treatment Resistant Depression

- No uniform definition exists
- Most define TRD as failure to remit with 2 treatments of adequate dose and duration

Previously available options in TRD

- Augmentation with:
  - CBT
  - Aripiprazole*, brexpiprazole*, quetiapine, other SGAs
  - Lithium
  - T3
  - Pramipexole
  - Stimulants, modafinil
- Combinations of antidepressants:
  - Mirtazapine or bupropion + SSRIs / SNRIs / TCAs
- MAOIs
- ECT, rTMS

* = Health Canada Approved augmentation treatments

CANMAT 2016 Depression Guidelines

Table 11. Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant.

Recommendation	Adjunctive Agent	Level of Evidence	Dosing
First line	Aripiprazole	Level 1	2-15 mg
	Quetiapine	Level 1	150-300 mg
	Risperidone	Level 1	1-3 mg
Second line	Brexpiprazole[a]	Level 1	1-3 mg
	Bupropion	Level 2	150-300 mg
	Lithium	Level 2	600-1200 mg (therapeutic serum levels)
	Mirtazapine/mianserin	Level 2	30-60 mg
	Modafinil	Level 2	100-400 mg
	Olanzapine	Level 1	2.5-10 mg
	Triiodothyronine	Level 2	25-50 mcg
Third line	Other antidepressants	Level 3	Various
	Other stimulants (methylphenidate, lisdexamfetamine, etc.)	Level 3	Various
	TCAs (e.g., desipramine)	Level 2	Various
	Ziprasidone	Level 3	20-80 mg bid
Experimental	Ketamine	Level 1	0.5 mg/kg, single intravenous dose[b]
Not recommended	Pindolol	Level 1 (lack of efficacy)	Not applicable

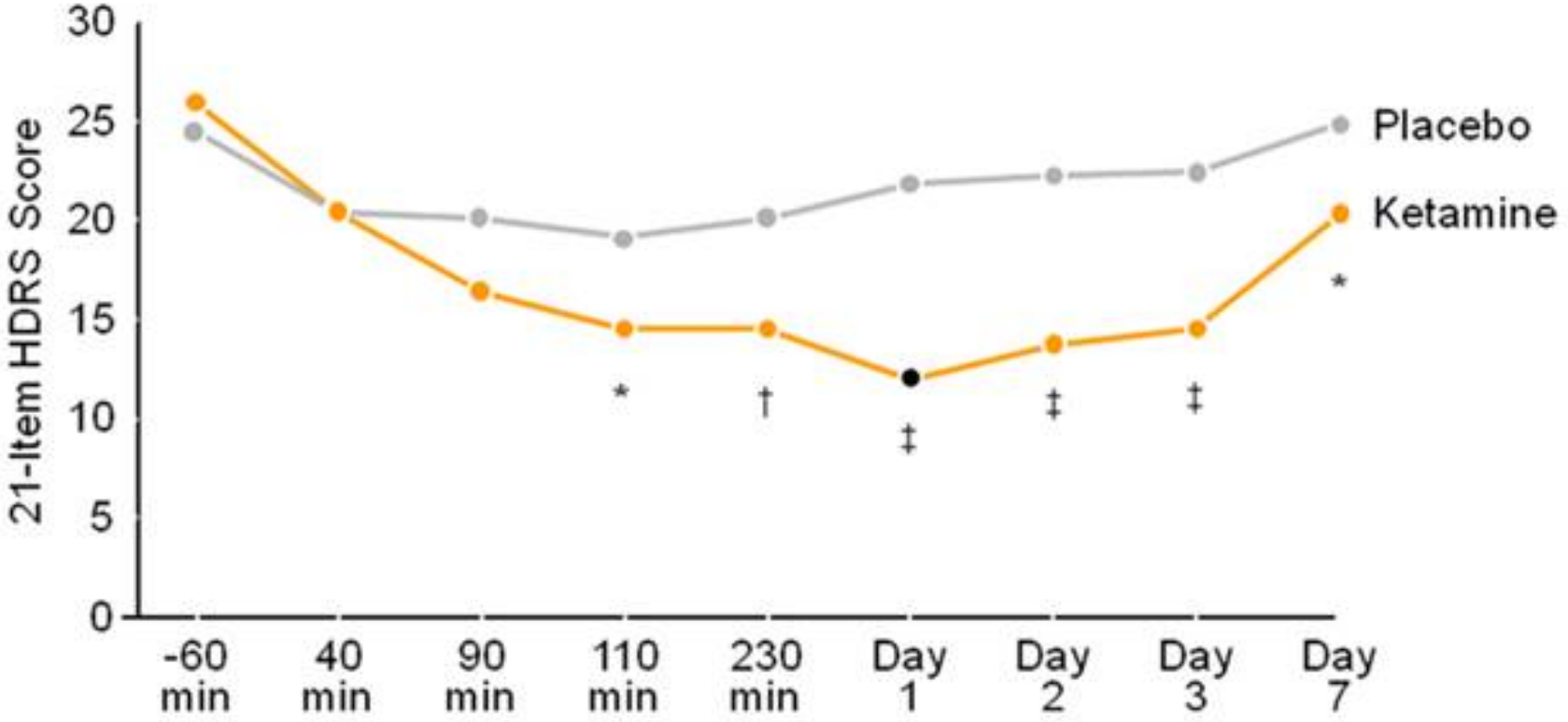
TCA, tricyclic antidepressant.
[a]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.
[b]For acute treatment.

Ketamine

- Used as anesthetic since 1960s
- Rapid antidepressant and anti-suicide effect of IV ketamine reported in mid-2000s

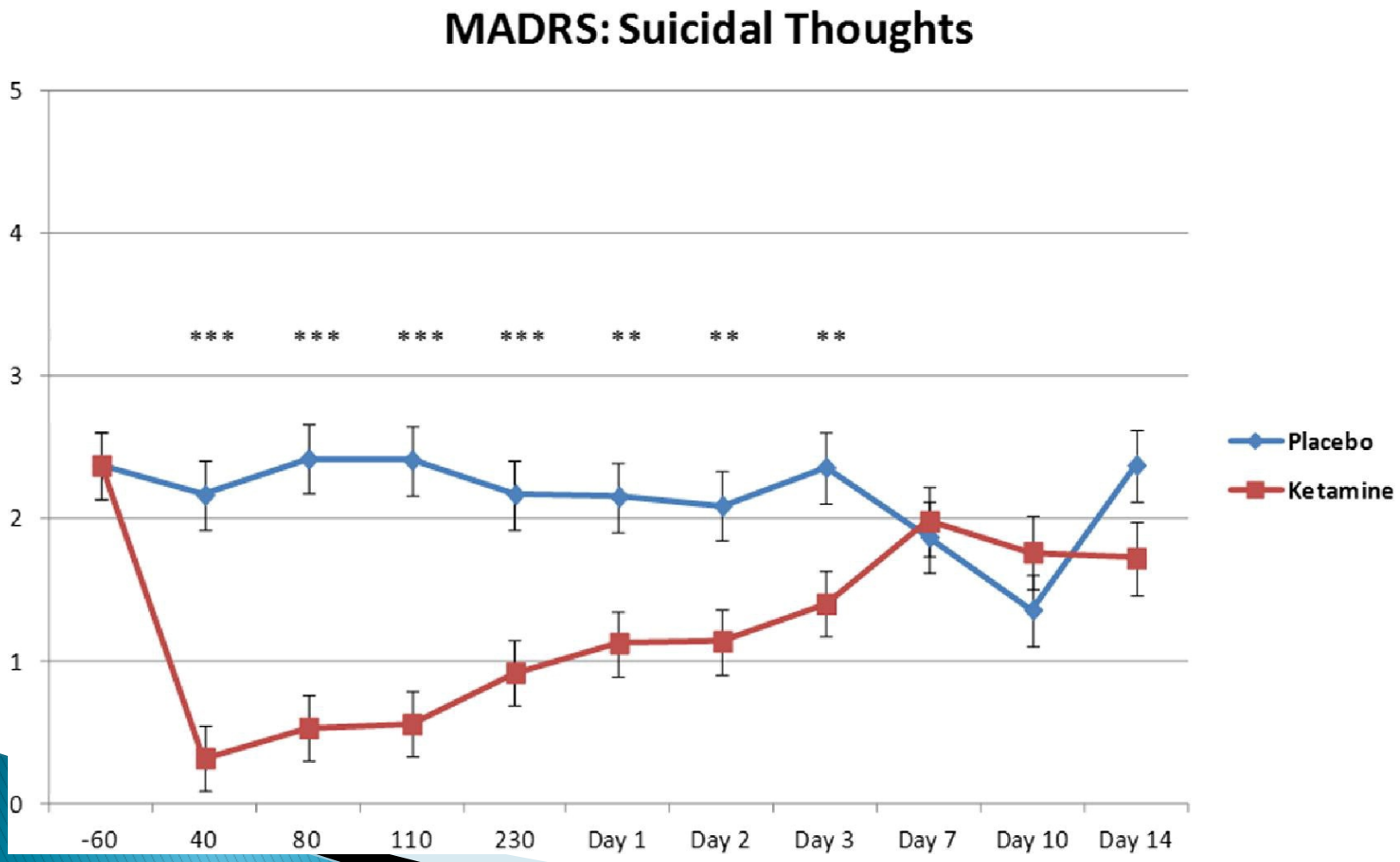
- Works on glutamate system as NMDA receptor antagonist
- Counterintuitively, may lead to increase glutamate release
- Increases BDNF (a neuronal GF that leads to formation of new synapses)

Antidepressant Effect of Ketamine Within Hours in Patients With Treatment-Resistant Depression



HDRS: Hamilton Depression Rating Scale
Zarate CA Jr et al. Arch Gen Psychiatry 2006;63:856-64.

Ketamine rapidly reduces suicidal ideation



Zarate, *Biol Psychiatry*, 2012

Ketamine leads to disinhibition of glutamate release and results in rapid release of BDNF

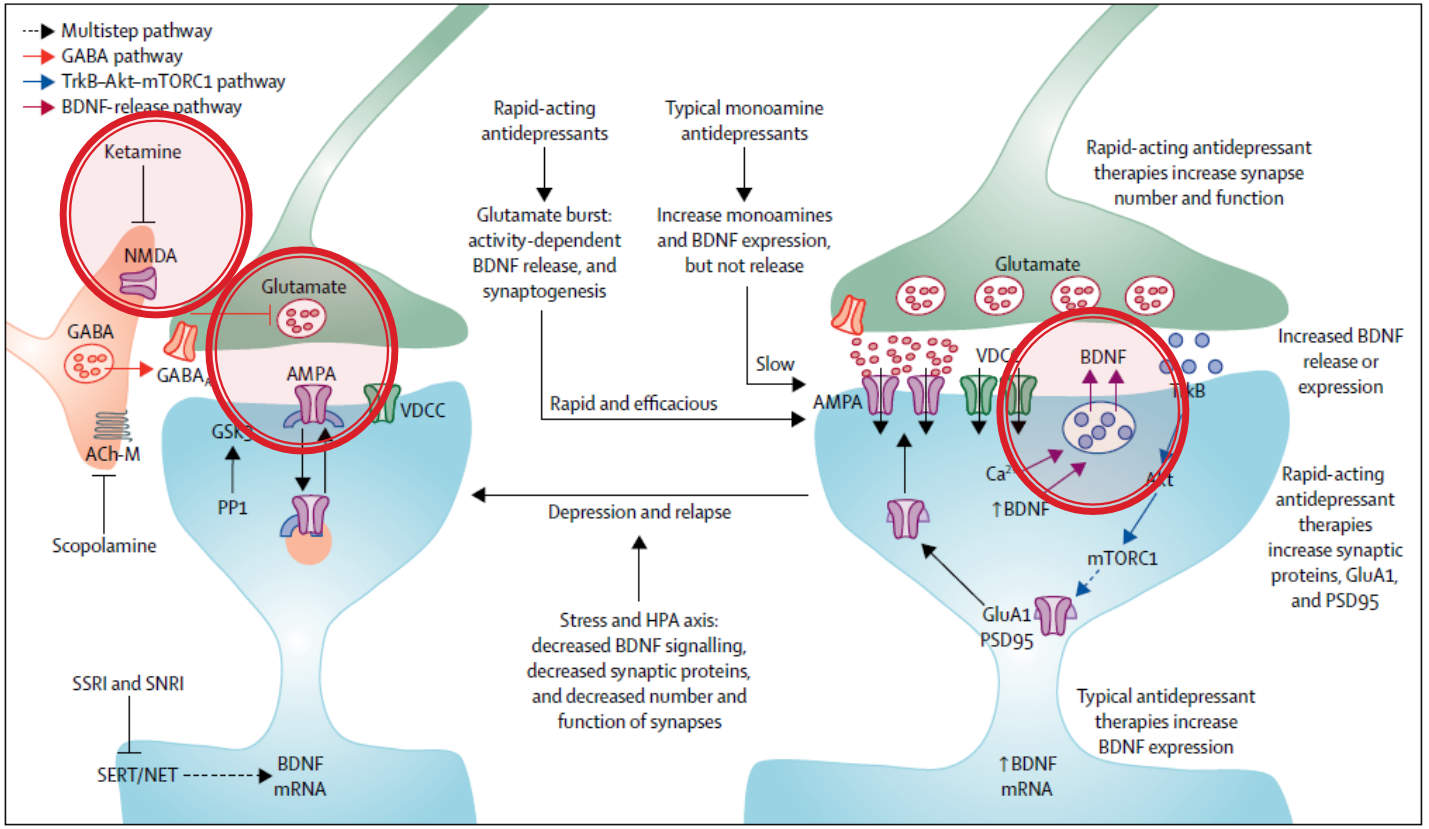
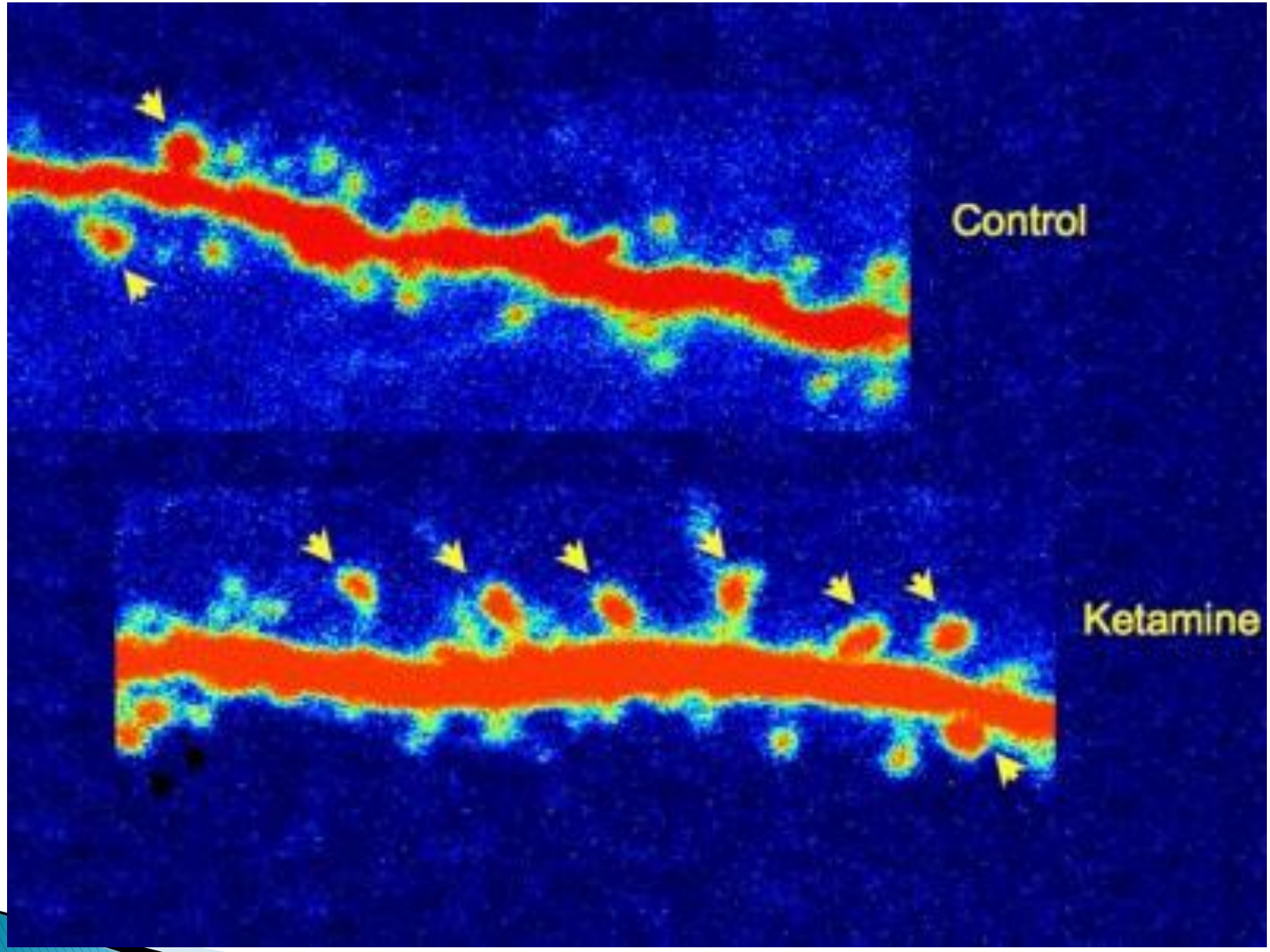


Figure 1: **The neurotrophic theory of antidepressant drug action**
NMDA=N-methyl-D-aspartate receptor. GABA$_A$=γ-aminobutyric acid receptor. Ach-M=acetylcholine muscarinic receptor. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor. VDCC=voltage dependent calcium channel. SSRI=selective serotonin reuptake inhibitor. SNRI=serotonin–norepinephrine reuptake inhibitor. SERT=serotonin transporter. NET=norepinephrine transporter. BDNF=brain-derived neurotrophic factor. HPA=hypothalamic–pituitary–adrenal.

Harmer, C. *Lancet Psychiatry*. 2017 May;4(5):409–418.



R.J. LIU, G. AGHAJANIAN & R. DUMAN

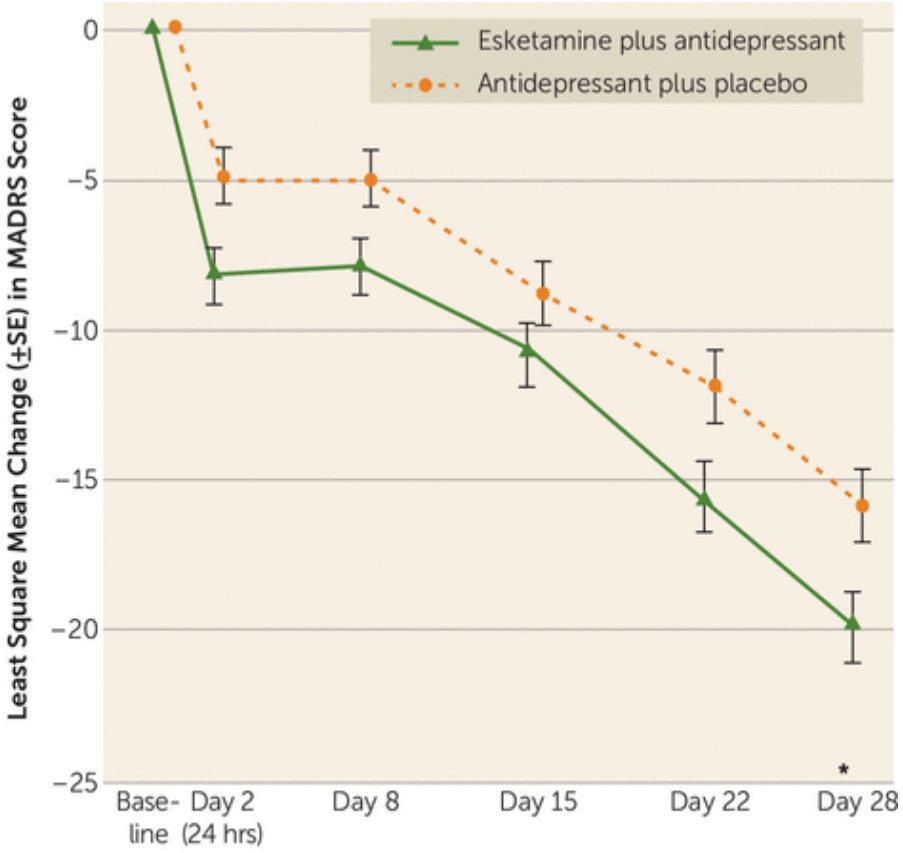
Why Intranasal Esketamine?

- Ketamine is generic, could not be patented
- IV ketamine not very practical
- Oral ketamine not well absorbed
- Unclear if pharmacological benefit vs. ketamine vs. arketamine
  - One small study showed IV esketamine noninferior to ketamine

Correia-Melo FS, *J Affect Disord*. 2020 Mar 1;264:527-534

Esketamine Trials

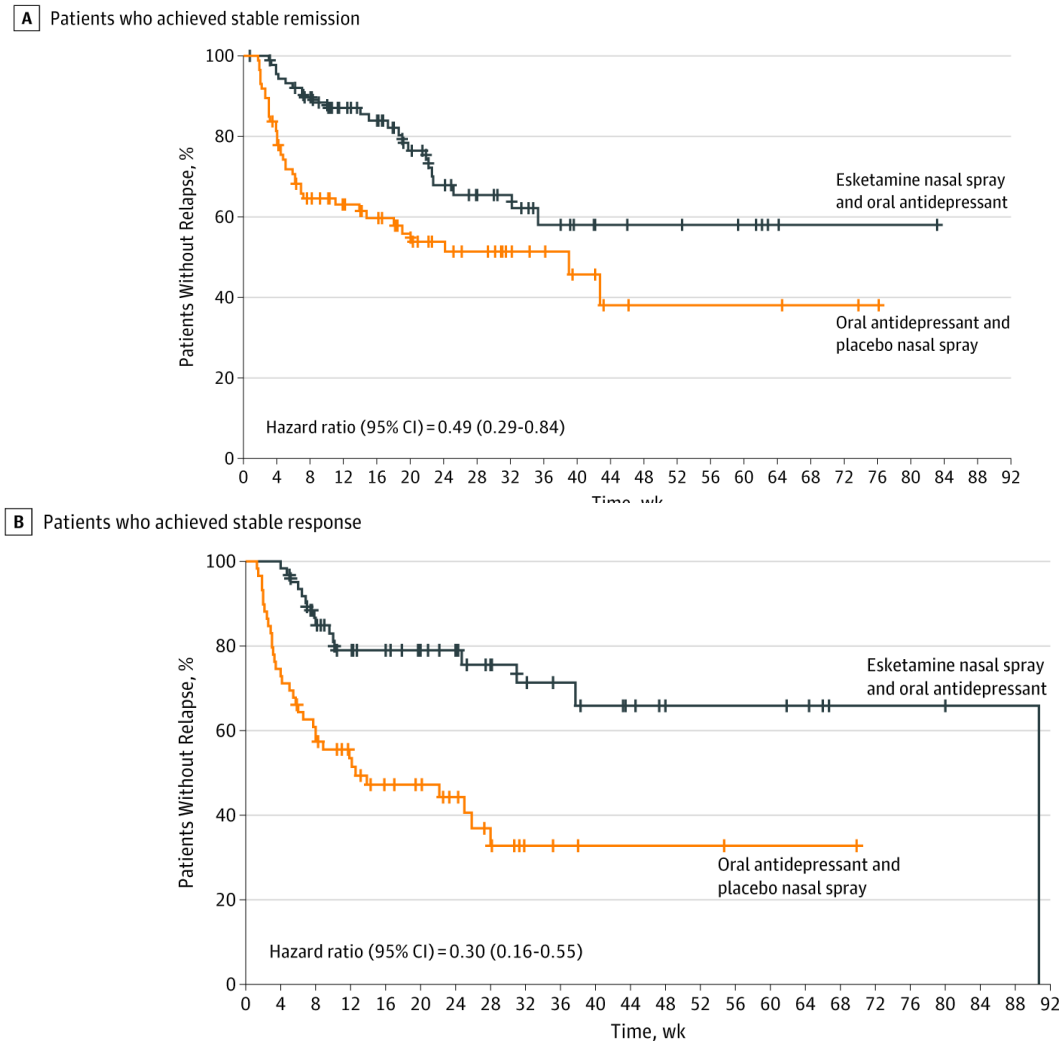
- 2-5 prev AD
- Randomized to:
  - new AD + ESK
  - new AD + placebo
- response
  - 50-60% vs 36-50%
  - NNT 8
- Remission
  - 30-40% vs. 20-24%
  - NNT 6



Popova, Am J Psychiatry. Volume 176. (6) June 2019. 428-43
Citrome. *J Affect Dis.*271, 15 June 2020, 228-23

Esketamine Continuation Trial

- Randomized D/C
- Up to 80 wk FU
- Time to relapse
- Remitted
  - 27% vs 45% relapsed
  - NNT = 6
- Response only
  - 26% vs. 58% relapsed
  - NNT = 4



Daly E, *JAMA Psychiatry*, 2019, 76(9):893-903.

Indications

- TRD = 2 prev AD treatments in current episode
  - Moderate to severe symptoms
  - As add on to an SSRI or SNRI
  - 18-65 years

Contraindications

- Conditions for which transient HTN would be dangerous
  - Aneurysms, AVM, hx ICH, recent MI or CVA
- Unstable medical condition
- Active substance use disorder
- Pregnancy
- Psychosis*
- Bipolar disorder*

Side effects

- Common
  - Dizziness, vertigo, nausea, sedation, dissociative sx, mild elevated BP
- Rare but serious
  - Risk of misuse (not seen in RCTs)
  - Interstitial cystitis (not seen in RCTs)

Precautions

- Must be taken at clinic w/ supervision of HCP
- No food 2 hrs, no liquids 30 min
- Remain on site 2 hours.
- Cannot drive for the remainder of the day
- No ETOH 24 hrs before and 24 hrs after

Treatment schedule

- 2x per week x 4 wk
- 1x per week x 4 wk
- 1x every 1–2 weeks

Drug Cost

- Esketamine not covered by RAMQ
- Needs pre-approval by insurance companies
- Cost for 56 mg is ~$640
- With a co-pay of 30%, 1st month is ~$1500, (more if needs 84 mg)
- Currently, no patient support program in Canada

Esketamine spray for treating depression 'not cost-effective'

4 September

A nasal esketamine spray for hard-to-treat depression has been rejected for use on the NHS for a second time because of uncertainty over cost.

Despite a need for new treatments for adults, it is also not clear how well the drug works long term, the healthcare watchdog NICE said.

Other barriers

- Clinical staff (usually RN) for monitoring
- Admin staff
- Hospital protocols
- Patients need transport
- Prior authorization delays

Summary

- Ketamine and Esketamine improve symptoms of TRD using a novel mechanism
- IN esketamine has proven effective in RCTs
- Most will require maintenance treatment
- Barriers including onsite monitoring requirement and high cost