Subanesthetic Ketamine Infusion in Reducing Symptoms of End-of-Life Depression

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No financial relationships to disclose

Why treat psychological distress in patients with terminal illness such as HF?

- Impairs patient's capacity for pleasure, meaning, and connection
- Erodes QOL, amplifies pain & other symptoms
- Reduces patient's ability to do emotional work - saying good-bye
- Causes anguish and worry in family members and friends.

Widera E, Block S. Am Fam Physician 2012; 86(3):259-264

Session Learning Outcome(s)

1. **Distinguish** between **major depression and preparatory grief** in terminal patients
2. **Categorize** the **antidepressants** used for patients with serious illness, emphasizing pros and cons **in the context of HF**
3. **Recognize** role(s) and **underlying mechanisms** for use of low-dose **ketamine infusion** in **treatment-resistant depression** at EOL

Case Presentation

HPI:

86 yo male with end stage heart disease and h/o **two cardioembolic episodes** resulting in **dysphagia**, was admitted to home hospice. Soon after initiating hospice, he was noted to have **progressive worsening of pre-existing depression**. His **mood** was **depressed**, **energy low** and **concentration poor**. He endorsed having **problems sleeping**, **difficulties concentrating** during conversations, having a **poor appetite** and **increased fatigue.** He also reported **feelings of anguish, annoyance and agitation** toward his step-sons who were not respectful to his wife (their mother).

Psychiatric history: depression, Ø admissions or ECT
Medications: escitalopram 20 mg; ***citalopram, bupropion, venlafaxine ineffective***

……**mirtazapine 30 mg** and **lorazepam 1 mg** added for sleep disturbance and **duloxetine 30 mg** for acute exacerbation of his chronic back pain.

Our **interdisciplinary team**, including chaplain, MSW, and RN also met regularly with the patient/family, providing **empathic support and counseling.**

Psychomotor, emotional and cognitive features often overlap at EOL, muddling the diagnosis

Anhedonia

Feelings of Worthlessness

Sadness

Hypoactive, quiet, withdrawn

Anorexia, insomnia, poor concentration

Major Depression

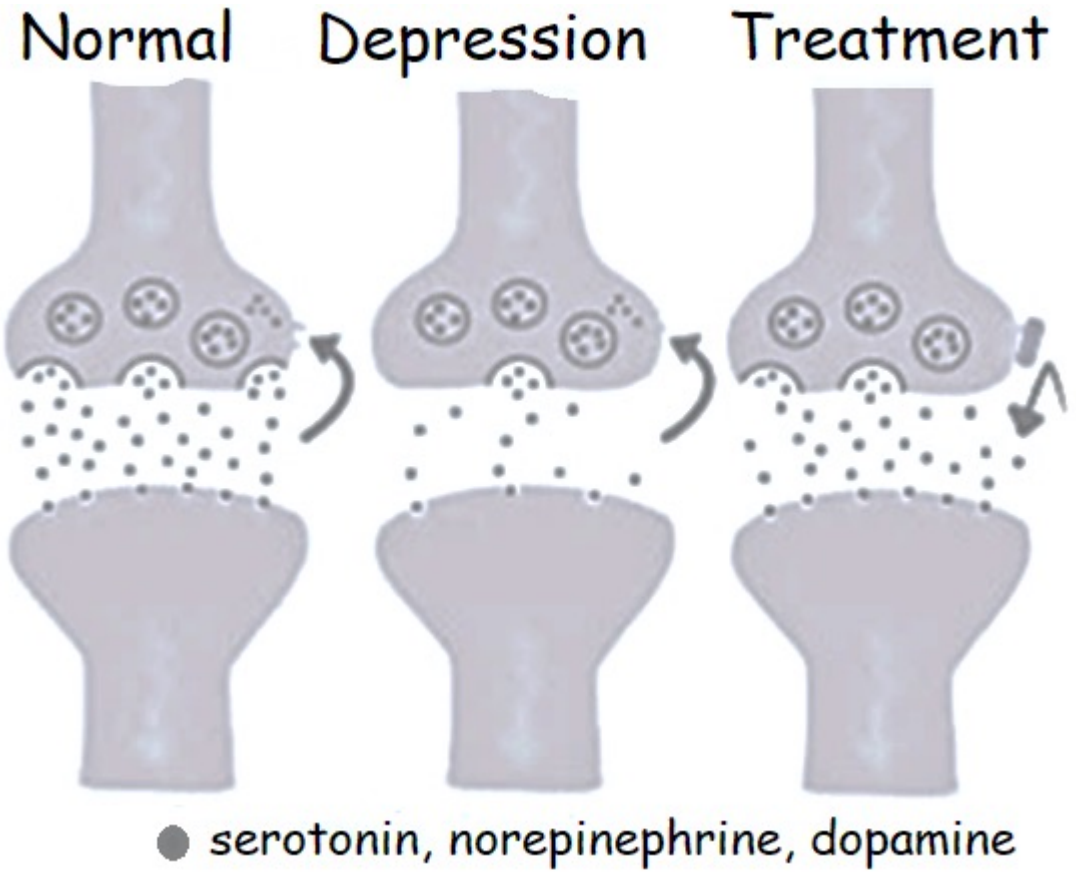
Preparatory grief

Delirium

Table 1. Differentiating Grief and Depression

Preparatory Grief	Depression
Waxes and wanes	Consistent sadness
Sadness about death	Suicidal ideation or active desire for death
Specific anxieties about dying process and loved ones left behind	Vague pervasive anxieties
Continued ability to take pleasure in favorite activities	Consistent anhedonia Hopelessness
Continued involvement with loved ones	Social withdrawal

2. Categorize the **antidepressants** used for patients with serious illness, emphasizing pros and cons **in the context of Heart Failure.**



Antidepressants

- TCA
- SSRI
- SNRI
- Atypical
- MAO-I

Imipramine
Nortriptyline
Amitriptyline
Doxepin
Desipramine

Sertraline
Paroxetine
Fluoxetine
Citalopram
Escitalopram

Duloxetine
Venlafaxine

Mirtazapine
Trazodone
Bupropion

Tranylcypromine
Phenelzine
Isocarboxazid

Our pt: previous trials of citalopram, bupropion, venlafaxine were ineffective

Antidepressants

SSRI

= Selective Serotonin Reuptake inhibitors

if life expectancy >8 wks

(Zoloft) **Sertraline**

(Paxil) **Paroxetine** – stimulating (a.m. dosing);

(Prozac) **Fluoxetine** – sedating, (h.s. dosing)

(Celexa) **Citalopram** dose dependent ↑QTc (>40 mg)

(Lexapro) **Escitalopram**

All SSRIs can prolong QTc

Antidepressants

SNRI

= Serotonin Norepinephrine Reuptake Inhibitors

(Cymbalta) **Duloxetine** –**Neuropathy and depression**
High dose – orthostasis; CKD dosing

(Effexor) **Venlafaxine** Withdrawal syndrome common (short $T_{1/2}$)

Cardiac concerns due to increase Norepi→ ↑BP, HR

Antidepressants

Effective as single agents and/or used to augment effectiveness of SSRIs and SNRIs

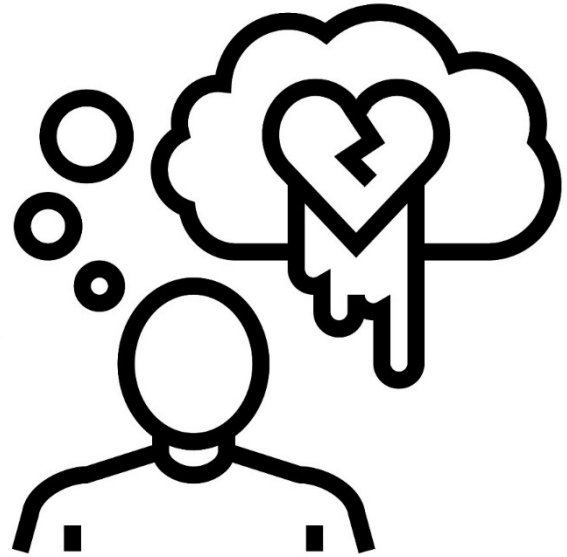
Atypical

(Remeron) **Mirtazapine**
- improve sleep
- ↑appetite

Orthostasis, ↑QTc (Desyrel) **Trazodone**
- improve sleep

Lowers seizure threshold (Wellbutrin) **Bupropion**
- may ↓fatigue

- Over subsequent months, hospice RN reported **worsening** of his **depressed affect**, with **hopelessness, lack of interest in self-care, persistent brooding**, and **passive thoughts of suicide**.
- As depression was contributing to his ongoing suffering, he agreed to a **psychiatric evaluation**, as well as to a trial **infusion of low-dose ketamine** in our inpatient hospice facility



3. Recognize role(s) and potential **mechanisms** for use of low-dose IV **ketamine** in **treatment-resistant depression (TRD)** at **end of life**

Intravenous Ketamine (Racemic) Hydrochloride

Anesthetic

- FDA approved 1970
- Induction (bolus): **1-1.5 mg/kg**
- **Dose dependent** cataleptic, amnestic, **dissociative,** analgesic effects
- Hemorrhagic or septic **shock**, **hemodynamic instability**, asthmatics
- Short term sedation/anesthesia
- **Maintains oropharyngeal/laryngeal** reflexes

Antidepressant

- Off-label use
- Infusion: **0.5 mg/kg** over **40 minutes**
- **Side effects:** Short-lived **symptoms of** nausea, headache dizziness; transient Δ's vital signs (↑); mild dissociative effects
- **Rapid antidepressant effects**, long-lasting
- **70-80% response rate** who failed multiple medical trials or ECT

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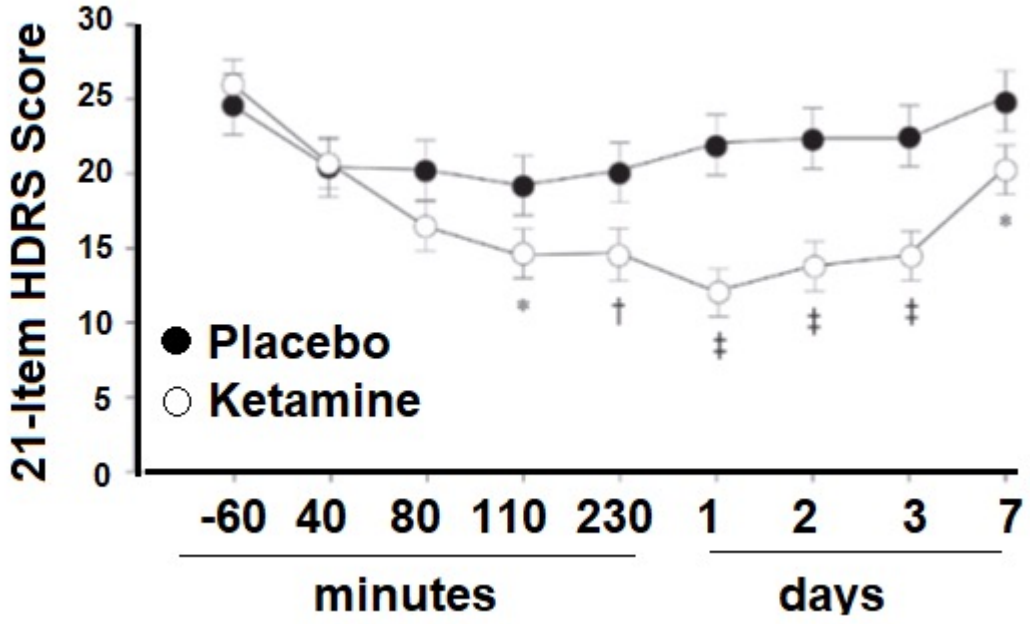
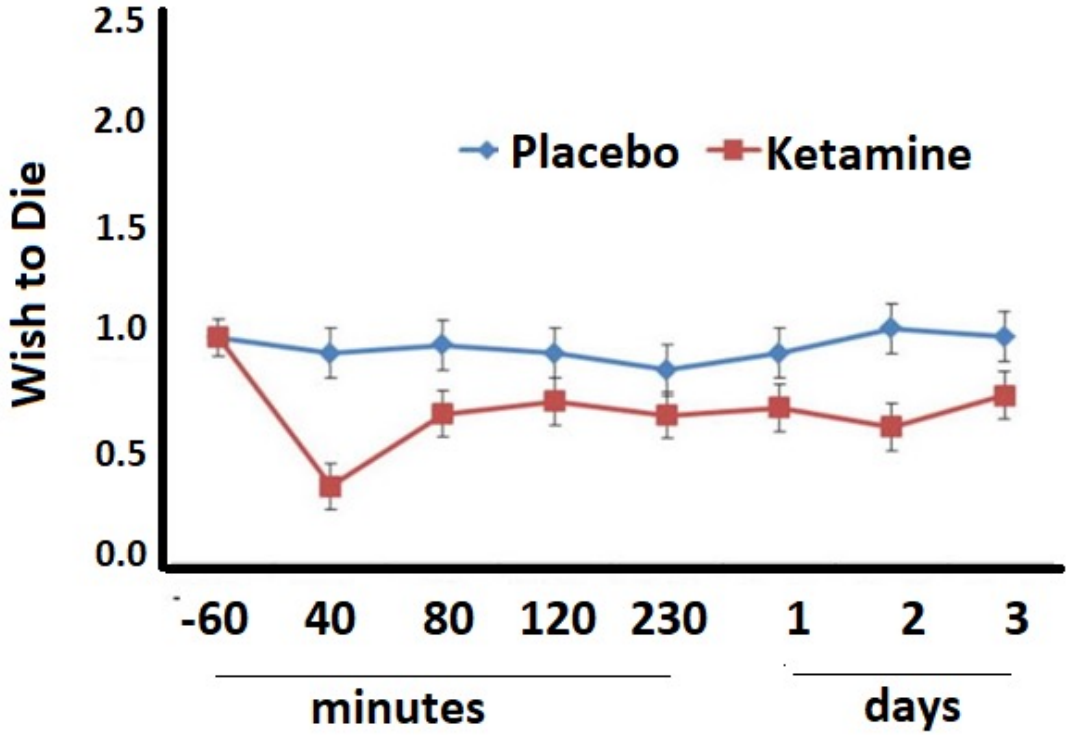
Change in the 21-item Hamilton Depression Rating Scale (HDRS) Over 1 Week (n = 18 TRD pts)



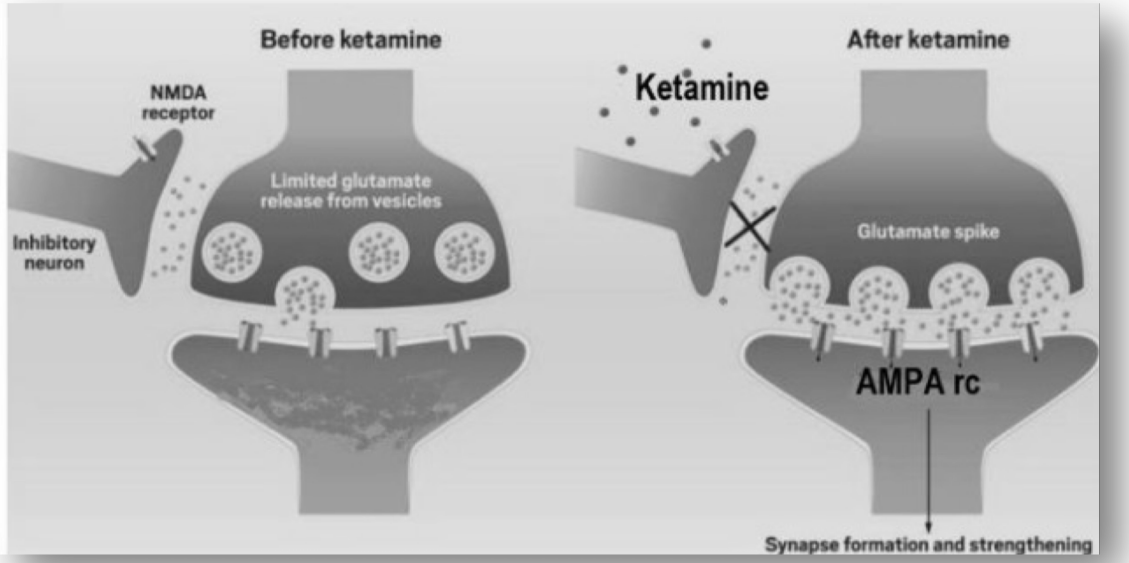
Zarate, CA et al. *Arch Gen Psychiatry* 2006;63:856-864.

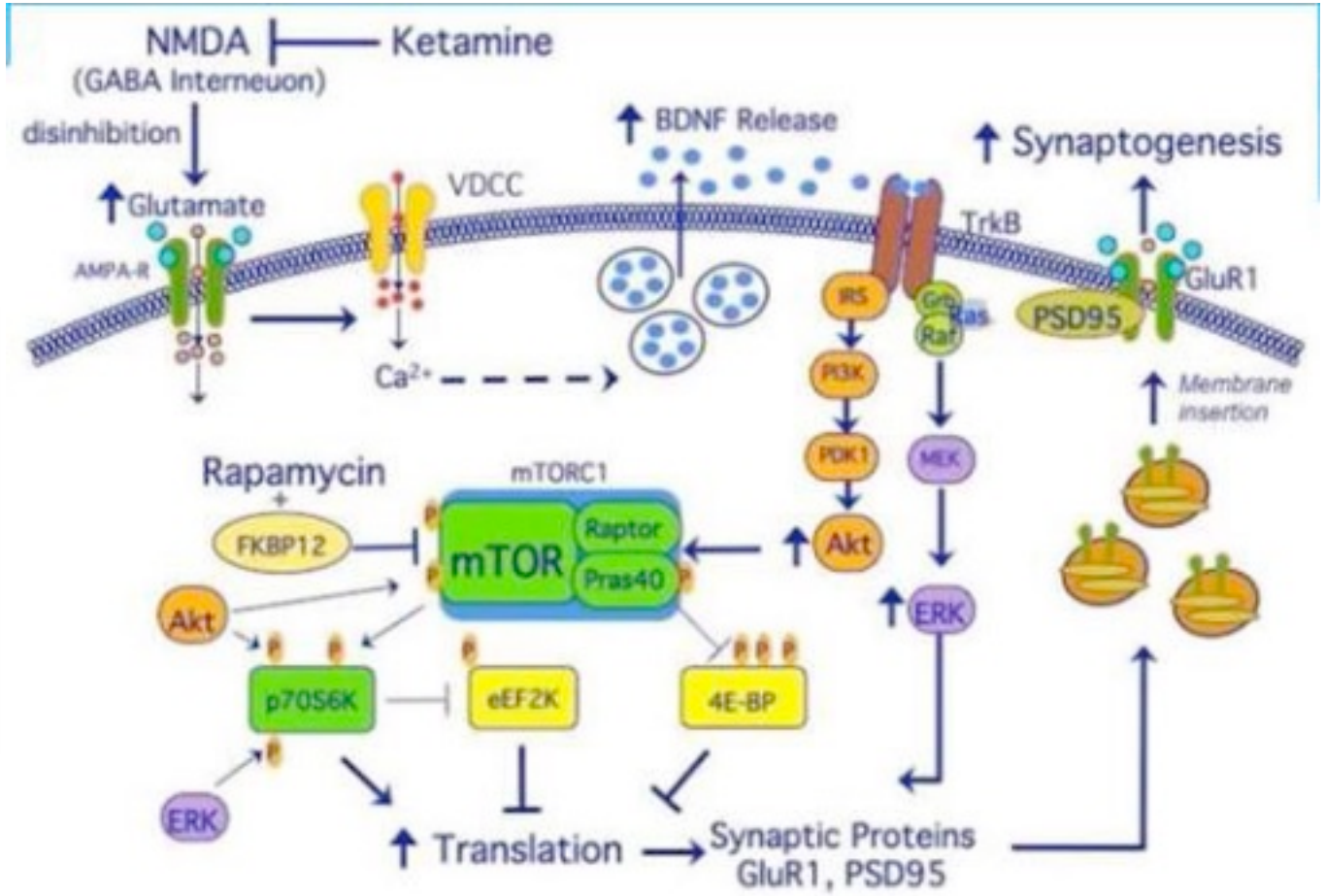
Change in suicidal ideation over time (n = 133 TRD pts), data from 4 independent clinical trials



Ballard ED, et al. *J Psychiatr Res*. 2014 Nov;58:161-6.

How does it work?





Carboni E. Repurposing Ketamine in Depression *Front. Neurosci*. Apr 2021 15:657714.
Duman RS. Signaling pathways underlying the rapid antidepressant actions of ketamine. *Neuropharmacology* 2012; 62 (1):35-41

Relative Contraindications (? Subanesthetic use)

Active psychosis

↑intracranial or intraocular pressure

Poorly controlled CV disease

Hepatic dysfunction

Previous adverse response to ketamine

Ketamine for depression: modes of administration

Route	Dosing	Frequency
Intravenous	0.5 mg/kg over 40 min	Induction: Q3 days x 6 infusions. Maintenance: Q3 wks or at relapse
Intranasal (S-ketamine)	10-50 mg	Q 3-7 days
Oral	10-100 mg	Q day to 3 times/day
Subcutaneous[1]	0.1–0.4 mg/kg x 2 hrs	Weekly up titration by 0.1 mg/kg

[1]Lee W, et al. Study protocol for SKIPMDD: subcutaneous ketamine infusion in palliative care patients with advanced life limiting illnesses for major depressive disorder (**phase II pilot feasibility study**). BMJ Open 021;11:e052312.

Case Presentation

Treatment of depression may be one of the most important interventions to improve a terminally ill patient's quality of life. Depression in terminally ill patients is a major risk factor for suicide and for requests to hasten death

- Admitted to inpatient hospice, GIP care level
- IV Ketamine 0.5 mg/kg over 40 minutes
- No overt Δ in BP (*automated cuff*) or HR (*continuous plethysmography*);
  Ø nausea, headache, or hallucinations
- Within 24 hrs, his deep-rooted exasperation toward his extended family subsided
- D/C home after 4 days with ↑appetite, reduced sleep disturbance and improved engagement with family
- Euthymia was maintained 2-weeks, before dying peacefully at home.

KEY TAKEAWAYS

1. **Psychomotor**, **emotional** and **cognitive features** of grief and major depression often **overlap at EOL**, muddling the diagnosis. A detailed history of onset and time course of mood helps to differentiate among conditions.

2. **SSRIs 1st line** antidepressant **for HF patients**, if **life expectancy > 2 months**. Due to = efficacies, initial choice is based on patient factors and drug nuances (e.g., stimulating or sedating, and least QTc prolonging).

3. **Atypical antidepressants** are effective as **single agents** *and/or* **used to augment** effectiveness of **SSRIs** and **SNRIs**

4. **TRD** is a critical problem among some hospice patients, as it contributes to **total body suffering**. Rapid effects of IV **ketamine**, **0.5 mg/kg infused over 40 min**, may be an effective treatment *for* **terminal patients** with **suicidal ideation** and **depressive symptoms**.

References

1. Widera EW, Block SD. Managing Grief and Depression at the End of Life. ***Am Fam Physician* 2012; 86(3):259-264**

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5. Wilkinson, S. T., et al. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. ***Am. J. Psych.* 2018; 175: 150–158**. https://doi: 10.1176/appi.ajp.2017.17040472

6. McIntyre RS et al. EVIDENCE FOR KETAMINE AND ESKETAMINE IN TREATMENT RESISTANT-DEPRESSION. ***American J Psychiatry in Advance* (doi:10.1176/appi.ajp.2020.20081251).**