Subanesthetic ketamine infusion in reducing symptoms of end-of-life depression: A case report

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1. Distinguish between major depression, anticipatory grief and hypoactive delirium in terminally ill patients with end-stage heart disease.

Clinical depression is a treatable condition, yet often overlooked in terminally ill patients because it may be misconstrued as anticipatory (or preparatory) grief. Because failure to treat impairs quality of life and contributes to total suffering, it is imperative that it is recognized and managed, even at the end of life. Feelings of generalized guilt, hopelessness, worthlessness, inability to feel pleasure, lack of response to social support and suicidal ideation are key factors that differentiate depression from grief. Anticipatory grief is associated with feelings of sadness, described as “good and bad days”, and a positive response to social supports. Unlike the depressed patient, a grieving patient’s hope often shifts over the course of the terminal illness from hoping for a cure or life prolongation to hoping for a good death. Another condition confused with depression in a patient with serious illness is hypoactive delirium. While depression and delirium may present with overlapping symptoms such as slow mentation, decreased concentration, withdrawal, apathy, changes in sleep and appetite, the timeline of symptom onset and progression is key to their differentiation; intermittent to chronic is often observed with depression whereas an acute or subacute onset is linked to delirium. Screening tests such as the Patient Health Questionnaire (PHQ-4) and 3DCAM are useful in distinguishing between these common sources of emotional and physical suffering at the end of life.

- Periywakoil VJ. Fast Facts #43 Is it Grief or Depression?

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

Treating depression at the end of life may alleviate both physical and psychological suffering and improve distressing symptoms for both patients and their caregivers. In a longitudinal study of patients with heart failure, worsening symptoms of depression were associated with increased hospitalization for heart disease. In another study, fewer than half with advanced heart disease received treatment for depression. Selective serotonin reuptake inhibitors (SSRIs—citalopram, escitalopram, fluoxetine, paroxetine, sertraline) and Bupropion (NE—Dopamine reuptake inhibitor) are probably the safest for patients with heart disease, with the need for increased caution when paired with the antibiotic erythromycin due to increased risk of arrhythmias. Serotonin-norepinephrine reuptake inhibitors (SNRIs – duloxetine, venlafaxine) may increase blood pressure. Tricyclic antidepressants (TCAs—amitriptyline, desipramine, doxepin, nortriptyline) may cause orthostatic hypotension, arrhythmias and QT prolongation. When life expectancy is short (<6 weeks), adding psychostimulants (methylphenidate, modafinil) for hypoactive depressive symptoms (e.g., fatigue, anorexia, lethargy) should only be considered in noncardiac patients. Tachycardia from psychostimulants can lead to cardiac decompensation in those...
with heart disease. Low dose mirtazapine is helpful in patients with insomnia, due to it antihistamine effects, and for weight gain. Trazadone may improve sleep quality and nocturnal awakening; yet can also promote orthostasis. If depression persists, augmentation of SSRIs with 2nd generation antipsychotics may be considered, yet with caution given that quetiapine has been linked to hypotension and olanzapine, quetiapine, and risperidone to QTc prolongation. If depression emerges in bipolar disorder, SSRI and SNRI’s can lead to exacerbated mania, and should be avoided. Abrupt discontinuation of SSRIs can lead to withdrawal symptoms and rebound depression; thus, tapering is recommended.

3. Recognize the therapeutic potential and underlying biological mechanisms for the use of low-dose ketamine infusion in the management of treatment-resistant depression.

Patients who do not respond to two or more antidepressants are classified as treatment-resistant-depression and are patients of choice for ketamine therapy. Evidence suggests that N-methyl-D-aspartate (NMDA) receptor antagonism by ketamine produces rapid and sustained antidepressant activity in resistant patients. A distinctive feature of major depression is the manifestation of suicidal thoughts and attempts. Although the brain circuitry responsible for the formation of suicidal ideas and the execution of suicidal acts is not known, several studies demonstrate that 0.5 mg/kg of ketamine infused over 40 min versus placebo or versus midazolam, reduced suicidal ideation and depressive symptoms. It is interesting to posit that the dissociative effect of ketamine triggers some mechanism that interferes with the generation of nightmares in the CNS or interferes in the transition between suicide and its realization. When the effect of ketamine on the reduction of nocturnal wakefulness may be involved in reduced nightmare remains speculative. Indeed, it is curious that in healthy individuals without depression, ketamine has caused unpleasant dreams. In general, it has been suggested that the response to ketamine is closely related to the emotional state of the individual and the extent of glutamate transmission – leading to differences in both its rapid and prolonged effects. It is worth noting that when used as an anesthetic (where dosing is 7 times higher than that for the management of depression), ketamine increases blood pressure, heart rate, and cardiac output - and, thus, is frequently the agent used for induction of anesthesia in those at-risk for hypotension.


### Key points for drug therapy

- SSRI, SNRI, mirtazapine, bupropion are all first-line antidepressants for MDD
- Initial choice is made empirically based on patient factors and nuances of each drug (e.g., sedating vs. stimulating)
- Drawback – effectiveness takes up to 6 weeks
- Psychostimulants work within hours to days. **TET may contribute cardiac decompensation** and can also aggravate insomnia and agitation

### Ketamine as antidepressant timeline

- 2013: Spravato or esketamine ($S$ isomer of ketamine) approved for use by for treatment resistant depression.
- Aug. 2020: FDA approved esketamine for depression, when used along with an oral antidepressant. Nasal spray version approved for use in supervised settings, with monitoring for 2 hours after administration.

Simplistically, ketamine blocks the NMDA receptor on inhibitory neurons and by blocking it, leads to an increase in activation. In other words, ketamine stops the inhibitory neurons from putting the brakes on, leading to an increase in glutamatergic signaling and binding to AMPA receptors.

### Potential Adverse Effects

- Transient changes in vital signs
- Mild dissociative effects, that rapidly regress (pretreat with BZ and/or low-dose haldo)
- Short-lived symptoms of headache, nausea, dizziness. (pretreat with anti-emetic, e.g., Zofran)