Madeline Li (Orcid ID: 0000-0002-3977-7437)

Is Ketamine a Litmus Test for Capacity in Assisted Dying with Depression?

Short Title: Ketamine as a Litmus Test for Depression in Assisted Dying

Joshua D. Rosenblat[1,2], *Madeline Li*[2]*

[1]Mood Disorders Psychopharmacology Unit, Poul Hansen Family Centre for Depression, Toronto Western Hospital, University Health Network, 399 Bathurst Street, Toronto, Ontario, Canada

[2]Department of Supportive Care, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada

*Corresponding Author:

Madeline Li MD PhD FRCP(C)

Psychiatrist, Department of Supportive Care

University Health Network - Princess Margaret Cancer Centre

16 - 749 610 University Avenue Toronto, ON M5G 2M9

Tel: 416-946-4501 ext. 7505 Fax: 416-946-2047

E-mail: madeline.li@uhn.ca

Keywords: Psycho-Oncology, Ketamine, Medical Assistance in Dying, Assisted Dying, Euthanasia, Depression, Capacity, Cancer, Palliative Care

Key Points

1. In patients with terminal illness requesting medical assistance in dying (MAiD), the contributing role of comorbid depression on capacity is often unclear
2. Intranasal ketamine is a novel rapidly acting antidepressant, well suited where the long onset of action with traditional antidepressants may exceed life expectancy
3. In three patients with terminal cancer, ketamine effected depression remission within 24 hours and had surprisingly divergent effects on their desire for MAiD
4. Ketamine might serve as a type of litmus test to help clarify the influence of potentially reversible depressive symptoms on the desire for death
5. In patients with cancer and co-morbid depression requesting MAiD, a trial of ketamine should be considered to ensure the safe and appropriate practice of assisted dying

Introduction

Amid the ongoing ethical and societal debate, there has been a growing global movement towards the legalization of medical assistance in dying (MAiD)(1,2). In patients with terminal cancer and comorbid depression, the contributing role of depression in the decision-making process to pursue MAiD can be challenging to determine. Ideally, a patient would be assessed in the absence of depressive symptoms, but waiting depression remission before MAiD eligibility assessment is not feasible given the lag time for traditional antidepressants to take effect and the high rates of treatment non-response (3,4). Ketamine has emerged as a well-tolerated, effective and rapid-acting treatment for depression (5). This case report describes three patients (see Table 1 for demographic and clinical information) who requested MAiD before enrolling in an ongoing open label clinical trial of intranasal ketamine for depression in patients with terminal cancer (ClinicalTrial.gov:NCT03410446). Consent for case publication was obtained from all patients.

All three patients had a clinical diagnosis of a current moderate to severe major depressive episode, as per Diagnostic and Statistical Manual of Mental Disorders (DSM–5) criteria, which was confirmed with administration of the structured The Mini International Neuropsychiatric Interview (MINI). Changes in depression severity are shown in Figure 1, with three flexibly dosed intranasal (IN) ketamine treatments (escalating doses of 50 to 150mg administered every 3 days), and day 8 Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary study outcome. To monitor duration of antidepressant effect, patients could be offered off-label ketamine only after day 14. The ketamine trial did not delay MAiD in any of the cases.

Patient 1 was a 67-year-old female with pancreatic cancer with short prognosis. This patient stated that she wanted to receive MAiD because she believed it was senseless to prolong an inevitable death, she would only become weaker and more bedbound, and her days seemed to be endlessly "dragging on." She denied suicidality (i.e. intent to self-harm or end their life without MAiD), stating that her request for MAiD was in no way related to her depression, but was driven by poor quality of life. Anhedonia was evident; she stated that she would normally enjoy things like going to movies, going out for meals with family, or playing games on her computer, but the physical accommodations required for such activities were too onerous, outweighing their pleasure. She was approved for MAiD by two assessors that were not involved in her clinical care or the clinical trial, although there were uncertainties about the influence of her depression in her decision making. Although she was certain she wanted to die through MAiD, she was indecisive about selecting a date, feeling guilty about leaving her family, who were distressed by her MAiD request, and how to inform her mother, who was not aware of her terminal cancer diagnosis.

After achieving an antidepressant response to ketamine, she had improved motivation, hedonic drive and energy. She went to a movie in a wheelchair seated in the aisle, organized a way to avoid long line-ups in a favorite restaurant with family, and enjoyed playing games on a smart phone. Surprisingly, with the improvement in her depression, her decision to receive MAiD became stronger. She was more easily able to prioritize her wishes over the distress of family members, pragmatically accepting that their grief would occur regardless of how she died. She wrote a letter in case her mother one day asked about her absence, explaining she did not inform her about the cancer in order to protect her and to say good-bye. She voiced feeling more at

peace with choosing to have MAiD with resolution of her guilt and indecisiveness. Then definitively set a date to receive MAiD after the weekend, but died due to natural causes prior to this date.

Patient 2 was a 60-year-old female with ovarian cancer with poor prognosis. Prior to the ketamine trial, this patient requested MAiD because of anticipating progressive loss of function and wanting to relieve her family of the burden of caregiving. She also denied suicidality, attributing her desire for MAiD to psychological suffering related to her terminal cancer diagnosis. She was clear that she wanted to have the option of MAiD, however she was uncertain about actually receiving MAiD, indecisive and turning to her husband for most care decisions, including whether to enroll in the ketamine trial. There was no evidence of coercion from her husband, who only wanted to support her decision either for or against MAiD. Patient 2's MAiD assessors struggled with distinguishing whether her desire for MAiD was driven primarily by her depression or by rationale psychological suffering related to her ovarian cancer, deferring a decision on MAiD eligibility until her depression was better managed.

After her first ketamine dose, she stated "Wow, I feel a lot better. I am so glad I finally decided to do the study"; this was confirmed by her daughter who stated "She really looked better after the first dose, but it only lasted a couple days." She reported feeling much more decisive, including being better able to assert herself. She was now able to articulate that her request for MAiD was largely driven by guilt and distorted self-perceived burden, because of low self-worth making her feel she did not deserve the care of others. She came to believe that her family wanted to care for her in her final days and she was confident in her decision to withdraw her

request for MAiD. She requested to continue intranasal ketamine off-label every 3 days outside of the study, and passed away due to natural causes on a palliative care unit several weeks after trial completion.

Patient 3 was an 80-year-old male with terminal prostate cancer. This patient had previously worked in mental health as head of social work at a hospital, and had suffered from life-long low-grade depression, which had not previously responded to antidepressants or psychotherapy. His metastatic prostate cancer was stable, but treatment was on hold until after recovery from a cardiac valve repair. He was discouraged about fatigue and a non-specific "feeling rotten" after his heart surgery, and presented to his oncologist's office stating, "What do I have to do? Go into the woods with a noose?", reflecting the presence of suicidal ideation. He requested MAiD as soon as he was informed by his oncologist that it had been legalized. He had a social grace that enabled him to mask depressive symptoms well, but his depression was marked by hopelessness, loss of motivation and severe psychomotor agitation in the evenings with insomnia. He showed no ambivalence in terms of his desire for MAiD, although he was sad to be leaving his wife. However, he was certain about refusing any further chemotherapy, as well as an offer of psychotherapy, stating "I would have jumped at the offer years ago, but I have run out of mental/emotional resources by now." He did not want his sister informed of his decision to have MAiD, believing that she would not care. His MAiD assessors were divided with respect to his capacity determination, one approving him and the second uncertain if his depression was driving his request.

Following the ketamine trial, he could appreciate that his depressive symptoms had significantly reduced and his wife stated "I haven't seen him like this in years. He's back to himself." He entertained friends in his hospital room, and agreed to engage in a psychotherapeutic life review, enjoying reminiscing about his past. He was sleeping well with resolution of his psychomotor agitation, but he was still fatigued and very deconditioned. He was consistent in his decision to pursue MAiD before, during and after the ketamine trial. He informed his sister and she visited him on the unit to say good-bye. On day 10 of the trial (i.e. 3 days after his final dose of ketamine), he received MAiD as an inpatient.

Discussion

In these three patients with terminal cancer, rapid resolution of depression with ketamine had divergent impacts on their desire for assisted dying, allowing for greater clarity regarding the underlying motivation for their MAiD request. Depression remission clarified that depressive guilt and worthlessness were the primary drivers of the MAiD request for Patient 2, impairing her capacity to decide if MAiD was the best option for her. On the other hand, Patient 1's decision for MAiD was based on her pragmatic value system, while depressive guilt and decisional uncertainty were a barrier to acting on her capable decision. The unwavering intent to receive MAiD despite resolution of depression in Patient 3 verified capacity, providing enormous reassurance to the MAiD assessor in this complex case.

While it is also possible that ketamine was behaviorally activating (6) provoking Patients 1 and 3 *to act on depressive suicidality by moving ahead with MAiD*, ketamine has in fact demonstrated mood-independent effects on reducing suicidal ideation (7,8). Furthermore,

depression symptom severity was substantially reduced for both patients (Figure 1) and there was no agitated impulsivity characteristic of antidepressant-associated suicides. Taken together, we believe it was unlikely that ketamine directly increased desire for MAiD.

Psychostimulants represent another category of agents with evidence for potential rapid antidepressant effects in the medically ill. However, psychostimulants primarily boost energy with minimal effects on other depressive symptoms making their utility for patients with moderate to severe depression limited compared to ketamine that may have broader effects on other depressive symptoms (9).

Ketamine as a type of litmus test for the influence of depression on the desire for MAiD has relevance in regions such as Australia and the United States where assisted dying is not permitted for depression alone, and in Canada, to inform the current legislative debates on this issue (10). MAiD eligibility assessment requires an equipoised balancing of the need to respect a patient's rights, with the need to protect patients who are vulnerable.

Acknowledgments: The primary clinical trial from which these cases were derived received funding from the Canadian Cancer Society, grant # 705385.

Conflicts of Interest: ML reports no financial relationships with commercial interests. JDR reports industry funding for speaker/consultation/research fees from Inagene, Allergan, Lundbeck and COMPASS and is the medical director of a private clinic providing intravenous ketamine infusions and intranasal esketamine for depression.

Data Availability Statement: Research data are not shared as these are preliminary results of an ongoing clinical trial.

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Table 1: Demographic Information, Baseline Measures and Case Details

	Patient 1	**Patient 2**	**Patient 3**
Age and Sex	67-year-old female	60-year-old female	80-year-old male
Cancer type	Pancreatic	Ovarian	Prostate
Life expectancy	1-2 months	1-3 months	2-3 months
Past psychiatric history	None	Major Depressive Disorder	Persistent Depressive Disorder (formerly Dysthymia)
Current psychotherapy	Seeing a cancer psychiatrist in individual and family counseling for 6 months	Engaged in individual end of life counseling with a cancer psychiatrist during admission	Refused multiple offers of psychotherapy
Current psychotropics	bupropion 150mg mirtazapine 45mg zopiclone 3.75mg	escitalopram 10mg clonazepam 0.5mg twice daily	trazodone 150mg zoplicone 3.75mg clonazepam 0.5mg
Baseline *MADRS	31 (moderate)	38 (severe)	25 (moderate)
Dosing of Ketamine	Day 1 – 50mg Day 4 – 100mg Day 7 – 75mg	Day 1 – 50mg Day 4 – 75mg Day 7 – 75mg	Day 1 – 50mg Day 4 – 75mg Day 7 – 100mg
Adverse Effects	- transient** drowsiness - vivid dreams resulting in 3rd dose reduction	-transient drowsiness and dizziness	-transient drowsiness and confusion

*Montgomery-Åsberg Depression Rating Scale (MADRS)
** resolving within 1-2 hours of each dose

Figure 1: Changes in symptoms of depression as measured by the MADRS. Patients received three escalating flexible doses of intranasal ketamine dosed every three days. Ketamine was administered intranasally using the Intranasal Mucosal Atomization Device (Teleflex ®). Black arrows indicate when doses of ketamine were received.