



**Treatment in Geriatric Mental Health:
Research in Action**

Rapid-Response Treatments for Depression and Requests for Physician-Assisted Death: An Ethical Analysis

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ABSTRACT

Depression is common at the end of life, and there is longstanding concern that it may affect terminally ill patients' decisions to request physician-assisted death (PAD). However, it is difficult for clinicians to determine the role of depression in a patient's PAD request. A recent case series described rapid responses to intranasal ketamine in three patients with terminal illness and comorbid depression who had requested PAD. One patient withdrew her request (which, in retrospect, had been driven by her depression) while the others maintained their requests; in all three, the rapid relief clarified the role of depression in the patients' decision-making. In addition to ketamine, there are other emerging rapid-response treatments for depression, including psilocybin with psychological support and functional connectivity-guided transcranial magnetic stimulation. We examine three key ethical implications of such treatments: their role in clarifying the decision-making capacity of depressed patients requesting PAD; the potential tension between the legal definition of irremediability in some jurisdictions and the ethical obligations of clinicians; and the likely obstacles to treatment access and their implications for equal respect for autonomy of patients. (Am J Geriatr Psychiatry 2022; 30:1255–1262)

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Highlights

- **What is the primary question addressed by this study?**

What are the ethical implications of emerging rapid-response treatments for depression for depressed patients who request physician-assisted-death?

- **What is the main finding of this study?**

The development of rapid-response treatments could have an important role in clarifying the decision-making quality of depressed patients seeking PAD, raise potential dilemmas for clinicians assessing the PAD eligibility criterion of irremediability in some jurisdictions, and challenge society's obligations for making such treatments available for patients in particularly vulnerable situations.

- **What is the meaning of the finding?**

Although the emergence of rapid-response treatments for depression will likely have important benefits to depressed patients requesting PAD, they also raise ethical challenges for those jurisdictions in which the practice is legal.

INTRODUCTION

Physician-assisted death (either euthanasia or physician-assisted suicide; PAD hereafter) is a controversial practice legal in Canada, 10 states in the United States, the Netherlands, Belgium, and other jurisdictions.^{1,2} Although the majority of PAD involves persons at the end of life, usually with cancer,¹ some jurisdictions allow PAD for nonterminal conditions such as psychiatric disorders and chronic disabilities.² In all jurisdictions, the patient's PAD request must be a competent, informed decision, and their condition irremediable.²

As most cases are at the end of life, PAD largely involves the elderly. In Oregon for example, the median age of those receiving PAD in 2021 was 75.³ Further, depression is common at the end of life. One systematic review found that 39% patients with incurable cancer are depressed, while another found that 50% of patients with extremely short prognoses (days to weeks to live) had clinically significant depressive symptoms.^{4,5} In a study from Oregon, 26% of those who requested or inquired about PAD had clinical depression.⁶

Major depressive episodes in persons requesting PAD has long been a concern in the PAD literature even among supporters of PAD⁷ because it can color a patient's evaluative perspective and treatment preferences,^{8,9} can cause decisional incapacity,^{10–12} and is associated with suicidal ideation.¹³ Though the extent of the similarities between suicide and PAD is contested,¹⁴ depression may make it unclear whether

a patient's request for PAD is part of suicidal ideation driven by depression, or is an exercise of autonomy consistent with their values. Because most traditional treatments for depression require a lengthy trial period (as well as potential systemic side effects in medically-compromised patients), treating the depression to clarify terminally ill patients' capacity and the role of depression in their request can be challenging.¹⁵ However, with the recent emergence of what might be called rapid-response treatments for depression (RRT), that is, with a potential to elicit a meaningful response even in patients with short life expectancies, there is a renewed need to consider their implications for the practice and policy of PAD.

We first briefly review the emergence of RRT for depression, including their use in the PAD context in some cases. We then discuss three primary ethical implications of this development.

EMERGENCE OF RAPID-RESPONSE TREATMENTS FOR DEPRESSION IN THE TERMINALLY ILL

Case series of Ketamine for Terminally Ill Patients

Recently, Rosenblat and Li reported on 3 patients who received intranasal ketamine in an open-label trial and showed rapid response.¹⁵

A 67-year-old woman with pancreatic cancer requested PAD; she stated that her request was driven by "poor quality of life" and "in no way related to her depression." Although approved for PAD, the

assessors felt “there were uncertainties about the influence of her depression in her decision-making,” as the patient was “indecisive about selecting a date, feeling guilty about leaving her family, who were distressed by her [PAD] request...” With improvement in her depression, her PAD decision “became stronger” and “more at peace” with her choice, “with resolution of her guilt and indecisiveness.” She died of natural causes, prior to her scheduled PAD.

A 60-year-old woman with ovarian cancer who requested PAD was “clear that she wanted to have the option” of PAD, but was uncertain about “actually receiving” PAD, and indecisive in most care decisions, including about receiving ketamine; her PAD assessors “struggled with distinguishing whether her desire for (PAD) was driven primarily by her depression” and were uncertain of her capacity, and therefore deferred their decision on eligibility; after resolution of her depression, she withdrew her PAD request. In retrospect, she saw her initial request as “largely driven by guilt and distorted self-perceived burden” which led her to feel “she did not deserve the care of others.” She died of natural causes several weeks after the ketamine trial.

An 80-year-old man with terminal prostate cancer, with life-long “low grade depression” that had not responded to treatments, expressed suicidal ideation, hopelessness, and loss of motivation, and had symptoms of severe psychomotor retardation and insomnia. Two PAD assessors disagreed about his capacity. His wife described his dramatic response to ketamine as “I haven’t seen him like this in years. He’s back to himself.” But he was “consistent in his decision to pursue (PAD) before, during, and after the ketamine trial.” Though his decision did not change, he began entertaining friends and family in his hospital room, “agreed to engage in a psychotherapeutic life review,” and informed his sister of his choice, whereas previously he believed she “would not care.” He received PAD three days after his final dose of ketamine.

Ketamine for Depression

A systematic review of the efficacy of intravenous ketamine treatment for treatment-resistant depression found support for the use of ketamine for rapid management of depressive symptoms.¹⁶ Similarly, a systematic review of ketamine for mental health disorders found robust evidence for the antisuicidal effects of ketamine.¹⁷

Finally, every study in a review of ketamine for treatment of depression in palliative care patients found antidepressant effects of ketamine, indicating its promise for treatment of depression in the terminally ill.¹⁸

Psilocybin for Patients With Life-threatening Cancer

A randomized double-blind crossover trial of high-dose psilocybin with psychological support (several meetings with two trained monitors before, during, and after sessions) in 51 cancer patients with life-threatening diagnoses (65% with recurrent or metastatic disease) and symptoms of depression and/or anxiety found that a single high dose session improved mood and anxiety, quality of life, and death anxiety.¹⁹ The Canadian government recently added psilocybin to their Special Access Program, which permits clinicians to use unapproved drugs that have shown promise in clinical trials or are approved elsewhere.²⁰ Several terminally ill cancer patients in Canada have already gained access for end-of-life distress, highlighting its potential use at the end of life.²¹

High Dose Functional Connectivity-guided iTBS

Intermittent theta-burst stimulation (iTBS) usually takes 6 weeks of treatment with suboptimal efficacy. However, in a sham-controlled RCT, individually targeted iTBS based on resting state fMRI connectivity analysis was highly effective in treating moderate-to-severe treatment-resistant depression after only 5 days of treatment.²² Although not yet tested in depressed persons at the end of life, the procedure had minimal side effects.

Each of these treatments is rapid acting, which is particularly important for depressed patients with limited life expectancy. The continued development and success of such therapeutics will have important clinical implications for treatment of depression at the end of life. But what are the ethical implications of this development in the context of PAD?

DISCUSSION

Clarifying Patient’s Decision-Making

Jurisdictions that permit PAD require that requesting patients are “capable of making decisions with

respect to their health.”²³ The Oregon Death with Dignity Act specifies that patients should not be “suffering from a psychiatric or psychological disorder or depression causing impaired judgment” while the Netherlands requires a patient’s decision to be “voluntary and well-considered.”^{24–26} But assessing the impact of depression on decision-making capacity (DMC) can be complex. For mild to moderate depression, the impact on DMC is likely minimal.²⁷ However, in persons with severe depression, especially if cognition is affected, the rate of incapacity may be significant.^{11,12,28}

But even when cognition is relatively preserved, depression can compromise a person’s DMC by impairing the ability to apply the relevant clinical and personal information to one’s own situation,²⁹ consider new evidence or alternative perspectives,³⁰ or adequately evaluate the future.³¹ In general, there has been an increasing focus in the DMC literature on the role of emotions and values (elements which may be affected by depression) and DMC, but as of yet no clear guidance on how such factors should be evaluated.³²

It is therefore not surprising that in the above cases reported by Rosenblat and Li, there was disagreement among evaluators in one case and consensus about uncertain capacity in another.¹⁵ The current guidance on DMC assessment of persons requesting PAD tends to be fairly general. For example, the University of California San Francisco PAD Psychiatric Assessment Protocol focuses on the cognitive aspects of DMC and does not provide much guidance on subtler impacts of depression on DMC³³—the kind of impact that Rosenblat and Li describe in their report (eg, “depressive guilt and worthlessness were the primary drivers of the [PAD] request for Patient 2, impairing her capacity to decide...”¹⁵). The Dutch Euthanasia Review Committees’ Code of Practice contrasts a PAD request as either “well-considered” or “a symptom of his illness,”²⁶ but in practice Dutch clinicians do not offer detailed (or often any) rationales for their judgment that a depressed person’s PAD was or was not “driven by depression.”³⁴

Given the difficulties of assessing the impact of depression on DMC, an effective rapid-acting treatment of depression in the terminally ill is obviously a powerful tool for clarifying these uncertainties in capacity assessment. If the patient

does respond to the treatment, it reduces the potential for erroneous capacity assessments—both false positives (of incompetence) leading to deprivation of a person’s legal right to receive PAD, and false negatives that lead to premature deaths and deprivation of potentially meaningful last days in people’s lives. Aside from this improved accuracy in capacity assessment, it is important to remember that even competent patients make sub-optimal decisions when influenced by depression; improving the quality of such decisions could have a positive impact on not only patients but also, importantly, those they leave behind. For example, one patient chose to inform his sister of his decision, allowing her to say goodbye, and agreed to a psychotherapeutic life review, “enjoying reminiscing about his past.”¹⁵ Whether or not a patient changes their decision, their end-of-life decision-making may be enhanced by RRT, benefitting them and their family.

Even if a patient’s depression does not respond to RRT, there could be important benefits to routinely offering RRT to depressed patients requesting PAD. As providing RRT to such patients becomes the norm, research studies may yield information on predictors of PAD request withdrawal or of factors that indicate incapacitous requests. Thus, a routine use of RRT in the PAD context may eventually yield evidence to guide difficult capacity assessments of persons who may not respond to RRT.

What about patients who refuse RRT? This is an important question to address because it is not unusual for patients to resist treatment for a psychiatric condition. It may be necessary to consider two decisions when conducting a capacity assessment: the decision to request PAD and the decision to refuse RRT, as both may be affected by depression. But the question arises: even if a person competently refuses RRT for depression, should this person be offered PAD? One important factor is whether the patient is deemed to have capacity to request PAD. But even if they do have such capacity, it creates a difficult situation for a clinician—one in which the clinician would be asked to accept a patient’s refusal of a low risk-high potential benefit procedure (the RRT), and then further comply with a request for an irreversible procedure that could have been avoidable had the patient accepted the recommended RRT and retracted their PAD request. This leads us to consider the

implications of RRTs for the evaluation of irremediability in various PAD jurisdictions.

Assessment of Irremediability of Suffering

The emergence of RRTs for treatment of depression in those requesting PAD will have different implications for clinicians depending on their jurisdiction's irremediability requirement. In the Netherlands, for example, a physician must conclude "together with the patient that there is no reasonable alternative" to PAD.²⁶ Under such a requirement, it is possible that even if a depressed patient competently requests PAD and refuses RRT as an alternative, a clinician could reasonably disagree with a patient's judgment that there are no "realistic options...that would end or alleviate [their] symptoms," as a patient's depression may affect the perceived tolerability of their medical symptoms. On this basis, a physician could find the patient not (or not yet) eligible for PAD.

Some jurisdictions, however, incorporate patients' subjective judgment as the sole basis for determining irremediability. The Canadian law requires a "grievous and irremediable medical condition" that must cause patients "enduring physical or psychological suffering that is intolerable to them and that cannot be relieved *under conditions that they consider acceptable*"²³ [emphasis added]. But relying solely on a patient's perspective may be problematic when their depression may be driving their perceptions of what is "intolerable to them" and what treatments "they consider acceptable." And, as noted, refusal of psychiatric treatment is not unusual; recall that the patient who changed her mind about PAD above was indecisive about enrolling in the ketamine trial. But in the Canadian system, even if a patient's suffering can be medically addressed through RRT (in effect, medically remediable), that patient can deem the option unacceptable—and the clinician must still find the patient eligible for PAD if they meet the other criteria.

From a clinical perspective, the emergence of RRTs for depression in terminally ill patients is a welcome development. It promises to relieve their unnecessary suffering as well as to increase the quality of their decision-making (including that regarding PAD) when they are at a particularly vulnerable point in their lives. But in some jurisdictions, clinicians may be forced to acknowledge a legally defined irremediability that is at odds with

clinical remediability. That the ready availability of RRT for depressed patients requesting PAD could lead to such paradoxical situations reveals a tension between the law's demands and professional ethics in such jurisdictions.

Treatment Access and Equal Respect for Autonomy

The above analysis shows the potential clinical and ethical benefits of RRTs for depression in the PAD setting, regardless of what a patient ultimately chooses regarding PAD. Access to RRTs could prevent needless psychological suffering at an especially vulnerable time in peoples' lives and can help clinicians clarify patients' capacity and judgment. Thus, ideally, RRTs would be made widely available to depressed patients who request PAD.

However, there could be obstacles to making RRT standard practice. Providing such novel treatments will likely be resource-intensive and expensive. Administration of psilocybin requires a highly supportive holistic approach that requires substantial resources.³⁵ Ketamine also requires various levels (depending on route of administration) of medical and psychiatric monitoring, with attendant resource needs.³⁶ Even old drugs can become increasingly commercialized, which could interfere with widespread access.³⁷ Similarly, high dose functional connectivity-guided iTBS relies on a technical proprietary procedure to identify which areas of the brain to target.²² All of these treatments will be expensive, and may require even more resources when provided for a medically fragile patient population.

In both the US and Canada, despite their very different health care funding structures, access to mental health care is suboptimal. In the United States, many are uninsured,³⁸ and affordability is the most common reason for not receiving mental health services,³⁹ while in Canada, only half of people with depression receive "minimally adequate" treatment.⁴⁰ In such health systems that struggle to provide accessible and adequate mental health services to its population, the extensive resources required to widely provide RRT may make it difficult to implement.

In such a setting of scarce resources, the problem of inequality is an obvious ethical concern. In the case of RRT for depressed persons at the end of life, unequal access has special ethical significance as it may

translate into unequal respect for autonomy. Autonomy is the central motivating principle underlying PAD.⁴¹ For example, Death with Dignity, a prominent PAD advocacy organization, seeks to “ensure people with terminal illness can decide for themselves what a good death means in accordance with their values and beliefs.”⁴² Ethically, a society that oversees PAD practice and policy should ensure that PAD requests are autonomous for all, not just for those who have sufficient resources. Bioethicists have argued that true autonomy requires genuine options, and that inadequate access to healthcare could drive some people to choose PAD.^{43,44} Recent Canadian cases support this worry. In 2019, a Canadian man with ALS chose to die after being transferred from a facility that provided all of his necessary care to a hospital that could not meet his care needs.⁴⁵ Another Canadian man with ALS chose to die after being offered 20-hour home care instead of the full 24-hour home care necessary for him to maintain an adequate quality of life.⁴⁶ Recently, a woman with severe chemical sensitivities requested a medically-assisted death after being denied the housing needed to manage her symptoms.⁴⁷

Making RRT available will make it more likely that those who choose PAD, both those with resources and without, do so autonomously, rather than as a forced choice in the absence of adequate alternatives. While those who withdraw their PAD requests after RRT may not live much longer, allowing them to “decide for themselves...in accordance with their values and beliefs” promotes their autonomy and gives them, rather than their depression, control over their deaths.⁴²

LIMITATIONS

Our ethical analysis largely focuses on PAD requests by those with terminal illnesses. Although most PAD is provided for the terminally ill, a significant minority is provided for those with nonterminal illnesses.⁴⁸ Many of these patients may suffer from comorbid depression, so our analysis would apply to them as well. Similarly, the development of RRT has implications for psychiatric PAD, which is legal in some jurisdictions.² The rapid effectiveness of these treatments may require a change in how clinicians evaluate irremediability for patients who request

PAD with a primary diagnosis of treatment-resistant depression. For PAD requests by patients with a psychiatric illness and comorbid depression,⁴⁹ RRT could help clinicians evaluate the effects of depression on capacity and irremediability, just as for patients with physical illnesses and comorbid depression. However, we cannot provide a full analysis of these issues here.

A further limitation is that the case series from Rosenblat and Li involved only three patients. Thus, it is difficult to know how often depressed patients who request PAD would change their minds if effectively treated with RRT. However, the literature on the impact of depression on end-of-life medical preferences supports the likelihood that there will be a sizable proportion of depressed persons whose PAD requests may change with effective treatment.^{8,9} This is further supported by the fact that nearly half of the persons who seek PAD for psychiatric reasons—among whom depression is the most prevalent diagnosis⁴⁹—withdraw their requests either during or after the evaluation process.⁵⁰

CONCLUSIONS

PAD is a controversial practice. In some jurisdictions, such as the United States, it is limited to self-administration of a drug by those with terminal physical illnesses, but in others, it involves euthanasia with broader eligibility conditions that include nonterminal disorders and psychiatric conditions. When a depressed patient makes a PAD request, the clinician’s role becomes challenging, as depression may affect a patient’s DMC and judgment, and “drive their desire for PAD,” but how to determine this role of depression is not always clear. In addition to the primary benefit of relief from depression, effective RRT for depression has ethical implications for PAD practice and policy. Widespread availability of RRT could help clinicians determine whether a patient’s request is competently made. On the other hand, the availability of RRT could also reveal a thorny ethical tension between a legal definition of irremediability (as in Canada) and the ethical obligations of clinicians. Finally, despite their clear benefits, the expensive and resource-intensive nature of these novel treatments may prove to be a barrier to access, especially for those

with fewer resources. Those with access to RRT will enjoy greater autonomy in decision-making—regardless of their final decision on PAD—whereas those without may experience unequal respect for their autonomy. In a controversial practice such as PAD, even a salutary development such as the emergence of rapidly effective treatment for depression can create ethical complexities for clinical practice and social policy.

AUTHOR CONTRIBUTIONS

Both authors conceived of the paper, conducted ethical analysis, and wrote the final manuscript.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

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