Ketamine for depression: a potential role in requests for Medical Aid in Dying?

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Medical Aid in Dying (MAiD) is the act of a healthcare provider ending a patient's life, at their request, due to unbearable suffering from a grievous and incurable disease. Access to MAiD has expanded in the last decade and, more recently, it has been made available for psychiatric illnesses in a few countries. Recent studies have found that such psychiatric requests are rapidly increasing and primarily involve mood disorders as the primary condition. Nevertheless, MAiD for psychiatric disorders is associated with significant controversy and debate, especially regarding the definition and determination of irremediability – that a given patient lacks any reasonable prospect for recovery. In this article, we report the case of a Canadian patient who was actively requesting Medical Assistance in Dying for severe and prolonged treatment-resistant depression until she experienced remarkable benefits from a course of intravenous ketamine infusions. To our knowledge, this is the first report of ketamine or any other intervention yielding remission in a patient who would have otherwise likely been eligible for MAiD for depression. We discuss implications for the evaluation of similar requests and, more specifically, why a trial of ketamine warrants consideration. *Int Clin Psychopharmacol* **XXX: XXXX–XXXX**

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Background

Medical Aid in Dying (MAiD) is a practice that has been defined as a terminally ill, mentally capable adult with a prognosis of 6 months or less to live, receiving medical assistance in bringing about their death so as to end intolerable suffering (Boivin and Barrette, 2016). MAiD is legalized in many countries (Kim and Lemmens, 2016; Ball *et al*., 2019; Guérinet and Tournier, 2021), of which a growing proportion are replacing the criterion of 'terminal' (e.g. life prognosis of 6 months or less) with a broader definition based only on grievousness and irremediability, rather than expected survival time (Guérinet and Tournier, 2021; van Veen *et al*., 2022b). Indeed, in Switzerland, Holland, Belgium, Luxembourg, and Canada, MAiD is indicated for non-terminal illnesses, potentially including psychiatric disorders (Guérinet and Tournier, 2021; van Veen *et al*., 2022b). In Canada, this change was recently adopted by the Canadian parliament via an amendment to the criminal code (Health Canada, 2022, van Veen *et al*., 2022b), with the caveat that patients seeking MAiD for mental illness would not be eligible until March 2023 so as to allow an expert committee to further study and oversee the implementation of this controversial change (Health Canada, 2022; van Veen *et al*., 2022b).

According to recent studies, MAiD requests for psychiatric conditions make up a small but increasing proportion of overall MAiD requests, rising in the Netherlands from two such granted requests in 2010 to 88 in 2020 (Yearly report of the Dutch Regional Euthanasia Review Boards, 2020 [in Dutch] cited in van Veen *et al*., 2022b). Most psychiatric MAiD requests involve mood disorders, particularly treatment-resistant depression (TRD) (Kim *et al*., 2016; Kim and Lemmens, 2016; Guérinet and Tournier, 2021; van Veen *et al*., 2022a). This expansion of MAiD to conditions like depression is associated with debate, uncertainty, as well as unique clinical challenges (Kim and Lemmens, 2016; van Veen *et al*., 2022a, 2022b). One central challenge is the determination of a given patient's prospects of recovery, relapse, and recurrence for depression or TRD. Indeed, numerous studies have found relatively poor accuracy in both clinical judgement and the latest data-based prediction models for assessing prognosis in depression (Moriarty *et al*., 2021). In this article, we report a case that highlights these challenges: a Canadian patient who was actively requesting MAiD for TRD until she experienced a remarkable, even surprising, degree of benefits from a course of intravenous ketamine infusions. Informed consent was received from the patient to publish this case report.

Case report

A 68-year-old woman was followed in psychiatry since 2004 for severe TRD according to psychiatric assessment

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and the Dutch-Modified Maudsley Treatment-Resistant Staging Method (DM-TRD) (Peeters *et al*., 2016), generalized anxiety disorder and dependent personality disorder, all diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (American Psychiatric Association, 2013). She had only partial or fleeting responses to adequate trials of more than a dozen psychotropic medications, transcranial magnetic stimulation, two courses of electroconvulsive therapy, and several courses of formal psychotherapy. She made two documented requests for MAiD, in January 2020 and April 2021, describing more than 15 years of suffering from severe depression, anxiety, nearly constant suicidal ideation, and no hope for her recovery. On both occasions, she was informed by her psychiatrist that MAiD was not yet available in Canada for psychiatric indications.

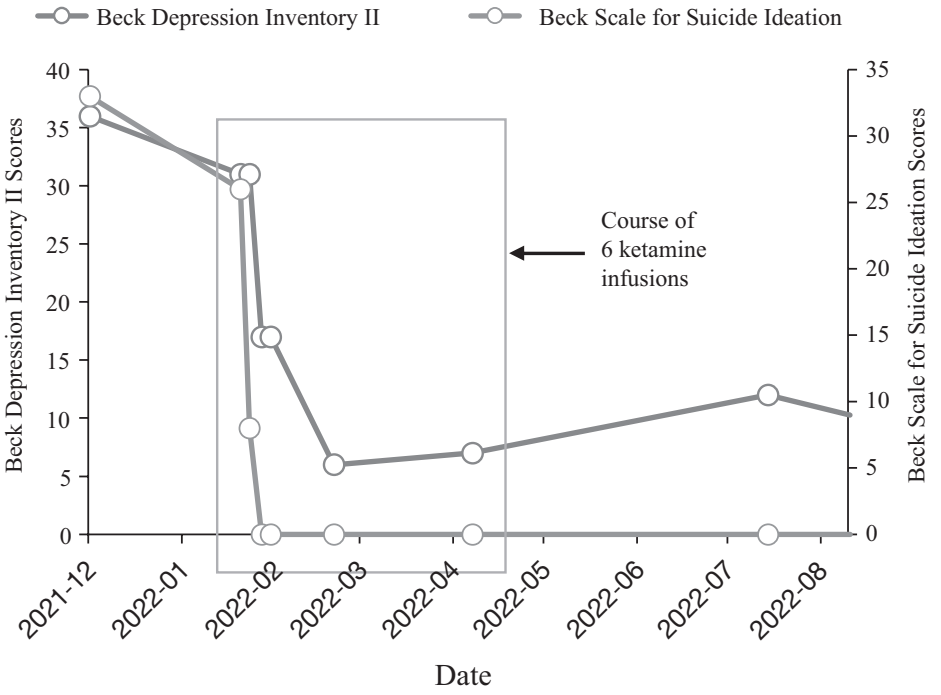
The patient was eventually referred to our institution's newly established service offering intravenous ketamine for TRD in December 2021. On evaluation, her medications included citalopram 40 mg three times a day, buspirone 5 mg three times daily, and nabilone 0.5 mg every night at bedtime. Her score on the DM-TRD was 22 of a maximum 27 (Peeters *et al*., 2016), qualifying her as severely resistant. She was accepted and consented to our standard protocol of six 40-min intravenous infusions (0.5 mg/kg bodyweight) over 4 weeks, alongside weekly supportive psychotherapy.

Despite her poor responses to numerous past psychiatric treatments, the patient rapidly and robustly remitted with intravenous ketamine in less than 2 weeks (Fig. 1). From baseline to after the fourth infusion, her Beck Depression Inventory-II (Beck *et al*., 1996) scores decreased from 40 to 6 and her Beck Scale for Suicidal Ideation (Beck *et al*., 1979) scores decreased from 38 to 0, in addition to significant improvements on measures of quality of life and anxiety. All such gains have since been sustained for more than 6 months following the initial treatment course, with only one additional 'boost' ketamine treatment for returning depressive symptoms (although not suicidality) after 6 months, in addition to occasional supportive psychotherapy sessions. The patient's request for MAiD remains withdrawn.

Discussion

This case illustrates a central challenge facing clinicians assessing requests for MaiD for psychiatric indications like mood disorders: evaluating an individual patient's prognosis and determining that all acceptable and potentially beneficial treatment possibilities have been exhausted. According to a recent and extensive report from the Netherlands, where MaiD is regulated by law since 2002, 46% of psychiatrists reported having already received at least one psychiatric MAiD request in their career (van Veen *et al*., 2022a). These respondents reported that patients requesting MAiD often had

Fig. 1



Baseline and pre-infusion scores on the beck depression inventory II and the Beck Scale for suicide ideation measures.

'severe and long-standing psychiatric complaints, with 60% having a treatment history of more than 10 years'. Indeed, in the absence of effective prognostic tools, a long personal history of treatment failures is a key component of psychiatric MAiD requests for them to be seriously considered and potentially granted. This has been acknowledged in districts beyond the Netherlands, as evidenced by the consensus shared by the National Canadian MAiD Committee recommending that 'as with many chronic conditions, the incurability of a mental disorder cannot be established in the absence of multiple attempts at interventions with therapeutic aims' (Health Canada, 2022).

However, the need for numerous past treatment failures in order to establish irremediability must be balanced against a patient's right to autonomy, including the right to refuse treatments that are deemed to be personally unacceptable. Experts have therefore identified the need for limits to the number of past treatments required for a patient requesting psychiatric MAiD (Dembo *et al*., 2018; Health Canada, 2022), but no clear guidelines exist as to how many or what sort of such treatment trials should be seen as sufficient. Irremediability is therefore operationalized as a judgement shared between patients and their psychiatrists about their prognosis, based on reviewing their past psychiatric history, exploring their current state, and discussing further treatment options (van Veen *et al*., 2022a, 2022b). Accordingly, it is essential for clinicians to have up-to-date and reliable evidence about all potential treatments, including less common psychopharmacological interventions such as tricyclic antidepressants and monoamine oxidase inhibitors, ketamine, and emerging treatments like the serotonergic psychedelics.

Indeed, ketamine may be easily overlooked by clinicians and patients considering MAiD for depression, but as our case highlights, it warrants serious consideration. Subanesthetic doses of intravenous ketamine have accumulated more than 20 years of evidence for unique benefits against refractory depression and suicidality (McIntyre *et al*., 2021; Alnefeesi *et al*., 2022) in both unipolar and bipolar depression. Multiple clinical trials have found high tolerability and acceptability of ketamine (Wan *et al*., 2015), particularly relative to electroconvulsive therapy. In responders, ketamine's benefits typically manifest within hours or days of one or several treatments, as opposed to weeks–months for conventional oral antidepressants (Malhi *et al*., 2020). This rapidity is not only valuable in terms of potentially reducing suffering, but it also facilitates the evaluation of response, given that external life events are less likely to obfuscate the clinical picture relative to treatments that require months for full therapeutic effect. Further, as intravenous ketamine is administered directly by medical personnel, treatment adherence and engagement are more reliably assessed versus oral antidepressants or psychotherapy. Lastly, there is preliminary evidence suggesting that greater treatment-resistance may be associated with greater odds of response to intravenous ketamine, whereas the reverse is true for conventional treatments (Price *et al*., 2022).

These unique benefits make a compelling case for intravenous ketamine to be considered when evaluating MAiD requests for depression. Indeed, the patient described above may well have received MAiD had a trial of intravenous ketamine not been available or offered before the pending Canadian legislative changes come into force in early 2023. Beyond ketamine, this case more broadly illustrates the potential for grave and irreversible consequences of psychiatric irremediability assessments that lack validity.

Conclusion

The increasing availability of MAiD for psychiatric indications raises important and complex ethical considerations, which have been subject to considerable debate (Kim and Lemmens, 2016; Dembo *et al*., 2018; van Veen *et al*., 2022b). Beyond debate, however, is that all patients grappling with the potentially irreversible decision to pursue MAiD deserve equitable access to evidence-based treatments. In particular, we suggest that intravenous ketamine is a particularly important treatment to consider given its strong evidence for unique and rapid benefits in exactly the sort of TRD cases where MAiD may be being considered. Our case highlights this potential role for ketamine and, more broadly, underscores the need for guidelines, prognostic tools, and resources to assist patients and clinicians considering MAiD for TRD in a landscape of growing demand.

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Conflicts of interest

S.R. holds a research scholar award from the Fonds de Recherche du Québec en Santé, Quebec, Canada. For the remaining authors, there are no conflicts of interest.

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