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Title: Medications and doses used in medical assistance in dying (MAiD): a cross-sectional study

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General comments (author response in bold)

Background

Mention of “assisted suicide” and “voluntary euthanasia” are problematic as those concepts have no resonance in current Canadian legislation. Furthermore, the intentional use of lethal drugs self-administered by patients (described as “assisted suicide” by the authors) is described as legal in Canada, but it is not authorized by the Quebec law. I would recommend that the authors provide a clear definition of Medical Aid in Dying based on current Canadian legislation at the beginning of the paper, and use descriptive language throughout the article (we have previously published an international descriptive classification of medical end-of-life practices, which could serve as inspiration).

Thank you, there is much confusion in the literature on the topics. We have changed the terms used in the introduction to re-reflect this. (Page, 2, introduction: A growing number of countries have decriminalized medical assistance in dying (MAiD) as a means for patients to avoid prolonged suffering(1-4). While each jurisdiction's legislative criteria allowing the intentional use lethal drugs by a clinician vary, in practice the act of hastening a patient's life can be done in two ways. Health care providers can directly administer a lethal medication, or they can prescribe a lethal medications to a patient for self-administration; or these two methods could be combined (5). In Belgium, The Netherlands, and Luxembourg, both clinician-administered and self-administered methods are allowed; Colombia allows only clinician-administered; and Switzerland, the Australian state of Victoria, and several US states permit self-administration only(5-8)..In Canada, Bill C-14 defined a process and criteria under which MAiD would be permitted, it did not specify which methods of hastening death could be used in Canada, and as a result MAiD includes both administration of medications by physicians and nurse practitioners, and prescriptions of lethal medications self-administration (excluding Quebec).)

It would be useful to provide an overview of the medication protocols recommended in Canada. Having a sense of current professional recommendations would be helpful to identify potential gaps between what is recommended vs. what is used in practice (eg. potassium chloride is not recommended in the CAMAD guidelines), which should be highlighted in the discussion.

Thank you, we have added this to the introduction. (Page 3, Introduction: The CAMAP guidelines recommend fixed-dosing of midazolam 10 mg (an anxiolytic), propofol 1000 mg (an anesthetic coma-inducing agent), and either rocuronium 200 mg or cisatracurium 40 mg (neuromuscular blockers to stop respiration).)

Methods

The study population is labelled as a “study cohort” and the method section of

the abstract identifies the study as a “retrospective cohort study” (this is also part of the title). I do not believe it is an appropriate description of the study design. Although the population includes data collected between 2016 and 2020, there is no data being collected from the same patient at multiple time points, which is the hallmark of cohort study designs. This should be corrected and removed from the title.

We have made these changes. (Multiple)

The study population is drawn from multiple databases, including the Chief Coroner of Ontario MAID database, as well as records from Ottawa Hospital, Hamilton Health Center and Vancouver Coastal Health. This results in a mixed study sample which merges a provincial-wide database with 3 hospital-specific databases. Although this study population can be appropriate to assess the relationship between medication choice and duration of death, it is problematic with regard to the stated objective of “describing medications used in MAID” in Canada, because the study population is biased toward patients receiving MAID in hospital (as opposed to drugs used in the community) and is largely focused around Ontario. This should be highlighted in the discussion. I would also remove the word “national” from the title.

Thank you we have made these changes and added this to the discussion. of note, the OCC database includes in-hospital and community deaths; and the total sum of cases included here is roughly half of all Canadian MAiD deaths at the time of analysis. We thus have some confidence in the generality of the findings here.

(Interpretation Page 14: As well, the demographics of patients in the study most closely relate to those in Ontario, from where the vast majority of study data was obtained. However, the relationships between medications, time of death, and complications is unlikely to vary greatly between regions.)

The article states that the Office of the Chief Coroner of Ontario MAID database includes “information on all Ontarians who have died with medical assistance” (my emphasis). This is partly true, as the Coroner database does not include MAID that is not reported by physicians to official authorities. Anonymous studies conducted in Europe suggest that a significant proportion of intentional lethal drug use by physicians are not reported to regulatory authorities². For example, in the years following legalization of euthanasia in Belgium, only 52% of cases of intentional use of lethal drugs by physicians were reported to euthanasia regulatory authorities³. These unreported cases tend to use medications that are not listed in MAID’s official protocols (eg. high-dose opioids and sedatives above what is needed for symptom control), which has a significant impact on the description of drugs used in MAID in Canada. To the best of my knowledge, no study has investigated the issue of non reporting of MAID in Canada. This line should be corrected and this limitation highlighted in the discussion section.

Thank you.

End of life practices appear to vary greatly between the European and Canadian contexts, and it appears that unreported instances of clinicians intentionally hastening death is much higher in the European countries than Canada—to be honest, when reviewing the European literature for the first time I was pretty shocked at the number of clinicians illegally hastening death.

The OCC cross-checks with pharmacy requests for medications and is quite certain that unreported MAiD deaths are much more uncommon in Ontario. While this does not mean unreported, purposeful hastening of patient deaths do occur using other medications, this is not relevant to the study as we are only interested in the effects of medications which are used and recommended in legal hastening of a patient's death.

We have added to the discussion section. (It is also possible that unreported MAiD cases may have been unreported, but these numbers are likely small. As well, the demographics of patients in the study most closely relate to those in Ontario, from where the vast majority of study data was obtained. However, the relationships between medications, time of death, and complications is unlikely to vary greatly between regions.)

How have the “low, standard and high” medication dosage threshold been established?
See response to editor point #12. (See response to editor point #12.)

Discussion

The authors conclude that “complications occurred in 41 (1%) of MAiD deaths, mostly related to venous access or need for a second medication administration.” However, reported complications included in the study database are limited to those observable directly by professionals (or family members). This excludes complications that may be experienced by patients, but not directly visible to external observers.

The use of neuromuscular blockers (administered in 98% of the 3557 study participants) limits the ability to externally assess patients’ experience of suffering because it causes full body paralysis and prevents patients to talk, breathe, cough or move.

A clinically significant potential complication of neuromuscular use in the context of MAiD is the risk of “conscious anesthesia”, where patients would be insufficiently sedated are aware of the feeling of suffocation provoked by respiratory muscle paralysis⁴. Conscious anesthesia is a well-documented complication of neuromuscular use in the context of surgery, where it occurs in approximately 1 to 2 cases in a 1000. The fact that barbiturate dosing reported in the current study occasionally fall well below recommended dosage (as low as 1mg of propofol) is of great concern in that regard.

In a scoping review of 329 empirical studies about the intentional use of lethal drugs by physicians published over a 24-year period, our research team did not identify a single study assessing the risk of conscious anesthesia in the context of medical aid in dying. A more recent scoping review published in 2020 confirmed this finding.

Post-mortem studies on the sequential use of barbiturates and neuromuscular blockers in lethal injection of prisoners in the USA have suggested that serological levels of barbiturates were compatible with conscious anesthesia in 43% of cases⁸. Similar risks have also been documented in the context of animal euthanasia; this is a reason why neuromuscular blockers are prohibited for animal euthanasia in several states⁹.

Highlighting this limitation is paramount for 3 reasons: 1) it points toward an important gap in existing scientific literature on MAiD pharmacology; 2) it sheds light on a potential complication that is not currently mentioned in Canadian MAiD practice guidelines (thus limiting physicians’ awareness of the reasons for carefully dosing drugs and assessing coma prior to neuromuscular injection; 3) it limits informed and shared decision-making with patients about potentially safer options, such as the use of IV barbiturates without neuromuscular use, as recommended in some European practice guidelines.

Thank you; we have highlighted this in the ‘Interpretation’ section. Unfortunately as noted it is not possible to assess patient symptoms as they are in a coma, and then paralyzed, and then deceased.

While conscious anesthesia is possible the ED95 (amount required for effect in 95% of the population) of propofol is 2-3 mg/kg; the most commonly used dose 1000 mg is roughly 5 times that and is generally considered a fatal dose on its own, and is much higher than that given in surgery, as the goal is usually to get the patient out of the OR alive!

We agree with the concerns that variations in dose may be used (indeed this was part of the rationale for the study). We have also noted our support for the use of fixed doses of medications in a specific order, with careful check and documentation of coma before neuromuscular blockers are given to avoid this complication. (Page 11, 12: One complication which may not be captured here is the possibility of consciousness during the MAiD procedure, a complication also not reported in recent literature reviews. Most anaesthetic doses given during MAiD are greater than those necessary for major surgery; however variations in dosing regimens, as reported here, raise the possibility that some patients could receive sub-therapeutic doses of anaesthetic agents, resulting in procedural awareness which would be difficult to assess. For this reason we encourage the administration of fixed (rather than titrated) doses of anesthetic agents, reviewed by pharmacists to ensure sufficient therapeutic efficacy, and diligent clinician assessment and documentation of coma induction.)

A recent study on information needs of patients, professionals and citizens have highlighted the need for more transparent public information on potential complications of MAiD to support informed patient choice¹³.

Thank you, we have added this to the “in-terpretation” section (Page 13: In addition to guiding further research on MAiD pharmacology and helping clinicians choose medications to be used for MAiD provision, the data from this study may be useful in developing decision-aids and educational materials for patients and families, who can make better informed choices, knowing about the medications, time until death, and potential complications of assisted dying.)

References

The reference list is rather limited. A few statements in the background and discussions could be better supported with relevant literature.

This has been expanded in response to the other comments and questions.