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SPECIAL ARTICLE

Oral medical assistance in dying (MAiD): informing practice to enhance utilization in Canada

L'aide médicale à mourir administrée par voie orale : comment éclairer la pratique pour en améliorer son utilisation au Canada

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Abstract *The legislation Bill C-14 legalized medical assistance in dying (MAiD) in Canada. After thorough assessments of eligibility by two clinicians, Bill C-14 allows for both intravenous-assisted death by a clinician (euthanasia) and prescription of oral medication for self-administration (assisted suicide). Nevertheless, since inception in June 2016, intravenous euthanasia is the main form of delivery of assisted death in Canada. The reasons why oral MAiD is underutilized in Canada are multifactorial. Currently, there is no consensus on either the medications or the protocols for oral administration, nor a comprehensive understanding of the potential side effects and complications associated with different regimens. The quality of evidence for optimal MAiD medications is low, so any suggested recommendations can only be informed by the global but generally anecdotal experience. The challenges for implementing oral MAiD in Canada include a need to enhance clinician comfort in prescribing oral medications as an alternative to intravenous administration. The goals for ideal oral MAiD medications are 100% effectiveness and minimal side effects, while ensuring that the needed dose is both palatable and deliverable in a tolerable oral volume. The Netherlands has the most experience worldwide and barbiturates have emerged as the most common, efficacious, and tolerable agents by patients. Based on this global experience and the over-arching goals for oral MAiD, we recommend the use of a secobarbital suspension combined with antiemetic prophylaxis.*

Résumé *Le projet de loi C-14 a légalisé l'aide médicale à mourir au Canada. Après une évaluation exhaustive de l'éligibilité par deux cliniciens, le projet de loi C-14 permet d'offrir une aide médicale à mourir administrée par un clinicien par voie intraveineuse (l'euthanasie) aussi bien qu'une aide médicale à mourir auto-administrée, soit la prescription de médicaments oraux pour auto-administration (le suicide médicalement assisté ou suicide assisté). Toutefois, depuis sa mise en œuvre en juin 2016, l'euthanasie par voie intraveineuse est la forme prépondérante d'aide médicale à mourir utilisée au Canada. Les raisons pour expliquer cette sous-utilisation de l'aide médicale à mourir auto-administrée au Canada sont nombreuses et multifactorielles. À l'heure actuelle, il n'existe pas de consensus quant aux médicaments ou aux protocoles d'administration orale, ni une compréhension exhaustive des effets secondaires potentiels et des complications associées à différentes posologies. La qualité des données probantes concernant la médication optimale pour une aide médicale à mourir auto-administrée est faible, donc toute recommandation proposée n'est basée que sur une expérience globale mais de nature généralement anecdotique. Les défis de la mise en œuvre de l'aide médicale à mourir administrée par voie orale au Canada comprennent la nécessité de rendre le clinicien plus à l'aise avec la prescription de médicaments oraux comme alternative à une administration intraveineuse. Les objectifs d'une médication idéale pour l'aide médicale à mourir auto-administrée sont son efficacité totale avec des effets secondaires minimaux, tout en garantissant que la dose*

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nécessaire ne soit pas désagréable au goût et puisse être prise dans un volume oral tolérable. Les Pays-Bas sont le pays ayant l'expérience la plus complète et les barbituriques y sont devenus les agents les plus répandus, efficaces et tolérables pour les patients. Sur la base de cette expérience mondiale et des objectifs globaux de l'aide médicale à mourir administrée par voie orale, nous recommandons d'utiliser une suspension de sécobarbitale combinée à une prophylaxie antiémétique.

With the passing of Bill C-14,[1] medical assistance in dying (MAiD) became legal in Canada in June 2016. The understanding of federal MAiD legislation in Canada (to be regulated and operationalized by the provinces) includes options for intravenous (IV) administration of medications by physicians or nurse practitioners (also referred to as voluntary euthanasia), or self-administration of oral medications (also referred to as physician-assisted suicide). The current legislation in Canada supports making both oral and IV methods of MAiD available for patients meeting the MAiD eligibility criteria. While choice is legislated, the freedom for patients to make a choice is more ambiguous, and must be matched against the experience and expertise of the clinician providing MAiD. For the vast majority of MAiD providers, IV administration has been widely accepted as the preferred method because of the reliability of IV administration and the effectiveness in achieving death in a timely manner. As a result, almost all MAiD procedures in Canada have been provided through the IV route. Nevertheless, for some patients, despite a slower onset of action and higher risk of failure, oral MAiD has been requested to avoid IV insertion, and to reduce the degree of willing clinician involvement.

Under Bill C-14 legislation,[1] healthcare professionals have been entrusted to legitimize, endorse, and implement the practice of MAiD. Since legalized, the various healthcare professions have worked hard to marry the legislation to the obligations of professional practice, while preserving autonomy for the individual clinician to participate and/or conscientiously object to this choice. The ethical debates on the scope of MAiD and the professional obligations are important, but beyond the scope of this analysis. Instead, this paper explores the need for and challenges with oral MAiD, and provides evidence-informed suggested recommendations for a pan-Canadian approach towards the implementation of this alternative for patients. Accordingly, this paper aims to offer practical and implementable guidance on the provision of oral MAiD, which has been lacking so far.

The need for oral MAiD

While oral MAiD is permitted in Canada, it is not commonly utilized for various reasons, including the lack of standardized medications and protocols surrounding oral provision. This cannot be said for IV provision, which has emerged as the route of choice by clinicians in Canada. One of the biggest concerns people have at the end of life is the loss of control. Evidence from other countries suggests that providing an oral option for self-administration in assisted dying can help restore some of that autonomy and agency.[2]

Data from the Netherlands has reported that the oral route is used in as many as 10% of all MAiD events, but those numbers have been decreasing since 1998.[3,4] In the latest report by Regional Euthanasia Review Committees,[5] 3.8% of all MAiD provisions in the Netherlands were completed via the oral route. This attrition is thought to be secondary to alternate channels for patient-controlled euthanasia, including infusion protocols and elastomeric pumps.[3] Unfortunately, these models and routes are yet to be evaluated in Canada.

Familiarity and experience with oral MAiD may also increase access to MAiD for patients by potentially increasing the number of clinicians willing to participate in the provision of MAiD. Nevertheless, if effective and predictable, self-administration by the patient may facilitate involvement for some clinicians who would prefer not to be as actively involved or present as necessary for a primary IV MAiD provision. Emanuel *et al.* confirmed through a survey of US physicians that when presented with the choice, they would be more willing to participate in prescribing oral MAiD than administering IV euthanasia.[6]

Canada is one of the least densely populated countries in the world, has a large rural and remote population, and is the largest geographic country where physician-assisted death is legal. MAiD is a legislated right of all Canadians, yet access to both a MAiD assessment and subsequent provision, as with many healthcare services, is inequitable, with most experienced service providers concentrated in the urban centres. Medical regulatory authorities have mandated appropriate referral of any patient requesting MAiD. Unfortunately, without consultant MAiD clinicians available in all communities, most referrals must be directed to the aforementioned urban centres. Because of the eligibility criteria, being in an advanced state of decline, and the underlying nature of their medical conditions, many MAiD patients are unable to travel. Alternatives to one, or both in-person consultations vary depending on provincial regulations. Telehealth services can address some assessment needs, but not the actual provision of MAiD by IV, which continues to require travel

by either the clinician or the patient. The oral alternative for MAiD offers the potential of increasing equitable access to MAiD across Canada, should there come a time when it can be offered everywhere in the absence of clinicians.

There are multiple desirable characteristics of an ideal oral medication regime. These characteristics include maximal autonomy, minimal side effects, relatively rapid onset of unconsciousness, minimal and predictable time between unconsciousness and death, high rate of effectiveness, palatability and tolerance, stability when compounded, ease of accessibility, and reasonable cost.

Challenges with oral MAiD

The major challenges with an oral route for MAiD include poor palatability, impaired absorption, and widely variable effectiveness, often resulting in either prolonged time to death, or failure to cause death. Barbiturates, the primary medication class that has been used in oral MAiD, can have a very bitter taste. Problems with the ability to consume or absorb the necessary volume of medication may result in incomplete doses being administered to the patient. As such, pre-existing significant nausea and vomiting or conditions that significantly impair absorption (e.g., inflammatory bowel disease, previous small bowel resection, known gastroparesis) can be considered relative contraindications to oral MAiD. In a Dutch study of patients who were given a barbiturate, 3.5% experienced nausea and vomiting, and 2.6% experienced extreme gasping.[7] Problems with progression to death occurred in 16% of cases including a longer than expected time to death, failure to induce coma, or induction of coma followed by re-awakening of the patient.[7] Based on global experience to date, to optimize tolerability and absorption, all patients should be prescribed antiemetic therapy prior to the consumption of the coma/death-inducing medication.

A further disadvantage of oral administration is the inability to supplement the initial dose with more oral medications in a semi-conscious or comatose patient. If the oral medication fails to cause death after a certain time after consumption, IV medication administration is necessary to ensure death as a definitive outcome. The result of such failures or prolonged delays of death is real and has been reported in the United States, where without provider presence and intervention, there have been prolonged oral-assisted deaths, occasionally in excess of 24 hr.[8]

As a result of the above considerations, it is currently advocated, and in some provinces required (e.g., British Columbia) that a willing clinician be present during the provision of oral MAiD because of relative inexperience and known possible failure with the oral route. Clinician presence facilitates obtaining a final consent; it also ensures that the lethal dose of medication is delivered securely, ingested safely, and successfully causes death. The willing clinician needs to be prepared to obtain vascular access and administer IV medications to complete the MAiD provision in a timely manner in the case of failure or prolonged delay in onset of coma or death resulting from the administration of the oral medications. This requirement is in direct conflict with the benefits of autonomy and agency for patients offered by an oral MAiD alternative. The introduction of clinician presence, by definition, reintroduces a more clinical experience, diminishes agency, and reduces autonomy. Having said that, we must recognize that the Canadian experience with oral MAiD is still in its infancy. As greater experience with effective and reliable oral medications is gained, as well as with regulations and increased comfort to guide safe dispensing practice and transport of MAiD medications, there may come a time when the oral medications can be offered to patients for administration in the absence of clinicians.

Concerns have been raised regarding the fate of unused medications that have been dispensed for oral MAiD. To maintain the security chain, the Canadian Association of MAiD Assessors and Providers advocate that oral MAiD medications should be passed from pharmacist to practitioner who, as above, gives it directly to the patient when they are present for the MAiD procedure. This should minimize any concern of the medication being used or administered by another person, and maximize the effective and timely use of the medication by the still competent person for whom it was intended. The practitioner should then return any unused portions to the pharmacy for documentation and disposal. This will ensure no residual drugs are consumed by others. This cautious approach does not mitigate the aforementioned need for rural and remote access where a willing clinician may not reside to complete the security chain. With experience, processes may evolve whereby security of medication can be maintained without actual clinician presence.

Finally, there has been a lack of consensus regarding oral MAiD procedures and protocols based on the available evidence. The overall quality of available evidence for oral MAiD medications is low. Most of the evidence is unpublished or limited to expert opinion, observational data, and experiential data from other jurisdictions. The lack of consistent comparative data of existing drug regimens makes it difficult to determine which mixture is most effective for the purpose of MAiD. While this could be informed by future research, the ethical implications will make definitive studies challenging. Current best practice medication and periprocedural guidelines have

been developed and are endorsed by the Canadian Association of MAiD Assessors and Providers.[9,10] Regardless, clinicians should acknowledge the newness of both MAiD and, in particular, the oral alternative, and when consulting with patients and colleagues disclose that much of the practice is informed by experience rather than evidence.

Table 1 Time to death comparison between barbiturate dosing of 9–10 g (1998–2011) and 15 g (2013–2015) in the Netherlands[3]

Time to death	*n* = 245 1998–2011 (%) (9–10 g dosing)	*n* = 165 2013–2015 (%) (15 g dosing)
< 30 min	70.2	82
30–60 min	17.3	12
61–120 min	9.2	4
> 120 min	3.3	2

Worldwide experience

In the Netherlands, the provision of oral and IV MAiD has been practiced since 1973 and was decriminalized in 2002.[8] The current oral protocol, in use since 2012, describes premedication with metoclopramide, an antiemetic and promotility agent, with 10 mg given orally every eight hours for the 24 hr leading up to the MAiD procedure.[11] This is followed by the consumption of a barbiturate solution containing either 15 g of pentobarbital or secobarbital. Ingredients are added to

Table 2 Available published data on the use of prescribed oral medication to assist suicide in the United States Adapted from the Oregon Health Authority, Death with Dignity Act Reports 2013–2017,[17] Washington State Department of Health Death with Dignity Act Reports 2013 and 2016,[18] and The Colorado End of Life Options Data 2017[19]

Medication	State	2016		2015		2014		2013		2012	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Secobarbital	Oregon	86	64.7	114	86.4	63	60	7	9.9	20	26
	Washington	77	32	109	51	112	64	16	10	18	17
	Colorado	21	42	-	-	-	-	-	-	-	-
Pentobarbital	Oregon	0	0	1	0.8	41	39	64	90.1	57	74
	Washington	2	1	4	2	64	36	142	89	84	81
	Colorado	-	-	-	-	-	-	-	-	-	-
Secobarbital & pentobarbital	Oregon	-	-	-	-	-	-	-	-	-	-
	Washington	-	-	-	-	-	-	-	-	1	1
	Colorado	-	-	-	-	-	-	-	-	-	-
Phenobarbital	Oregon	39	29.3	-	-	-	-	-	-	-	-
	Washington	1	< 1	-	-	-	-	-	-	-	-
	Colorado	-	-	-	-	-	-	-	-	-	-
Phenobarbital/chloral hydrate	Oregon	-	-	16	12.1	-	-	-	-	-	-
	Washington	106	44	88	41	-	-	-	-	-	-
	Colorado	-	-	-	-	-	-	-	-	-	-
Chloral hydrate	Oregon	-	-	-	-	-	-	-	-	-	-
	Washington	1	< 1	-	-	-	-	-	-	-	-
	Colorado	-	-	-	-	-	-	-	-	-	-
DDMP2	Oregon	-	-	-	-	-	-	-	-	-	-
	Washington	-	-	-	-	-	-	-	-	-	-
	Colorado	28	56	-	-	-	-	-	-	-	-
Morphine sulfate	Oregon	-	-	-	-	-	-	-	-	-	-
	Washington	52	22	4	2	-	-	-	-	-	-
	Colorado	-	-	-	-	-	-	-	-	-	-
Other	Oregon	8	6	1	0.8	1	1	-	-	-	-
	Washington	1	< 1	-	-	-	-	1	1	1	1
	Colorado	1	2	-	-	-	-	-	-	-	-

DDMP2 = diazepam 50 mg, digoxin 50 mg, morphine 15 g, propranolol 2 g

enhance the flavor, neutralize the pH, act as a preservative, and prevent crystallization.[11] Prior to 2012, the KNMP (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie – The Royal Dutch Pharmacy Organization) and KNMG (Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst – The Royal Dutch Medical Association) recommended 9 g of barbiturate. Increasing the dose to 15 g significantly improved the likelihood of inducing death within 60 min.[3] Administration of 15 g of secobarbital caused death in less than 60 min 94% of the time. This contrasts with lower doses of 9–10 g, which, according to the KNMP and KNMG report, only resulted in death within 60 min in 87% of patients.[3] No data exists for higher standardized doses (i.e., 20 g), which have the potential advantage of further reducing time to death. Nevertheless, pharmacokinetic and pharmacodynamic profiles do not support this hypothesis, and could add complexity to an oral provision with the necessity to compound the drugs with a greater volume of suspension.[12,13]

In the United States, both IV administration and physical assistance with oral medication are illegal.[8] Prescription by a physician of oral medication to assist suicide is legal in six states and the District of Columbia, but data collection on their practices is not standardized (Table 1). For antiemetic premedication, the trend is to use dual antiemetic prophylaxis one hour prior to ingestion of the coma-inducing medication. This is variable between states, but usually includes two of the following three medications: metoclopramide 20 mg, haloperidol 2 mg, or ondansetron 8 mg. This is largely supported by postoperative nausea and chemotherapy-induced nausea literature; nevertheless, most of this literature also mentions dexamethasone 8 mg as a useful adjunct to ondansetron or metoclopramide.[14,15]

The current trends in prescribed oral medication to assist suicide in the United States are listed in Table 2. As is evident from this limited data, pentobarbital-based regimens were predominant in 2012, but their use subsequently transitioned to secobarbital, morphine, or the DDMP2 regimen (diazepam 50 mg, digoxin 50 mg, morphine 15 g, propranolol 2 g).[16] This transition occurred because availability of pentobarbital was lacking in the commercial market. Alternatives to secobarbital were developed in response to price increases in the United States with a lethal dose of secobarbital costing approximately 3,000 USD. Secobarbital, in doses of 10–15 g, is significantly more affordable in Canada. The DDMP2 mixture has been used for the last two years in both Washington and Oregon, with an average time to death of just over two hours.[16]

Unpublished data from Washington's Death with Dignity program does yield some insight into effectiveness of different oral regimens[18] (Table 3). Comparisons between the different medication regimens indicate an average fastest time to death occurring with a secobarbital and propranolol combination and followed by secobarbital as a single agent. The challenge with a secobarbital and propranolol combination is the relative lack of experience compared with the more commonly used secobarbital alone. All other medication regimes had an average time to death longer than two hours.

Canadian experience

The total number of MAiD deaths in Canada between December 10 2015 and October 31 2018 is reported as 6,749 deaths according to the most recent report by Health Canada.[20] It is estimated that MAiD accounted for approximately 1.12% of all deaths in Canada between January 1 2018 and 31 October 31 2018. This most recently available reporting of MAiD in Canada is still an estimate, as it predates mandatory federal monitoring; reporting and data is also incomplete or approximated for several provinces. When MAiD became legal, several

Table 3 Unpublished oral combination data from Washington Death with Dignity Program[16]

	Cases (*n*)	Average time to sleep (min)	Max time to sleep (min)	Average time to death (min)	Maximum time to death (min)
Secobarbital 10 g	200+	5	-	68	1,620
Secobarbital 10 g with inderal 2 g	41	5	-	41	420
DDMP	70	9	30	187	1,860
DDMP2	14	8	28	145	450
MVP	3	6	10	377	1,080
Chloral hydrate	77	-	-	205	4,280

DDMP = digoxin 25 mg, diazepam 0.5 g, morphine 10 g and propranolol 2 g

DDMP2 = diazepam 50 mg, digoxin 50 mg, morphine 15 g, propranolol 2 g

Table 4 Dutch preparation called "Mixtura nontherapeutica pentobarbital"[11]

Pentobarbital sodium (or secobarbital)	15 g
Alcohol 96% V/V	16.2 g
Purified water	15 g
Propylene glycol	10.4 g
Saccharin sodium	250 mg
Syrup simplex	65 g
Star anise oil	1 drop

provinces developed oral MAiD protocols given this option was included under the legislation. These protocols varied greatly between provinces, and most were never activated by patients and/or clinicians.

As of January 2019, there were 13 known cases of orally administered MAiD medications in Canada (personal communication, K Trouton, 2019).[21] Details are available for ten of the cases that were performed in British Columbia where the prescription and process are standardized. Seven utilized phenobarbital as the main barbiturate, and three used secobarbital, which only recently become available in Canada. Phenobarbital has reduced solubility and a much slower onset of action—longer than 60 min compared with secobarbital, which has an onset of 10–15 min—but can still be used as an alternative.[22,23] Of these ten cases, three achieved death within 60 min, two achieved death between 60 min and 90 min, and five needed IV supplementation with propofol and rocuronium when death was not achieved in an acceptable time limit (between 60 and 90 min) as previously discussed between the physician, patient, and patient's family. Of the five cases requiring IV supplementation, two had received secobarbital.

Recommendations

Given the lack of robust evidence to guide clinicians, recommendations from this analysis are based on global experience and focused on achieving the desirable characteristics described earlier.

Antiemetic and antireflux premedication prevents nausea and vomiting, and thus maximizes delivery of the coma-inducing drugs to the gut for absorption. Based on the literature about chemotherapy and postoperative nausea and vomiting, and experience from the Netherlands, it is recommended to mitigate nausea and vomiting with a one-time dose of oral metoclopramide 20 mg and either oral ondansetron 8–24 mg and/or oral dexamethasone 8 mg, dependent on patient intolerances or allergies. This antiemetic prophylaxis should be given a minimum of one hour before administration of the coma-inducing agent.

Based on the previously described experiential data, barbiturates offer the most clinical predictability. Pentobarbital and secobarbital have the most favourable pharmacodynamic and pharmacokinetic profiles because of their predictability to induce respiratory arrest in the shortest amount of time. Phenobarbital has been used successfully in a small number of cases in Canada and the US, but has a slower onset of action. Secobarbital's easy solubility for compounding and rapid onset of action makes it an ideal barbiturate for MAiD. Secobarbital is available in Canada, and can be ordered by participating compounding pharmacies. Several suspensions have been described to make the barbiturates more palatable. A Dutch preparation called "Mixtura nontherapeutica pentobarbital"[11] is a published recommendation for administering secobarbital and could be used in Canada (Table 4). It is recommended that a single dose of 15 g be used for MAiD administration.

The DDMP2 preparation is an alternative to barbiturates. Its main disadvantage is the variability of sedation and respiratory depression of benzodiazepines and opiates, especially in a patient population that may have increased tolerance with comorbid chronic pain diagnoses. It also has the drawback of being dispensed as a powder and must be mixed with clear juice or water immediately prior to ingestion. It should only be considered if there are financial barriers or limited access to secobarbital.

The presence of a willing clinician at all oral MAiD provisions is recommended to facilitate final consent, ensure appropriate oral administration of the medication, and to intervene with IV medications to complete MAiD if necessary.[9] Clinician presence would also provide an opportunity to systematically collect data regarding the efficacy of recommended oral MAiD protocols to inform quality improvement and best practice.

Conclusions

Oral MAiD is still relatively unused in Canada, a country that has only allowed MAiD since 2016. The Canadian public, under Bill C-14, is permitted an oral self-administration option, but this option is currently not widely offered. MAiD is at a juncture where offering an oral option to Canadians is achievable based on best practices, with input from clinician providers and patients. This is an opportunity for Canada to clearly document and inform the oral MAiD experience both for quality improvement and global dissemination. Ultimately, while the practice of oral MAiD in Canada may change in the future, the recommendations herein can serve to

standardize a medication regimen that did not previously exist in Canada. These recommendations offer an evidence- (albeit somewhat limited) and experience-based regimen, which may allow a MAiD service to offer more autonomy to patients and less direct clinician involvement than with current practice. With greater experience, an oral mediciation-based process may ultimately increase access to MAiD for Canadians.

Conflict of interest None declared.

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