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Canadian Association of MAiD Assessors and Providers

Association canadienne des évaluateurs et prestataires de l'AMM

The Oral MAiD Option in Canada Part 2: Processes for Providing

Review and Recommendations

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Canadian Association of MAiD Assessors and Providers (CAMAP)

The Canadian Association of MAiD Assessors and Providers (CAMAP) is the unique association of professionals involved in the delivery of medical assistance in dying (MAiD) care in Canada. Founded in 2016, the mission is to support MAiD professionals in their work, educate the health care community about MAiD, and provide leadership on determining standards and guidelines in MAiD practice. CAMAP members strive to achieve the highest level of care for our patients and to model this care for a national and international audience. CAMAP works with governments in Canada at all levels, provincial medical and nursing regulatory bodies, national medical and nursing colleges, national professional groups, medical and nursing colleagues, and national organizations supporting MAiD.

Executive Summary

Medical Assistance in Dying (MAiD) has been legal in Canada since Bill C-14 received royal assent in June 2016. Following approval against eligibility criteria, MAiD can be provided in the majority of Canadian provinces and territories, by either intravenous administration of medications by physicians or nurse practitioners, or self- administration of oral medications by the patient themselves. The main advantage of offering patients an oral option is the autonomy it provides for patients to take the medications themselves, and re-establish some control during a challenging time in their disease or illness.

The purpose of this paper is to outline best practices for the safe dispensing, administration, and evaluation of the plausibility of an oral MAiD provision. Guidance will be provided for both clinicians and pharmacists in the provision of oral MAiD. The medications recommended for oral MAiD are covered in Part 1 of this guideline.

The following are summary recommendations:

1. Clinician presence is currently recommended for all oral MAiD provisions in order to be able to evaluate success and effectiveness and, if needed, intervene with intravenous medications in the case of delay or failure.
2. With greater experience with oral medications in Canada and greater knowledge of the effectiveness of oral regimens, there may come a time when clinician presence need not be required for oral MAiD provisions.
3. Clinicians should write prescriptions for both oral and IV medications for patients requesting oral MAiD.
4. Regular communication with the patient should be maintained to confirm that the patient's preference and the ongoing appropriateness for an oral route has been preserved for the planned date/time.
5. To optimize absorption, patients should refrain from eating 6 hours prior to taking the coma-inducing medications. Clear, non-carbonated fluids can be continued.
6. The patient is recommended to take an anti-emetic regimen at least 1 hour before consumption of the coma-inducing agent.
7. Secure delivery of the medication is important to prevent harm to others from this lethal dose of medication. Secure delivery of the medication could be accomplished by dispensing the medication directly to the providing clinician, either on their way to the provision or by a participating pharmacy to a clinician already present at the site of provision.
8. In preparation for potential delay or failure of the oral medication, ease of vascular access should be assessed, as with all patients requesting MAID. If vascular access may be difficult, clinicians, in consultation with the patient, may opt to start an IV prior to oral ingestion.

9. Clinicians should come to an agreement with patients prior to the MAiD procedure on an agreed upon time (for example, 1 hour) that if death has not occurred, there will be IV supplementation with standard IV MAiD medications to cause death.
10. Where applicable, instructions from pharmacies should be followed explicitly with respect to reconstitution of the oral MAiD regimen.
11. Immediately prior to the start of the procedure clinicians should obtain final consent for MAiD, which should include both the oral MAiD procedure as well as consent for potential IV MAiD supplementation.
12. Clinicians should witness the ingestion of the medication. The patient should assume a standard Fowler's position (60 degrees) when consuming the medication and remaining sitting for at least 20 minutes, even if unconscious, to optimize absorption and prevent regurgitation.
13. The patient should consume all of the medication within 4 minutes. Use of a straw should be avoided as its use can slow the rate of consumption. Clear fluids between swallows are allowed as long as it does not prolong duration of consumption.
14. After consuming all the medication, the aftertaste can be mitigated by consumption of a strong liquor (1/4 cup of vodka or whiskey), or a room temperature non-carbonated beverage (1/2 cup). Creamy and milky liquors or beverages should be avoided.
15. Any unused medications should be returned to the pharmacy for proper disposal.

Improving Access to Oral MAiD for Canadians

Providing options for Canadians

The provision of MAiD through the administration of intravenous (IV) medication by a provider, while safe and highly effective, for many patients may feel “institutionalized” and/or “proceduralized”. While providers always strive for a patient centred experience through provisions in the home, an intravenous MAiD can be perceived by some patients as very clinical. The clinical perception is somewhat unavoidable given the requirement for vascular access and the necessary bedside participation of a clinician with IV MAiD, which can extend the intimacy of the moment beyond a circle of friends and family. Some patients may want to feel empowered to control this final act of their life. The availability of oral medications for MAiD may facilitate a more intimate and empowered process for a patient by lessening some of the procedural aspects and a need for bedside clinician intervention through IV medications.

Improving access to MAiD across Canada

Currently there is no accurate or stable data for the number of clinicians providing MAiD services in Canada. In a pre-legislation survey by the Canadian Medical Association (CMA), only 29% of physicians surveyed said that they would consider providing MAiD, and as many as 63% said that they would refuse (Vogel, 2015). No differentiation was made between providing the prescription or IV medications and completing a consultation for MAiD. Increasing the complexity of accurate data is that some physicians opt to only be involved in the assessment portion of the process, and not be involved in the actual provision of MAID. While this data may have shifted since Bill C-14 was legislated, it can be inferred that at the time there are far fewer physicians providing MAiD services than those who conscientiously object.

While an oral option has existed in most provinces and territories since Bill C-14 was legislated, almost all provisions in Canada to date have been through the administration of IV medications. The proportion of those clinicians willing to complete assessments and to physically provide MAiD versus those only willing to complete MAiD assessments is probably multifactorial and includes the psychological burden of being a more active participant in the death as well as a lack of comfort with vascular access and knowledge of the medications used. With an estimated 0.3-4.6% of all deaths provided by MAiD in countries with a longer history and greater experience (Health Canada, 2017), we can safely assume that there are currently not enough practitioners willing to provide MAiD in Canada. Recent polling has suggested that the introduction of reliable oral medications for the provision of MAiD may increase access by increasing the comfort for “assessor-only” practitioners to expand their practice to provisions by mitigating some of the concerns outlined above. This assumption may be incorrect, at least short term, as prescribing physicians should still need to be present to obtain final consent and ensure the lethal dose of medication is delivered securely and successfully. This will also mean that clinicians will still need to be prepared to obtain vascular access, or otherwise have an IV

established before the oral provision, and administer IV medications in the case of failure or excessive delay in death.

Geographically, Canada is the largest country where physician assisted death is legal. As a result, the population is widely distributed. While MAiD is a legislated right of all Canadians, access to it, from both an assessment and provision point of view, is very likely inequitable, with most service providers concentrated in the urban centres. Appropriate referral of any patient requesting MAiD has been mandated by medical regulatory authorities. Unfortunately, without consultant MAiD clinicians available in all communities, most referrals must be directed to the aforementioned urban centres. While we acknowledge that this can be similarly true of many medical and surgical services, a major goal of any MAiD service is to remain patient-centred. Due to the nature of the eligibility criteria many MAiD patients are unable to travel. Alternatives (ie. phone or e-consultation) to in person consultations, to mitigate inability to travel, vary depending on provincial regulation. However, the provision of MAiD will, at least in the short term, require travel by either clinician or the patient. With greater experience with the effectiveness and reliability of oral medications, as well as regulations to guide safe dispensing practice, there may come a time when the oral medications can be offered to patients for administration in the absence of clinicians and increase equitable access across Canada.

Key Collaborations in the Provision of Oral MAiD

The planning and provision of an assisted death with oral medication requires communication and collaboration with the patient, their family, the practitioner, the pharmacist and potentially other supportive healthcare professionals such as nursing and social work. Once a patient is assessed as eligible and the decision is made to choose the oral option, a date for the provision is made that is agreeable to patient, practitioner and pharmacist. This date should take into account the 10-day mandatory reflection period unless there is concern that the patient will either lose the capacity to provide informed consent within that time frame or the patient is at imminent risk of death before the end of the 10-day waiting period (House of Commons Canada, 2016). However, in the interval between confirmation of eligibility and selection of the method, the clinical condition may change, and should be regularly assessed. The patient may prefer the IV option if unable to ingest an oral dose on the planned date.

Practitioner and patient

Patients who choose oral MAiD often have the desire to plan their assisted death as more of an event. This may take some coordination among various people, and likely requires some flexibility on the part of the clinician, as this type of medically assisted death may require more time. Depending on the illness, disease or disability, the clinical status of the patient may change between the decision to have oral MAiD and the date set to ingest the medication. If the patient is unable to tolerate oral MAiD, but wants an assisted death, the practitioner should discuss the option of starting directly with the IV MAiD medications.

Clinicians should discuss pre-medication with an anti-emetic to help prevent or treat any nausea or potential regurgitation. Ideally, the patient should refrain from eating 6 hours prior to the provision. This optimizes the absorption of the coma- inducing medication.

Clinicians should discuss the approximate time to coma and death with the patient and family, and should explain to the patient that the oral route has a higher risk of failure. Clinicians should discuss the time frame for an intravenous (IV) intervention in the case of a delayed or failed oral provision. The pre-determined time frame should ideally be established prior to the day of the MAiD provision (for example, 1 hour or 2 hours as a time frame). An IV may be started prior to the oral procedure or only after the oral procedure has failed. This decision should be made taking into account the clinician's comfort in starting an IV, the predicted ease in establishing IV access, and the patient's desire or comfort in having an IV prior to the start of oral ingestion.

Emphasis should be placed on continuing usual medications right up to the time of the provision, especially pain and anti-emetic and pro-motility medications. While the continuation of some cardiac medications may not seem to be necessary, clinicians do not want the patient experiencing chest pain or shortness of breath prior to the provision as this will only contribute

to their suffering. To prevent any prolonging of time to death, pacemakers and defibrillators should be deactivated if possible. If such access to cardiology services is not available, you should be able to obtain a magnet from a local hospital for placement over the device to turn off the ICD function. Oxygen should be discontinued immediately after the person loses consciousness. The family should be prepared for signs and symptoms that the dying person may exhibit such as snoring, gurgling, changes in rate of breathing, and increased paleness or greying or duskiness of skin. As in all MAID cases, the events for after the procedure, such as body disposition should also be clarified and confirmed with the family prior to start.

Practitioner and pharmacist

Prior to offering MAiD, and particularly oral MAiD, practitioners should identify pharmacies that are willing and competent to provide the service. The specific pharmacy standards around MAiD are governed by the provincial colleges of pharmacy and vary from province to province. Some pharmacies do not offer collaboration with practitioners providing MAiD, or with the MAiD coordinating service due to conscientious objection or the lack of facilities to properly compound products. Compounding pharmacies are undergoing more regulation as a result of cases of inaccurate potencies and contamination in compounded products (Riley, 2017). There are variations in multiple aspects of MAiD provision including drug protocols, preparations of medications, storage, dispensing, destruction, documentation and inclusion of regulated pharmacy technicians in preparation (Verweel L et al., 2018). Each practitioner must be familiar with individual provincial medical and pharmacy standards.

Early communication between the practitioner and the pharmacist about the anticipated date of the provision is key to success. This allows the pharmacy to have all the appropriate medications and ingredients available to compound the prescription and have the agreeable staff available to carry out the compounding. Formulations that are compounded into suspensions or solutions have a limited expiry date and should not be prepared until immediately before the scheduled assisted death. The practitioner and the pharmacist must discuss the appropriate antiemetic regimen, as well as the need and format of the IV back-up kit. This should be done prior to writing the MAiD prescription.

The security chain of these lethal medications should be clearly delineated and transfer of medications should be understood by physician and pharmacist. Ideally, the medication should be prepared and then picked up immediately prior to the scheduled provision so there is no need to secure it for extended periods of time after dispensing. Alternatively, arrangements could be made to have the medications delivered to the site of MAiD provision. In such circumstances the clinician would need to be present to receive the medications to maintain the chain of security.

Pharmacist and patient

Bill C-14 (House of Commons Canada, 2016) outlines the pharmacists' role in dispensing the medications and does not include direct participation in administering medications. However, pharmacists do have to provide the dispensing service and if they do not have the ability to compound the medication or are conscientious objectors, they have the responsibility to help the physician and/or the patient find an alternative pharmacy that can provide this service. Pharmacists do have the responsibility of providing patients and families with information around MAiD when enquiries are made including which drugs are used, maintaining security of the medications and correct administration procedures.

Safe Acquisition and Administration of Oral MAiD Medications

Safe compounding

The preparation of oral MAiD formulations requires adherence to strict compounding procedures to protect the safety of staff preparing the product and to ensure an accurate, stable and palatable product. In the absence of MAiD specific published literature, these recommendations rely on references such as the US Pharmacopeia Non-sterile Compounding Guidelines (US Pharmacopeia, 2016) and the Canadian Society of Hospital Pharmacists Guidelines on Non-sterile Compounding (Canadian Society of Hospital Pharmacists, 2014) These references recommend using compounding monographs from standardized pharmacopeia's or peer-reviewed journal articles. It is also recommended that a regulated health professional, either a pharmacist or a regulated pharmacy technician, are primarily involved in the compounding procedure. Some provinces do not allow the involvement of a regulated pharmacy technician in the MAiD preparation and dispensing.

Since the preparation of oral MAiD formulations often requires manipulation of powders with strong pharmacological actions, compounders should wear personal protective equipment (PPE) such as a clean gown, powder-free gloves, mask, beard guard (if necessary) and eye protection to avoid inhalation or absorption through the skin. An `independent double check' of all measures is advisable to ensure accuracy to the weighted powders/doses.

Safe Dispensing

There are some general practices of safe dispensing that will be applicable to all oral preparations. Ideally, formulations should be dispensed in a ready-to-use format that can be easily consumed by a person in less than 4 minutes. The preferred format is a suspension or solution of less than 120 mL. This ensures a tight security chain and minimizes time that is required to store the medication at home. The disadvantage of this format is that the stability of the medication cannot be guaranteed beyond a certain period of time. If oral MAiD prescriptions are dispensed in powder format, there is a need for the person to mix the powder with water and juice prior to consumption, increasing the risk of complications such as decreased palatability, failure to consume total dose and failure of completion. In those situations, it is recommended the compounding of the product should not happen until immediately prior to the scheduled assisted death.

The phenobarbital, chloral hydrate and morphine combination must be compounded into a suspension as the phenobarbital has some solubility in water and alcohol, but the aqueous solution is not stable (Gerald, 2018). The chloral hydrate is quite soluble in water, but easily volatizes when exposed to air, and decomposes when exposed to light. Therefore, it is

recommended to dispense this formulation in an amber glass bottle with minimal air space at the top. Since this formulation is a suspension, it must be shaken well prior to administration. There is no standardized pharmacopeia formulation that guides us on an expiry date so the determination is based on the US Pharmacopeia (2016) approach of aqueous preparations of moderate compounding complexity. It advises that water containing oral formulation could have a `beyond use date' of 14 days from preparation if stored at controlled cold temperatures and 7 days if stored at room temperature. The British Columbia MAiD protocols have opted for a 72 hour expiry date to ensure the stability and potency of the preparation and discourage the dispensing of the preparation too far ahead of the schedule date of the assisted death (MAID BC Pharmacy, 2018) The formulation should include auxiliary labeling to "shake well prior to administration", "lethal Dose", and "protect from extreme temperature fluctuations".

Dispensing of secobarbital will differ from other agents and practices are largely based on Dutch experience. The Dutch protocol provides a compounding procedure for pentobarbital and secobarbital (KNMG/KNMP, 2012) It advises a beyond use date of 1 month for the unopened bottle if stored at room temperature. This formulation should NOT be stored in the fridge. Secobarbital solution should NOT be shaken as the high pH of the solution causes it to form bubbles in a soapy manner. Therefore, auxiliary labeling should include "lethal dose", do NOT shake, and do NOT store in fridge. Keep at room temperature.

The digoxin/Diazepam/Morphine/Propranolol (DDMP2) combination was developed in Washington state and has now been adopted by some Canadian provinces. There has been no formulation that guides the compounding of this into a suspension or solution. Therefore it is dispensed as a mixture of the four drug powders with directions to mix powder into 100-125 mL of water, clear juice, or alcoholic beverage. The mixture must be shaken or stirred well until smoothly mixed and milk- like. The entire contents should be consumed within 1-2 minutes. The requirement to mix it immediately prior to consumption makes this option less desirable in that the powders can be aerosolized and inhaled by providers or surrounding family and friends. The patient also may have trouble consuming the full amount in 1-2 minutes as it also has a bitter taste. This increases the risk of incomplete dosing, extended dying periods and/or failure to achieve death.

The antiemetic agents may be dispensed in tablet format anytime prior to the scheduled date and consumed as directed. There may be a need to dispense a solution format, depending on patient specific factors. This requirement can be discussed with the pharmacist during the planning phase.

IV backup kits can be provided in a ready-to-use format (medication drawn up in syringes), appropriately labelled to minimize the delay in administration when the decision is made to complete the provision with one or more IV medication. This eliminates possible mistakes on site and minimizes the time needed to draw-up the medications.

In order to maintain the security chain, oral MAiD medications should be passed from pharmacist to practitioner who provides it to the patient at time of MAiD provision. This will 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 then should return any unused portions to the pharmacy for documentation and destruction. This will ensure no residual amounts are consumed by others at the patient's location, or by pets or animals.

Safe Administration

Safe administration of these medications will optimize absorption, which is crucial to maximizing the effectiveness of the regime. To optimize absorption, patients should refrain from eating 6 hours prior to taking the coma-inducing medication if possible. Clear non-carbonated fluids can be continued. Ensure the anti- emetic regimen is taken at least 1 hour before consumption of the coma-inducing agent. Usual medications should be continued right up to the time of the provision, especially pain and anti-emetic/pro-motility medications. In particular, while the continuation of some cardiac medications may not seem to be necessary, experiencing chest pain or shortness of breath prior to the provision will only contribute to suffering.

Read the directions on the bottle of the coma inducing medication: some formulations such as suspensions need to be shaken well before administration and some should NOT be shaken. Patients should remain in a Fowler's position (60 degrees) when consuming the medication and for at least 20 minutes after consumption, even if becoming unconscious, to optimize absorption of the medication and prevent regurgitation. After that time, they can be lowered to a semi-reclined position.

Patients should consume the medication as quickly as possible to ensure they have consumed the entire dose before becoming sedated or losing consciousness. Use of a straw may slow down the rate of consumption. Sips of water or clear juice may be taken in between swallows as long as it is done quickly and does not prolong the consumption of the coma inducing medication.

MAiD medication is often bitter tasting. To help rinse away the bitter aftertaste and enhance the effect of the medication, ¼ cup of strong liquor such as vodka or whiskey OR ½ cup of room temperature, non-carbonated beverage can follow the consumption of the MAiD medication.

Optimizing the Patient and Family Experience for Oral MAiD

Preparations for a successful process

Individuals eligible for MAiD may indicate a preference for oral medication, however, their commitment to that route of administration may change at anytime up to the provision of MAiD. Furthermore, their preference may be altered by a change in their status which renders them incapable of either holding a container or swallowing effectively. In preparation for these potential changes, oral and IV medications should always be concurrently ordered and preparations taken so that both are options at the time of provision. As with any MAiD provision, regular and timely communication ensures capacity and consent to proceed with a planned date and time.

On the day of the oral MAiD provision, individuals often spend their final moments with family and friends. Events may include wishes to consume food, beverages, alcohol, and/or other substances. As with any MAiD provision (oral and IV routes), any consumption must be balanced against maintaining capacity for final written and/or verbal consent to proceed with the planned provision. If an oral route is preferred, individuals should be informed of enhanced efficacy of medications on an empty stomach, and as such, should ideally avoid solids and full fluids in the preceding 6 hours. Clear fluids can be continued up to the planned provision. Individuals should also be informed of the risks of nausea and vomiting associated with these bitter medications, and if applicable, burning associated with chloral hydrate. Antiemetic regime adherence is crucial to promoting a successful oral procedure.

Obtaining final consent prior to MAiD provision

In all provinces and territories in Canada, the MAiD process requires both a written request from an individual and 10 “clear” days between the written patient request and the date of the event. A final consent is obtained prior to the administrations of IV medications, and the same should obtained prior to the ingestion of any oral medications. These requirements ensure that there is no coercion and full capacity of the individual to receive medications that will result in death. We suggest that a MAiD provider must be present at the time of an oral provision to confirm capacity and consent. Presence is also highly recommended to witness actual ingestion of the medication, as the provider is ultimately responsible for the prescription of the medication.

Preparing for a delayed or failed oral medication process

Examining the Canadian experience of using phenobarbital, chloral hydrate and morphine, coma typically occurs in 15 and 20 minutes, and death between 45 and 75 minutes (Trouton, 2018). The variability in the onset of death is well documented in the literature. Unarousable

coma was followed in a stepwise fashion by slow and shallow breathing, agonal breathing, obstructed breathing, apneic spells, and death. These latter stages can take several minutes and can be very difficult for families to observe. Considering these factors, final MAiD consent prior to oral administration should include the insertion of an IV either prior to ingestion or within reasonable time frame post ingestion. Securing vascular access can ensure that all MAiD provisions in Canada are successful, and that any potential failure in our system has been reduced to the lowest acceptable risk. This will also ensure the most compassionate provision of MAiD for patients and their families.

Oral MAiD Provider Experience in Canada

There have been 11 cases of oral MAID provision in Canada – one in Ontario, 1 in Saskatchewan, 1 in the Yukon and 8 in British Columbia. The summary of the 8 cases in BC is as follows:

	Oral medication used	Time from drink to death	Pre medication	Diagnosis
1	Phenobarbital, morphine and chloral hydrate	60	Ondansetron	Glioblastoma
2	Phenobarbital, morphine and chloral hydrate	60	Ondansetron and lorazepam	Spinal stenosis, CAD
3	Phenobarbital, morphine only	45	Marijuana	End stage COPD
4	Phenobarbital, morphine and chloral hydrate	75 *	Marijuana	End stage COPD
5	Phenobarbital, morphine and chloral hydrate	n/a patient was too ill to hold or ingest	none	Metastatic breast cancer
6	Phenobarbital, morphine only	60*	none	Frailty, CAD and COPD
7	Phenobarbital, morphine only	83	Ondansetron	Progressive supranuclear palsy
8	Phenobarbital, morphine only	90*	none	Hepatocellular carcinoma

Barbiturates are believed to work as GABAA receptor agonists. Direct binding to the receptor at multiple binding sites leads to its action as an anxiolytic, hypnotic, anticonvulsant and can induce total anesthesia. In large doses, barbiturates will result in respiratory arrest and subsequent cardiac arrest. Safe compounding of these medications is critical to ensure a stable and palatable product. There is no peer- reviewed literature to guide best practice in compounding these medications. A joint effort in the Netherlands between their national body of physicians and pharmacists has developed a formula for “Mixtura Nontherapeutica Pentobarbital”, which can be applicable to all barbiturates. The components of this formula include:

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

Preparation instructions are described:

1. Mix the purified water, propylene glycol and the alcohol
2. Dissolve the Pentobarbital sodium (or Secobarbital) in this mixture whilst stirring
3. Dissolve the saccharin sodium in this mixture
4. Mix with the sugar syrup and the star anise oil

Secobarbital
Secobarbital has recently become available for use in Canada and is currently one of the most widely used barbiturates for oral MAiD in Oregon, Washington and the Netherlands. The reason for the interest in this agent is its favourable fast onset of sleep and respiratory arrest as compared with other barbiturates such as phenobarbital. Due to issues with pricing in the last several years in the United States, Secobarbital has become increasingly difficult to obtain for patients. These pricing issues are less extreme in Canada and it is currently available from a single supplier in powder form. Secobarbital has been available since 1929, however, several trades of manufacturing rights have taken place in the 21st century and now the rights are owned by Valeant Pharmaceuticals.

Pentobarbital
Pentobarbital was historically used with much success under Oregon’s Death with Dignity program. However, due to its use and association with capital punishment, manufacturers no

longer have it available for use in North America (Shankaran, 2017). Switzerland, which does allow assisted suicide for Swiss and non-Swiss persons of all ages does often use pentobarbital in doses of 10-15g as a sole barbiturate (Gauthier, Mausbach, Reisch & Bartsch, 2015). The Netherlands also continues to advocate Pentobarbital as a barbiturate of choice as well in 15g dose (KNMP-KNMG, 2012).

Phenobarbital
Phenobarbital has also been used for MAiD purposes in several regions as a single agent. However, issues with longer times to sleep and death do not make this medication an ideal MAiD coma- inducing agent. Drug databases quote time to onset as being >1 hour (UpToDate, 2017).

Drug	Mean onset of action (minutes)	Time to peak concentration (hours)	Bioavailability (%)	Half life elimination (hours)
Secobarbital	10-15	2-4	90	15-40
Phenobarbital	>60	0.5-4	95	53-118

Table 1. Selected pharmacodynamic and pharmacokinetic profiles of selected barbiturate agents.

Combination regimens

Phenobarbital/chloral hydrate/morphine
This combination has been used in British Columbia for oral MAiD with some success. However there have been complaints about the use of chloral hydrate in mixtures because of associated oral mucosal burning. As previously explained, phenobarbital is also not an ideal medication to induce coma because of the longer mean time to onset of action after taking it orally. Finally, because of the high rates of opioid use for chronic pain in MAiD patients, morphine would not consistently offer the same level of sedation and respiratory depression across this population.

DDMP1 and DDMP2
Developed in Washington, the DDMP1 mixture consisted of Digoxin 25mg, Diazepam 0.5g, Morphine 10g, and Propanolol 2g. This was an effort to develop an oral regime that would be more affordable after increases in the price of Secobarbital. The average time to sleep and death were 9 minutes and 187 minutes respectively (n=70) (Wood, 2017). Some deaths were as long as 1860 minutes, however, no patient has woken up from the DDMP1 mixture. This

prompted increasing doses to Digoxin 50mg, Diazepam 1g, Morphine 15g, and Propanolol 2g, which is known as the DDMP2 mixture. This gave an average time to sleep and death of 8 and 145 minutes respectively (n=14) (Wood, 2017). Still some deaths with this mixture are as long as 450 minutes, but again, no person has awoken after the DDMP2 mixture. Appropriate compounding of these combination regimens is critical to maximize efficacy.

Other coma-inducing medications

Opioids

Opioids are a very commonly used group of analgesic medications for moderate to severe pain. They work through binding to opioid receptors in the central nervous system (CNS), causing inhibition of ascending pain pathways, altering the perception of and response to pain. They produce generalized CNS depression (LexiComp Online®, 2018). The mechanism by which opioids would produce coma is through central respiratory depression inducing a respiratory arrest and subsequent cardiac arrest.

Patients at the end of their life often experience a degree of pain and suffering for which they commonly are taking opioids. These patients are often resistant to the respiratory depressant effect of the opioid that one is hoping to take advantage of for induction of coma and so there is a subsequent lack of certainty from using these drugs to achieve reliable and quick time to sleep and coma. For this reason, the Netherlands advises against use of opioids in their oral and IV MAiD regimens (KNMP-KNMG, 2012).

Additionally, there is a known side effect of nausea associated with opioids that may make them likely to cause vomiting or regurgitation of the MAiD medications prior to these drugs being fully absorbed from the gastrointestinal tract. It is also well documented that opioids cause slowing of gastric motility which may delay the absorption of co-administered medications.

There is currently no data or experience with more potent opioids (i.e. fentanyl, sufentanil, remifentanil) administered orally for MAiD. However, the pharmacokinetics and pharmacodynamics of the medications support future exploration for their use in MAiD.

Drug	Mean onset of action (minutes)	Time to peak concentration (hours)	Bioavailability (%)	Half life elimination (hours)
Morphine	30	1	17-33	2-4
Hydromorphone	15-30	<1	24	2-3

Table 2. Selected pharmacodynamic and pharmacokinetic profiles of selected opioid agents.

Benzodiazepines

Benzodiazepines have been used as premedication with success in several cases of induction of MAiD, but because of the incredibly high doses and unpredictable reduction in consciousness, the Dutch do not recommend benzodiazapines as a primary medication for induction of a medically assisted death (KNMP-KNMG, 2012). Benzodiazepines are not known to predictably cause respiratory or cardiac depression in isolation. In combination with opioids they may produce a more profound respiratory depression than with opioids alone. However, the anxiolysis that it affords does make them a reasonable choice as a premedication in the case of IV MAiD. In the patient who requires a small dose of anxiolytic premedication prior to oral MAiD provision, lorazepam would be the most ideal agent because of its rapid absorption through the sublingual route.

Drug	Mean onset of action (minutes)	Time to peak concentration (hours)	Bioavailability	Half life elimination (hours)
Lorazepam	30-60	2 (1 if sublingual route use)	90	12
Diazepam	Not available	0.25-2.5	>90%	44-48

Table 3. Selected pharmacodynamic and pharmacokinetic profiles of selected benzodiazepine agents.

Chloral hydrate

A general CNS depressant that also depresses cardiac contractibility, and has sedative and anti- anxiety effects. Its exact mechanism of action is unknown but is thought to be mediated through its active metabolite, trichloroethanol (LexiComp Online®, 2018).

This medication has been used in multiple jurisdictions with varying degrees of success but several features make it less attractive to use as single agent or in combination with other agents for MAiD. Specifically, it is known to be toxic to oral and gastric mucosa and causes significant burning.

Drug	Mean onset of action (minutes)	Time to peak concentration (hours)	Bioavailability (%)	Half life elimination (hours)
Chloral hydrate	10-20	0.5-1	Not available	8-10

Table 4. Selected pharmacodynamic and pharmacokinetic profile of chloral hydrate.

Cardiotoxic adjuvants

Digoxin

Digoxin is a cardiotonic glycoside that is primarily used in the treatment of heart failure, atrial fibrillation or flutter, and paroxysmal atrial tachycardia (LexiComp Online®, 2018). Digoxin in large enough doses will produce lethal arrhythmia and/or conduction block, which will lead to cardiac arrest.

Digoxin was examined as part of a MAiD regime in Washington in an effort to create a death inducing mixture that was affordable and could replace secobarbital. An effort between several internal medicine specialists, an anesthesiologist and a toxicologist in Washington found data through the American Association of Poison Control Centers' National Poison Data System that doses of digoxin greater than 25mg had a 100% mortality rate (Parrott, 2017). As such it was included as part of a multi- drug solution.

Drug	Mean onset of action (minutes)	Time to peak concentration (hours)	Bioavailability (%)	Half life elimination (hours)
Digoxin	60-120	1-3	60-80	36-48

Table 5. Selected pharmacodynamic and pharmacokinetic profile of digoxin.

Propanolol

Propanolol is a non selective beta blocking agent and it is clinically used to control arterial hypertension, in postinfarct prophylaxis, and in several forms of cardiac arrhythmia. One of the pharmacologic effects of this compound is the reduction of cardiac conduction and contractility (LexiComp Online®, 2018).

There are a few case reports of its potential for inducing cardiac arrest (Srettabunjong, 2017; Dabek et al., 2013; Amundson, 1988) in doses ranging from 2.4-6g. Currently it is being used as part of a mixture in some areas of the United States in doses of 2g.

Drug	Mean onset of action (minutes)	Time to peak concentration (hours)	Bioavailability (%)	Half life elimination (hours)
Propanolol	60-120	1-4	25%	3-6

Table 6. Selected pharmacodynamics and pharmacokinetic profiles of selected beta blocking agents.

Anti-emetics/Pro-motility Agents

Most of the oral formulations used in assisted deaths contain some sort of barbiturate and all barbiturates have quite a bitter taste which makes the compounded solutions less palatable. Bitter taste slows gastric emptying and often induces nausea. (Peynot des Gachons et al. 2011) The large doses that are required in MAID provision make it necessary to dispense the barbiturate-containing product in a solution or suspension, rather than as capsules and this format further amplifies the bitter taste.

In most jurisdictions in Canada, a final consent is required immediately prior to administration of the oral or IV medications. Therefore, the selection of any anti-emetic or pro-motility agent must be such that the ability of the person to sign or verbalize final consent is not compromised.

Pre-treatment with anti-emetics and/or pro-motility agents is recommended to improve the absorption of the medication and decrease the likelihood of nausea or emesis. These problems not only contribute to additional suffering for the patients, but also interfere with complete absorption of the medication and may increase the likelihood of a failed completion. Many patients who are opting for an assisted death are frail with multiple co-morbid conditions that affect their ability to tolerate and absorb the medications. Patients at the end of their lives may be on opioids, which slow gastrointestinal transit, thereby affecting the absorption of the medication. While the risk of experiencing adverse effects with a single dose of an anti-emetic prior to MAiD provision is low, the effects may be additive in patients who are frail, elderly and on other mediations that have similar effects and contribute to unnecessary symptoms or suffering at time of MAiD provision. Some patients may already be on antiemetic or prokinetic agents and the decision of an appropriate regimen should consider specific patient factors.

Metoclopramide
Metoclopramide blocks dopamine and serotonin receptors to prevent and treat nausea and vomiting, and enhances gastric emptying and gastrointestinal motility (LexiComp Online®, 2018). The Dutch protocol recommends metoclopramide as the drug of choice because of these dual mechanisms of action. (KNMG/KNMP Guidelines 2012). Metoclopramide can cause drowsiness, confusion, and/or extrapyramidal symptoms such as tremors, restlessness and dystonia and may be contraindicated in Parkinson's disease or in patients who are already exhibiting these symptoms. The usual recommended dose is 20mg taken 1 hour prior to MAiD provision as the onset is from 30 to 60 minutes and onset is from 30 to 60 minutes and peak effect occurs in 1-2 hours.

Ondansetron
Ondansetron is a selective 5- HT3 receptor antagonist that blocks serotonin to prevent and treat severe nausea and vomiting. (Lexi-Comp Online®, 2018). Doses of 4-8mg can be given 1 hour before MAiD provision with the onset at approximately 30 minutes and peak in 1 to 2 hours.

Ondansetron can cause headache, fatigue, drowsiness and serotonin syndrome (agitation, tachycardia, flushing, tremor, rigidity), especially if given concurrently with other serotonin enhancing medications. Higher doses (i.e. up to 24 mg) can be considered in patients at higher risk of induce nausea and vomiting. The acute side effects to higher dosing are minimal.

Haloperidol

Haloperidol is a butyrophenone antipsychotic that nonselectively blocks postsynaptic dopaminergic D2 receptors in the brain. (Lexi-Comp Online®, 2018). Its anti-emetic action is thought to be due to blocking the dopamine receptors in the chemoreceptor trigger zone. Haloperidol is sometimes used off-label in nausea and vomiting associated with palliative care and post-operatively. End of Life Washington State recommends the use of haloperidol 2mg orally along with metoclopramide 20mg 1 hour prior to consumption of death-inducing medication. Haloperidol is contraindicated in patients at high risk of extrapyramidal reactions (dystonia, rigidity, tremor, restlessness), and should be avoided in patients with Parkinson's disease.

Cannabinoids

Cannabinoids have been shown to have anti-emetic effects through their actions on the chemoreceptor trigger zone in the medulla (Navari et al. 2006) and decreasing gastric motility and contractility in the gut (Goyal et al, 2017). Pharmaceutical grade cannabinoids dronabinol and nabilone have been found to have some benefit in chemotherapy-induced nausea and vomiting. Dronabinol is no longer on the Canadian market. Many patients use medical and/or recreational marijuana for multiple purposes, including as an anti-nauseant and anxiolytic, and may prefer this option prior to an assisted death. Oral consumption of a cannabinoid would not be suitable for this situation due to its slow and erratic absorption, variable bioavailability, slow onset and delayed peak of action. (Grotenhermen F. 2003). Inhaled cannabis, through either smoking or vaporizing, results in an almost immediate onset, and peak within minutes and therefore should be administered approximately 5 to 10 minutes before consumption of the MAiD medication. Two cases in Canada have used inhaled cannabis as a single agent antiemetic for oral MAiD with no nausea/vomiting side effects thereafter.

Prochlorperazine

Prochlorperazine is a piperazine phenothiazine which blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain, including the chemoreceptor trigger zone. Its onset of action is 30-40 minutes and therefore should be given at least 1 to 2 hours prior to MAiD provision. It has a high incidence of hypotension and extrapyramidal effects that might limit its use in some patients (i.e. contraindicated in patients with Parkinson's disease).

Dexamethasone
Dexamethasone is a longer acting corticosteroid that is often used with a 5-HT3 antagonist for highly emetic chemotherapy. The mechanism of its antiemetic action is unknown. (Lexi-Comp Online® 2018). There are no case reports or other data regarding its efficacy or usefulness as an antiemetic for MAiD provision. However, there is a strong breadth of evidence to support dexamethasone for both post- operative nausea/vomiting, and post chemotherapy. It has a relatively low acute side effect profile. Given the similar mechanisms of action of MAiD medications to those of anesthetic drugs, dexamethasone should be strongly considered and studied for oral MAiD.

Aprepitant
Aprepitant is a substance P/neurokinin 1 (NK1) receptor antagonist that has been primarily studied and used to treat acute and delayed phases of chemotherapy-induced emesis. (LexiComp Online®, 2018) It also can augment the antiemetic activity of 5-HT3 receptor antagonists and corticosteroids. There are no case reports or other data regarding its efficacy or usefulness as an antiemetic for MAID provision and its cost may be prohibitive. It also has a slow time to peak plasma concentrations and effect (hours) which makes its usefulness in MAID provision limited.

Dimenhydrinate
Dimenhydrinate has multiple anti-emetic mechanisms of action including H1 histamine receptor competitive agonism, blocking of chemoreceptor trigger zone, diminishing vestibular stimulation and depressing labyrinthine function through its anticholinergic action. (LexiComp Online®, 2018) It is a commonly used, inexpensive anti-emetic at doses of 25 to 50mg with an onset of action of approximately 15 to 30 minutes. There are no case reports or other data regarding its efficacy or usefulness in MAID provision and its tendency for drowsiness and anticholinergic side effects may limit its usefulness for MAiD.

Current Global Practices/Experiences

Netherlands

In the Netherlands, the provision of oral and intravenous MAiD has been practiced since 1973 and has been formally legalizaed in 2002.

The current oral protocol, in use since 2012, describes premedication with metoclopramide, an antiemetic and promotility agent, at a dose of 10mg orally every 8 hours for 24 hours leading up to the MAiD procedure. This is followed by the consumption of a barbiturate solution containing either 15 grams of pentobarbital or 15 grams of secobarbital. Because barbiturates taste bitter, one or two ingredients are added to enhance the flavour, to neutralize the pH, and to act as a preservative and prevent crystallization.

A physician is required to attend the patient administration of any oral agents and if the oral agent is not successful within a predetermined amount of time, the physician is able to initiate an IV protocol to complete the process of MAiD. The Dutch Guidelines suggest a maximum period of 2 hours be allowed before intervening with administration of an IV protocol. (KNMP-KNMG, 2012).

A review of the clinical problems associated with the performance of euthanasia and physician-assisted suicide in the Netherlands was published using data from cases in the 1990's (Groenewoud, 2000). In cases of assisted suicide, 3.5% experienced nausea and vomiting and 2.6% experienced extreme gasping. Problems with completion occurred in 16% of cases including a longer-than expected time to death, failure to induce coma or induction of coma followed by awakening of the patient. The attending physician decided to administer IV medication in 18% of the cases because of either problems with completion or inability of the patient to take all the medication.

Prior to 2012, the KNMP and KNMG recommended that doses of 9 grams of barbiturate be used. The dose was increased to 15g to increase the efficacy. The likelihood of inducing death within 60 minutes increased from 87% with 9g to 94% with 15g.

Time to death	N=245 1998-2011 (%) (9-10g dosing)	N=165 2013-2015 (%) (15g dosing)
<30 minutes	70	82

31-60 minutes	17	12
60-120 minutes	9	4
>120 minutes	3	2

Table 7. Time to death comparison between barbiturate dosing of 9-10g (1998-2011) and 15g (2013-2015) in the Netherlands.

Between 1998-2011, intravenous backup was used 20% of cases. Between 2013-2015, intravenous backup was used in 9% of cases. Intravenous backup is discussed prior to the procedure and the time to intervene is mutually agreed upon by patient and clinician. In some cases it is 2 hours, however, some patient may prefer 1 hour or even less. As a result, the times to death listed include those in whom IV MAiD backup was used as well and aren't differentiated.

Of the 165 cases, between 2013-2015, 9 patients displayed some element of retching, 3 patients fell asleep before finishing 100mL of the barbiturate drink and 2 patients displayed some muscular contractions (Horikx, 2016). 3 patients complained of a bad taste, 1 patient reported throat pain and 1 reported stomach pain.

Belgium

In Belgium, both euthanasia and physician assisted death have been legal since 2002 (Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, Cohen J, 2016). Administration of an antiemetic followed by pentobarbital is published as the typical oral MAiD provision in Belgium. The dosing or specifics of provision are not available (Bilson et al, 2005). Between 2002 and 2007 in Belgium only 1% of cases of MAiD were oral route (n=34) (Rurup et al, 2011).

Luxembourg

In Luxembourg, both euthanasia and physician assisted death have been legal since 2009 (Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, Cohen J, 2016). Very little published information is available on the medications used for oral MAiD provision as well as statistics on MAiD deaths since legalization.

Switzerland

Switzerland legalized assisted suicide in 1918 and is the only country to allow non-clinicians to assist in suicide (Hurst and Maroun, 2003). In public health reporting, the Swiss do not

differentiate assisted suicide from non-assisted suicide and therefore it is difficult to find data on physician assisted deaths specifically. Formal statements by the Swiss Medical Association in 2002 stating that assisted suicide is not part of a physician's activity prevents Switzerland from developing formalized protocols for oral MAiD. Some physicians do still participate despite this climate, however, no formalized protocols exist. Intravenous MAiD is still illegal.

United States

Currently there are 7 states that allow MAiD by the oral route through a prescription which patients fill and administer themselves or with family. A physician may be present but must not be involved in the medication delivery. No states have legalized intravenous MAiD and thus the option for an "IV rescue" is not possible under any of their legislation. Nurse practitioners are not legally allowed to provide MAiD under their legislation. As indicated in Table, the trend in many states has recently been away from Pentobarbital and towards Secobarbital and other nonbarbiturate medications for MAiD.

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	-	-	-	-	-	-	-	-

Table 8. Available published statistics use of MAiD medications in the United States. Adapted from Adapted from the Oregon Health Authority, Death with Dignity Act Reports 2013-2017, Washington State Department of Health Death with Dignity Act Reports 2013 & 2016, and The Colorado End of Life Options Data 2017.

Oregon

Oregon's Death with Dignity law has been in place since 1994. Since its inception, Oregon's medication practice for MAiD has been oral administration of a physician prescribed medication. Initially, the vast majority were barbiturates only. Under this program, the clinician writes the prescription for the oral regimen and the patient is responsible for filling the prescription at a pharmacy and taking the medication in a location of their choosing without a clinician present. Initially it was either pentobarbital or Secobarbital that would be filled through a pharmacy. Since 2012, however, there have been issues with the barbiturate based regimen. Pentobarbital is no longer available in North America and secobarbital has become very expensive. Therefore, other options have been developed in Washington and are becoming more common (see below for details on the DDMP2 method). For those who can afford it, Secobarbital is still used, usually in 9-10g doses as a single barbiturate drink.

Washington

Washington's Death with Dignity legislation has been in place since March 5, 2009. Since its inception, Washington's medication practice has been oral administration of a death inducing medication, initially primarily secobarbital or pentobarbital. Eventually pentobarbital was unavailable and secobarbital underwent a huge price increase in 2015 making it unaffordable for many patients. An alternate mixture of phenobarbital, chloral hydrate and morphine was formulated and used for a brief period of time. However, after approximately 100 cases, this formulation fell out of favour because of clumping and crystalizing in and out of solution when mixed by the patient prior to ingestion, and severe oral mucosal burning was attributed to the chloral hydrate. (End of Life Washington, 2017 & Trouton, 2017). In June 2016, End of Life Washington assembled a small group of experts including a toxicologist, pharmacologists, two anesthesiologists, a cardiologist and two internists to identify a new formulation for assisted dying and this was when DDMP (Diazepam, Digoxin, Morphine, Propranolol) was developed.

Similarly to Oregon, the clinician writes a prescription for medication, which the patient then is responsible for filling and taking, unaided by a clinician. The current oral preparations recommended under Washington's most recent guidelines as of January 30, 2017 are premedication with Metoclopramide 20 mg and Haloperidol 2mg orally 1 hour prior to the ingestion of one of two life ending regimes. The first regimen includes Secobarbital 10g and Propranolol 200mg orally. The regimen suggests mixing both into 2-3oz of the patient's choice (ie. Scotch, gin or rum) or water. The alternative option that they have worked on developed

since 2014 is Diazepam 1g, Digoxin 50mg, Morphine sulfate 15g, and Propanolol 2g. This is being referred to as the DDMP2. This regimen suggests mixing all these powders into a glass jar (as diazepam is absorbed by plastic) and further mixing with 3-4oz of warm water, a favourite liquor, or clear juice. Both mixtures should be consumed within 1-2 minutes of mixing.

	Cases (n)	Average Time to Sleep (minutes)	Max time to sleep (minutes)	Average time to death (minutes)	Maximum time to death (minutes)
Secobarbital 10g	200+	5	-	68	1620
Secobarbital 10g with Inderal 2g	41	5	-	41	420
DDMP	70	9	30	187	1860
DDMP2	14	8	258	145	450
MVP	3	6	10	377	1080
Chloral hydrate	77	-	-	205	4280

Table 9. Unpublished oral combination data from Washington Death with Dignity Program Adapted from Wood, 2017 – Personal communication.

Montana

Since a court ruling in 2009, physician assisted death via a prescription for oral medication has been legal (Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, Cohen J, 2016). However, no legislation has been passed yet. A review of state departments does not reveal any published data on MAiD provisions since the court decision was made. Review of the literature has also yielded no information on practices or procedure in this state.

Vermont

In 2013, Vermont passed a law allowing physician assisted death by lethal prescription (Vermont Agency of Human Services, 2018). Vermont's statistics only specify that 29 patients used a prescription under this legislation between 2013-2017 and do not quantify which

medications were used. They also have not published any protocols dictating which coma inducing medications or anti-emetics were used.

California

Since 2015, physician assisted death by prescription of an oral medication is has been legal. (Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, Cohen J, 2016). California's practice has closely mirrored that of Oregon and Washington and their prescriptions for lethal doses of coma medications includes Secobarbital 9-10g for those that are covered under Medi-Cal (California's Medicaid). For those that are either not covered under Medi-Cal or who cannot afford this option, they are now using the DDMP2 mixture that was developed in Washington is now being used.

Colorado

In November 2016, Colorado passed a law allowing physician assisted death. Protocols have not been published but from data published by the Colorado Department of Public Health (2017), the two main forms of coma inducing medication appear to be Secobarbital and DDMP. It is unclear which doses of coma inducing medication and which antiemetic regime are being used.

District of Columbia (D.C.)

In February 2017, D.C. became the 6th jurisdiction in the United States to pass a law allowing oral MAiD. No published data sets are available from the D.C. Department of Public Health yet and a review of the literature does not yield any information about this state's medication practices or procedures.

Canada

In Canada, oral and intravenous MAiD has been legal since June 2016. Practice of oral MAiD has been largely heterogeneous and has not been streamlined to one singular protocol. Canada's legislation allows for both IV MAiD and oral MAiD. In most provinces, for oral MAiD, a clinician is required to be present at the time of MAiD provision and must carry an "IV backup" kit in case death after oral MAiD provision has not occurred within an agreed upon time.

Newfoundland, Nova Scotia, PEI, New Brunswick, Nunavut
MAID via the oral route is permitted but no oral MAiD protocol exists. No patients have exercised this option.

Quebec
The province has MAID legislation separate from the federal law and oral medication for MAID is not permitted. Only the IV route may be used.

Ontario
MAID via the oral route is permitted but, no oral MAiD protocol exists. One oral MAiD provision has occurred. Details are not publicly available.

Manitoba
Manitoba has developed an oral MAID protocol that involves premedication with Ondansetron 8mg and metoclopramide 20mg 1 hour prior to the procedure for antiemetic prophylaxis. The coma inducing compound is a mixture of Phenobarbital 20g, Chloral hydrate 20g and morphine 3g. The protocol also allows Haloperidol 5mg subcutaneously or intravenously if emesis is encountered. It also includes Lorazepam 0.5-4mg sublingual as needed 5-10 minutes prior to taking the coma inducing compound for anxiety. No patients have exercised this option.

Saskatchewan
Saskatchewan has developed an oral MAiD protocol that involves premedication with metoclopramide 20mg 1 hour prior to the procedure for antiemetic prophylaxis. The coma inducing compound is a mixture of Phenobarbital 20g, Chloral hydrate 20g and morphine 3g. The protocol has Haloperidol 5mg subcutaneously or intravenously if emesis is encountered. It also includes Lorazepam 0.5-1mg sublingual as needed prior to taking the coma inducing compound for anxiety. Prior to the development of a provincial oral protocol, there were 2 prescriptions written and filled for oral MAiD. Only one has been used, and required IV to complete the process the following day. Further details are not publicly available.

Alberta
Alberta has developed an oral MAiD protocol that involves premedication with haloperidol 2mg and metoclopramide 20mg 1 hour prior to the procedure for antiemetic prophylaxis. If there is an allergy to metoclopramide, then they suggest ondansetron 8mg is suggested instead. The coma inducing compound is the DDMP2 mixture (Diazepam 1g, Digoxin 50mg, Propanolol 2g and Morphine 15g). It also includes Lorazepam 0.25-0.5mg sublingual as needed prior to taking the coma-inducing compound for anxiety. This protocol replaced the original protocol involving phenobarbital. No further details are available on why the change was made. No patients have exercised this option.

British Columbia
British Columbia has developed an oral MAiD protocol that involves premedication with ondansetron 8mg and metoclopramide 20mg 1 hour prior to the procedure for antiemetic prophylaxis. The coma-inducing compound is a mixture of Phenobarbital 20g, Chloral hydrate 20g and morphine 3g. The protocol has Haloperidol 5mg subcutaneously or intravenously if

emesis is encountered. It also includes Lorazepam 0.5-1mg sublingual as needed prior to taking the coma-inducing compound for anxiety.

Thus far, 8 cases of oral MAiD have taken place in British Columbia. 4 of these cases were performed with a phenobarbital, morphine and chloral hydrate combination with varying oral antiemetic regimes. The other 4 cases were phenobarbital and morphine only. The average time to death was 1 hour. There were no fasting restrictions used in these cases. To mitigate the oral mucosal burning in one case when chloral hydrate was used, benzocaine spray to the back of the throat was utilized before administration of the oral MAiD regimen. This was reportedly helpful for patient symptom reduction.

Yukon
Yukon has developed an oral MAiD protocol that involves premedication with haloperidol 5mg and metoclopramide 20mg 1 hour prior to the procedure for antiemetic prophylaxis. The coma inducing compound is the DDMP2 mixture (Diazepam 1g, Digoxin 50mg, Propanolol 2g and Morphine 15g). It also includes Lorazepam 0.25-0.1mg sublingual as needed prior to taking the coma-inducing compound for anxiety. Thus far, one MAiD provision has taken place under this protocol and time to death was 135 minutes. No physician or nurse practitioner was present for the death.

Northwest Territories
The Northwest Territories has developed an oral MAiD protocol that involves premedication with metoclopramide 20mg 1 hour prior to the procedure for antiemetic prophylaxis. The coma-inducing compound is a mixture of Phenobarbital 20g, Chloral hydrate 20g and morphine 3g. The protocol also has Haloperidol 5mg subcutaneously or intravenously if emesis is encountered. It also includes Lorazepam 0.5-1mg sublingual as needed prior to taking the coma-inducing compound for anxiety. No patient has exercised this option.

Discussion

Overall the quality of evidence available is low. Most of the evidence is unpublished or limited to expert opinion, observational data, and experiential data from other jurisdictions. There is some difficulty in determining which coma inducing mixture has the most evidence based on the lack of comparative data between each existing drug regime and different dose trials for the purpose of MAiD. This is a large area for potential research in the future, however, it has foreseeable potential difficulties because of the ethical implications of such studies. There is an opportunity in Canada to clearly document our experience both for quality improvement and to disseminate our learnings globally. As such, recommendations from this analysis will largely be based on experience and will be based on desirable characteristics described at the beginning of this paper.

The greatest body of data, and therefore the most experience with clinical predictability for oral MAiD is with the barbiturates. Based on the pharmacodynamics, it appears that for MAiD, pentobarbital and secobarbital have a more favourable profile, and in doses of 15g MAiD providers in the Netherlands have found it will result in death 94% of the time in less than 30 minutes. This is in contrast to lower doses of 9-10g, which the KNMP and KNMG report as causing death in 30 minutes only 87% of the time. It is hard to ignore the effect this dose increase has had on the success rate of the procedure. No collected data exists at higher standardized doses (i.e. 20 grams), with the potential advantage of a further decreased time to death. However, this hypothesis is not supported by the pharmacokinetic and pharmacodynamic profiles of these drugs, and would add complexity to an oral provision with the necessity to compound the drugs with a greater volume of suspension.

Pentobarbital is currently not available in Canada. The favourability of pentobarbital as a MAiD drug necessitates its pursuit as an option for oral administration. Secobarbital reportedly does have similar results to Pentobarbital in similar doses with reliable (98%) time to death in less than 30 minutes. The United States had challenges with the dispensing of Secobarbital in 100mg capsules. In Canada, Secobarbital is supplied as a powder in 1g, 5g, 25g and 100g units to compounding pharmacies which then prepare a solution which can be premixed and supplied to patients. Secobarbital may be more bitter than Pentobarbital; however, this has not been verified by any published expert opinion to date. Several modifications have been made to the barbiturate cocktail to make it more palatable and currently the most experience with this seems to be with the Dutch preparation.

Washington's DDMP2 mixture has been used effectively for the last 2 years in both Washington and Oregon because Secobarbital has proven cost prohibitive in the United States. However, there is far less experience with this mixture than any of the barbiturates. Based on expert experience in Washington, DDMP2 has an average time to death of just over 2 hours (Parrott,

2017). DDMP2 should only be considered if there are financial barriers or limited access to secobarbital prevents its use.

In order to ensure the maximal delivery of medication to the stomach, it is important to prevent regurgitation. This has been accomplished by administering either Metoclopramide 20mg every 8 hours for 24 hours by mouth prior to the procedure or Metoclopramide 20 mg and Haloperidol 2mg 1 hour prior to ingestion. Neither of these has been compared to one another to determine the best regime for prevention of regurgitation and could be an area for further investigation. Providers of MAiD have reported that in their practical experience, Haloperidol in 1-2mg doses by mouth 1 hour prior to taking a barbiturate drink may provide antiemesis as well as some anxiolysis as compared to ondansetron 4-8mg 1 hour prior to procedure (Parott, 2017). Consideration should be given to increasing ondansetron to between 8-24mg and/or dexamethasone 8mg based on patient and regimen risks factors for nausea and vomiting. With the pending legalization of cannabinoids in Canada, the application of inhaled marijuana should be explored and investigated as an anti-emetic for oral MAiD, given that its route of administration avoids the gastrointestinal tract.

Summary Recommendations

1. Oral medication absorption is probably most efficacious on an empty stomach.
2. Coma inducing medication should be preceded by an antiemetic to reduce nausea, vomiting, and regurgitation to promote maximal delivery of medication.
    a. Recommended antiemetic regimen includes metoclopramide 20mg plus either ondansetron 8-24mg or dexamethasone 8mg taken orally 1 hour prior to the coma inducing medication.
3. Recommended 1st line coma inducing medication is Secobarbital 15g by mouth as a single agent barbiturate drink that is compounded in a stable and palatable mixture. “Mixtura Nontherapeutica Pentobarbital” (applicable to Secobarbital) is a compounding formula from the Netherlands with demonstrable experience and success.
4. Recommended 2nd line coma inducing medication regimens include:
    a. DDMP2 that is compounded properly (ie. ideally professionally) just prior to ingestion to ensure efficacy. Requires consumption over 1-2 minutes for maximal efficacy.
    b. Phenobarbital, chloral hydrate and morphine.
5. Clinician presence is recommended for all oral MAiD provisions to obtain final consent, determine if oral administration is still desired and possible, ensure the lethal dose of medication is delivered securely, verify ingestion, and confirm death. This mean that clinicians will still need to be prepared to obtain vascular access and administer IV medications in the case of failure or significant delay in effect of the oral medications.

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