



The Oral MAiD Option in Canada

Part 1: Medication Protocols

Review and Recommendations

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Executive Summary

Medical Assistance in Dying (MAiD) became legal in Canada in June 2016. The understanding of MAiD in Canada (to be regulated and operationalized by the provinces) includes options of intravenous administration of medications by physicians or nurse practitioners, or self administration of oral medications. The main advantage of offering patients an oral option is the autonomy it provides for patients to take the medication themselves, and re-establish some control during a challenging time of their disease or illness.

The scope of this paper is the exploration of the oral medication protocols available for MAiD, to inform recommendations for a pan-Canadian approach towards the implementation of this alternative for patients. The medications examined are limited to those that have been used for MAiD in other jurisdictions, or have been hypothesized as potentially useful for MAiD. While recommendations regarding the safe dispensing, administration, and monitoring the effects of oral MAiD medication will be addressed, those issues will be covered more comprehensively in part 2 of this guideline. A review of intravenous medication protocols will be explored in a subsequent guideline.

Canada has been informed with respect to the oral medication option for MAiD by countries and jurisdictions where physician assisted death has been legal for years. Most of the evidence for different oral regimens is based on experience through case reports and case series. Further recommendations can be based on the pharmacokinetic and pharmacodynamic properties of different medications. Finally, any recommendation needs to be somewhat informed by the cost of the various medications.

The following are the summary recommendations from this review:

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.
 - 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. "Mixture 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 means 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.

Choosing the Oral Option for MAiD

Introduction

Canada legalized medical assistance in dying (MAiD) in 2016 with the passage of Bill C-14 (House of Commons Canada, 2016). Since the law was passed, there have been initiatives in different regions of Canada to require or offer different oral drug regimes for MAiD. Various methods, informed by global experience, have been developed and used with varying degrees of success. The purpose of this review is to explore various oral medications used in MAiD and make recommendations for Canadian practitioners. The details outlining the specifics of prescribing and dispensing, ensuring a successful medically assisted death and the role of the practitioner will be addressed but a detailed review is outside the scope of this paper.

The scope of this review will focus on oral medications used in MAiD. A later review will discuss IV medications used in MAiD. An inherent problem in developing these guidelines is the lack of quality research on which to base recommendations. Most published literature in this area is based on case series experience. As a result, current practice is based on expert opinion, pharmacologic properties of various drug categories and the cost of the various medications.

Why an option for oral self-administration may be desirable

There are several reasons oral medication administration may be desirable. Firstly, for patients, this route offers a more autonomous opportunity to actually take the medication themselves and have a better perceived experience of controlling the timing and circumstances of their own death. It has been studied extensively in the literature that one of the largest concerns people have at the end of life is the loss of control and an oral method would help to restore some of that control (Ganzini et al., 2003).

Additionally, the oral route can offer the possibility of easier access to MAiD than IV. Canada is a geographically wide country with a large rural population. While the Canadian Association of MAiD Assessors and Providers (CAMAP) currently advocates clinician presence at the time of oral administration, with more experience, a system could develop that safely dispenses and confirms appropriate use and effectiveness of the medication, but does not necessarily require clinician presence. This could eventually improve access to MAiD in rural populations where availability of providers may be reduced.

Finally, it may also increase access by providing increased comfort to some clinicians who may perceive providing an oral option as less active in the patient's death than intravenous administration and therefore more acceptable for them to participate.

Advantages and disadvantages compared to an intravenous option

The obvious advantage to oral MAiD is the return of autonomy to the patient at a time when the disease or illness process is outside of their control. This is in contrast to IV routes where the practitioner needs to establish an intravenous (IV) and administer medication on a date, and at a time and location mutually agreed upon between patient and practitioner. Having said that, at least in the short term, prescribing physicians should still need to be present at the time of an oral MAiD provision to obtain a final consent, and ensure the lethal dose of medication is delivered securely, ingested safely, and successfully causes death. This will mean that clinicians will still need to be prepared to obtain vascular access and administer IV medications in the case of failure or delayed effect of the oral medications.

Disadvantages of an oral route when compared to IV administration include issues with impaired absorption or intolerances. Problems with the ability to consume the volume of medication may result in incomplete doses being delivered to the patient. As such, pre-existing significant nausea and vomiting or conditions that significantly impair absorption (e.g Crohn's disease with significant previous bowel resections) may make one consider an IV over an oral route. There is also the disadvantage that you are not able to supplement with more medication via the oral route as it is essentially a one-time dose. If it were deemed ineffective past a certain time point, starting an IV would be necessary to ensure death as an outcome. This contrasts to the IV protocols, where the IV access has already been established and one is able to easily inject more medication if required.

Desirable characteristics of an oral regimen for the purposes of MAiD

A discussion of medications used in MAiD must be framed in reference to the main goals of MAiD in Canada. This process is patient-centred and should aim for:

1. Maximal autonomy
2. Minimal side effects (i.e. burning, nausea, vomiting, regurgitation)
3. Fast onset of unconsciousness
4. Minimal time between sleep and death
5. High efficacy (lower failure rate or need for backup IV rescue)
6. Palatability and tolerance
7. Stability when compounded
8. Easy accessibility and reasonable cost to public health care

Relative contraindications to an oral regimen for the purposes of MAiD

1. Incapable of swallowing sufficient volumes of liquids (i.e. 120 mL)

2. Pre-existing severe nausea, esophagitis, or gastritis
3. Severe dehydration
4. Pathology of the gastrointestinal tract to likely interfere with absorption

Coma Inducing Medication Regimens

Unless otherwise stated, the pharmacokinetics and pharmacodynamics listed for the medications below are at typical therapeutic dosing, not MAiD dosing. There has been little to no research into their parameters at such high doses as seen with MAiD. The scope of this review includes medications that are common to the practice of MAiD, and are commonly available to community pharmacies in Canada.

Single agent coma-inducing medications

Barbiturates are believed to work as GABA_A 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, remifentanyl) 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
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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 benzodiazepines 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)
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Chloral hydrate	10-20	0.5-1	Not available	8-10
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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

Propranolol

Propranolol 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)
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Propranolol	60-120	1-4	25%	3-6
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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 medications 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 legalized 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
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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 regimens. 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 Propranolol 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	28	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, Propranolol 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 regimens. 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.
 - 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 means 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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