CAMAP | ACEPA

Canadian Association of MAiD Assessors and Providers

Association canadienne des évaluateurs et prestataires de l'AMM

Intravenous MAiD Medication Protocols in Canada

April 2020

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 Recommendations

The following are the summary recommendations of this review:

1. Medication errors are preventable and can be minimized utilizing the following strategies:
    - Usage of pre-filled syringes or single-use vials from which to draw up medications
    - Clear drug labelling as to contents and dosing in syringe
    - Utilizing differently sized syringes for each medication
    - Implementing colour-coded labels for each drug
    - Using high alert labels for high-risk drugs such as rocuronium and cisatracurium
    - Discarding unlabelled syringes or returning them to pharmacy

2. Good intravenous access is essential in the context of MAiD. To minimize the risk of vein compromise, and the need for lidocaine to mitigate discomfort with medications, venous access should be established in as large a vein as possible. Unless a patient has central venous access (ie. PICC line), two larger bore intravenous catheter sites are strongly recommended (i.e. avoid 24 gauge IVs and butterfly needle sets). Both intravenous catheters should be checked for proper position inside the lumen of the vein prior to providing MAiD. This can be done with a one-time saline flush or the use of a straight line IV solution “drip” to gravity.

3. To simplify the protocol, all medications are to be administered as IV push according to peripheral IV site and IV cannula size. The main advantage of more rapid administration in rapid succession is the mitigation of undesirable side effects of any medications and a more rapid death. The major risk to more rapid administration is vein integrity, which should be monitored throughout the injection.

4. Saline flushes between medications unnecessarily complicate the protocol, when using an IV saline lock. There are no interactions or precipitation from the mixing of the recommended medications requiring saline flushes between doses (i.e. subsequent medications serve as the flush to previous medications). A saline flush may be considered following the administration of all medications when IV tubing of significant length and volume is employed.

5. In any circumstances, where an essential medication is not eliciting a desired/ therapeutic effect, it is most likely that the intravenous has migrated interstitial. The same recommended doses from the second kit should be administered in the same order through a different intravenous. Alternatives and deviation from

essential medications is unnecessary and introduces significant risk. Refer to CAMAP guidelines on “Failed MAiD in the Community in Canada” for an approach to loss of vascular access.

6. All medications are stable at room temperature. Although rocuronium should be stored under refrigeration, the unopened vials can be stored up to 90 days at room temperature.

7. Simplification and standardization of medications and doses minimizes the risk of medication errors. Doses of medications should be given in total in the recommended order to minimize medication error and maximize desired effects of the medications. There is no proven benefit and perhaps even potential harm in splitting doses of medication.

8. The essential medications and dosages to induce death are recommended based on 4 to 10 times the ED95 of each drug for a 70kg individual to ensure therapeutic effect and prolonged duration of action across a wide population of patients (ie. different ages and weights). ED95 is the dose required to achieve the desired effect in 95% of the population. Suggested dosing has been adjusted against those goals with consideration of dose per vial provided by the pharmaceutical companies to avoid unnecessary wasting of any medication. In this paper, there is no reference made to the half-life of medications, as drug metabolism is irrelevant in the context of MAiD due to the rapid in-sequence administration of drugs that will effectively induce death in a timely manner.

Administration Order	**Agent**	**Purpose**	**ED95 (mg/kg)**	**Suggested dosing for MAiD**
#1	Midazolam	Anxiolysis/ Sedation/ Amnesia to Propofol-induced Pain	0.033	10 mg
#2	Propofol	Coma Induction	2.56	1000mg
#3	Rocuronium **OR**	Neuromuscular blocking agent	0.305	200mg
	Cisatracurium		0.04	40mg

Optional medications include lidocaine and bupivacaine.

Agent	Purpose	Suggested dosing for MAiD
Lidocaine	Reduction propofol-induced pain on injection	40mg
Bupivacaine	Cardiac Arrest	500mg

9. Patients are not required to be NPO. The proposed protocol is associated with minimal risk for nausea/vomiting. If there is a concern about nausea/vomiting due to the patient's underlying medical condition, positioning a patient upright can be considered.

Background

Medical Assistance in Dying (MAiD) in Canada was first legalized in the province of Quebec on December 10, 2015 (Government of Canada, 2016). It was subsequently legalized in the remaining provinces and territories in 2016 (Government of Canada, 2019). Besides Canada, MAiD via intravenous administration is currently legal in the Netherlands, Belgium, Luxembourg, Colombia, and the state of Victoria in Australia (Emanuel, Onwuteaka-Philipsen, Urwin & Cohen, 2016; Smith, 2017).

Health Canada has released 4 federal interim reports since the legalization of MAiD. The fourth and latest report covers a period from January 1, 2018, to October 31, 2018. The percentage of deaths in Canada attributable to MAiD in the last interim report was 1.12% and most patients had received MAiD via the intravenous option (Government of Canada, 2019). The high uptake of the intravenous route of administration warrants a national guideline for clinicians.

The main advantages of the intravenous medication option for MAiD are ease of administration in the presence of a well-functioning IV, effectiveness in bringing about death, and reliability in the presence of clinicians for administration of the drugs. It also facilitates a MAiD request in patients who are otherwise incapable or intolerant of ingesting oral MAiD medications as well as when oral medications are ineffective.
Previous research has also shown that providers are less comfortable with the oral route for MAiD because of concerns that patients may not be able to effectively self- administer the medications and thus experience associated complications (Kouwenhoven et al., 2013). The main disadvantage of the intravenous option is that administration relies on the presence of a skilled clinician, potentially impacts patients' autonomy and agency in the final stages of their lives, and may be perceived as more clinical than natural.

The scope of this paper is to explore current practices regarding the intravenous administration option nationally and globally in order to make recommendations towards a standardized Canadian protocol. Such a standardized protocol would aim to provide an evidence-based medication regimen that can be reliably used by clinicians in the context of MAiD.

Global Experience

Netherlands

In the Netherlands, MAiD (both oral and intravenous) has been practiced since 1973 and has been legal since 2002 (KNMP & KNMG, 2012).

The most up-to-date guidelines for the provision of MAiD in the Netherlands were published by the Royal Dutch Medical Association (KNMG) and the Royal Dutch Pharmacists Associations (KNMP). The protocol describes the induction of a coma with thiopental 2000mg or propofol 1000mg with 2mL of 1% lidocaine without epinephrine via injection, infusion, or via elastomeric pump. The administration has to occur within 5 minutes regardless of mode of administration. This is followed by neuromuscular blockade using rocuronium 150mg as a bolus. Alternatives to rocuronium include atracurium 100mg or cisatracurium 30mg. Optional pre- medications include 2.5mg of intravenous midazolam (KNMP & KNMG, 2012).

Only a physician is permitted to provide intravenous MAiD. Before the administration of the neuromuscular blocking agent, it is the physician's duty to determine the presence of a medically induced coma, which is defined by KNMP & KNMG (2012) as:
No response to verbal stimuli
Circulatory depression (slow, weak pulse)
Ventilatory depression (slow, shallow breaths)
Lack of protective reflexes (i.e. eyelash reflex)

Once the neuromuscular blocking agent has been administered, death usually occurs shortly thereafter. However, the time between respiratory arrest and cardiac arrest may extend to up to 20 minutes.

Belgium

The legalization of oral and intravenous MAiD occurred in Belgium in 2002 (De Laat, De Coninck, Derycke, Huysmans, & Coupez, 2018).

There is no formalized national guideline for all of Belgium, as the country is separated into three highly autonomous regions: Flanders (north), Wallonia (south), and the Brussels Capital Region (Brussels Federation for Palliative and Continuing Care., n.d.). However, as part of an initiative of the Federation of Palliative Care Flanders, guidelines were published for the Flanders region in 2018. These Flemish guidelines describe the induction of coma via 2000mg of thiobarbital diluted in 20mL of normal saline, followed by a neuromuscular blocking agent, most commonly 100mg of atracurium or 20mg of cisatracurium. Alternatives for coma induction include propofol 1000mg and for neuromuscular blockade 20mg mivacurium or 100mg of rocuronium. Optional pre-medication includes 5-15mg of intravenous midazolam (De Laat, De

Coninck, Derycke, Huysmans, & Coupez, 2018).

Luxembourg

Oral and intravenous MAiD options have been available in Luxembourg since 2009 (Ministère de la Santé & Ministère de la Sécurite sociale, 2010). The Luxembourg Euthanasia Commission releases semi-annual reports to summarize MAiD statistics and to make recommendations for the future. In its fifth overall report in 2019, the Luxembourg Euthanasia Commission Times reported a total 71 cases of oral and intravenous MAiD in the decade since its legalization (Commission Nationale de Contrôle et d'Évaluation, 2019). Of these 71 patients, 68 opted for intravenous administration over oral. According to the report, a majority of patients received a combination of a coma-inducing agent, most commonly thiopental, and a neuromuscular agent for the intravenous option of MAiD. No further specifications regarding medication dosage were made.

Colombia

The initial decriminalization of MAiD in Colombia occurred in 1997, but it was not until 2014/15 that the Constitutional Court legislated the Ministry of Health and Social Protection to publish national guidelines for the administration of MAiD. The most recent change to the legislation occurred in 2018, when MAiD was legalized for children (Patients Rights Council, n.d.).

The 2015 national guidelines by the Ministry of Health and Social Protection outline the MAiD procedure from initial request to patient death, make recommendations on how to determine disease prognosis, thoroughly describe suggested medication dosages, and provide evidence-based rationale for the oral as well as intravenous MAiD protocol. For the intravenous MAiD option, the guideline recommends the delivery of lidocaine (2mg/kg over 10 seconds), midazolam (1mg/kg over 30 seconds), fentanyl (25mcg/kg over 30-45 seconds), propofol (20mg/kg over 30-45 seconds) or thiopental (30mg/kg over 30-45 seconds), followed by vecuronium (1mg/kg over 90 seconds) (Ministro de Salud y Protección Social, 2015). If 5 minutes after initial administration of the above drugs, the patient is found to have a central pulse and a blood pressure as determined by non-invasive measures, repeat administration of midazolam, fentanyl, and propofol at the same previous dose is suggested (Ministro de Salud y Protección Social, 2015).

Australia (state of Victoria)

Most recently, the state of Victoria in Australia legalized MAiD in 2019. No formalized protocol has been established as of yet and the details available are limited.
According to Greg Mewett, a palliative care physician in Ballarat, Victoria (personal communication, August 13, 2019), oral administration usually includes pentobarbital 15 000mg, dissolved in 100mL with a mixing solution and sweetener. For patients unable to self-administer or orally ingest the solution, the most responsible physician for that patient can apply for a

Practitioner Administration Permit, allowing for IV administration using a coma-inducing agent such as propofol and a neuromuscular blocking agent such as rocuronium or alternatively for the administration of a pentobarbital solution via nasogastric tube or percutaneous endoscopic gastrostomy tube.

National Experience

The oral as well as the intravenous option for MAiD was legalized in all provinces and territories in Canada in 2016 (Government of Canada, 2019). Although the intravenous method of administration for MAiD is widely used in Canada, there is no national protocol and thus practice has been heterogeneous across the provinces and territories.

Atlantic Canada (Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland)

Nova Scotia has a pre-printed order for MAiD via intravenous administration, and is administered in the following sequence (Nova Scotia Health Authority, 2016):

- 20mg of midazolam, an anxiolytic, over 2 minutes
- Local anesthetic lidocaine (2%) in a dose of 40mg over 30 seconds
- If the patient is allergic to lidocaine, they are given 1000mg magnesium sulfate.
- 1000mg of propofol via slow injection OR phenobarbital 3000mg over 5 minutes to induce coma
- 10mL of 0.9% sodium chloride flush
- 200mg rocuronium bromide via rapid injection
- If unavailable, 30mg of cisatracurium besylate is given via rapid injection
- 10mL of 0.9% sodium chloride flush

Loss of consciousness should occur within 1-2 minutes after coma induction. Coma must be confirmed prior to administration of a neuromuscular blocking agent and uses the same criteria as the Dutch guidelines. If coma cannot be confirmed after the first dose of the coma-inducing agent, an additional dose of 500mg propofol if using propofol or 3000mg phenobarbital if using phenobarbital may be administered. To ensure full dose injection and to prevent precipitation of the neuromuscular blocking agent after use of phenobarbital, the line is flushed prior to the rapid IV administration neuromuscular blocking agent.

New Brunswick, PEI, and Newfoundland appear to have similar protocols using anxiolytics, lidocaine, a coma inducing agent, and a neuromuscular blocking agent.

New Brunswick's protocol suggests the following:

- 20mg IV of midazolam slowly over 4 minutes (option for second dose if required)
- Propofol at same dosage utilized in Nova Scotia OR 1500mg of phenobarbital over 5 minutes to induce coma
- If coma cannot be confirmed, a second dose of 1000mg of propofol if using propofol or a second dose of 1500mg of phenobarbital if choosing the barbiturate may be administered as part of this protocol (Horizon Health Network, 2017).

The only difference between Nova Scotia and PEI is:

- Midazolam at a range from 2.5-10mg IV, most commonly used at a dose of 10mg

according to Dr. Baglole in PEI (personal communication, November 14, 2019; Health PEI, 2016).

The difference between the Nova Scotia and the Newfoundland protocol is as follows (McKim, 2018)

- Midazolam 2.5-10mg IV over 1-2 minutes with a one-time repeat option (lower dose of midazolam than in Nova Scotia)
- Repeat of propofol 1000mg IV instead of 500mg IV if a second dose is required

Quebec

Given that MAiD was legalized in Quebec in 2015 prior to anywhere else in Canada, the Quebec protocol was the first available protocol in the country. Only the intravenous option of MAiD is currently permitted in Quebec (Association des pharmaciens des établissements de santé du Québec, 2017):

- Midazolam at a dosage of 5-10mg via IV over 2 minutes
- 10mL of 0.9% sodium chloride flush
- 40mg of 2% lidocaine over 30 seconds
- If allergic to lidocaine, magnesium sulfate 1000mg IV over 5 minutes
- 10mL of 0.9% sodium chloride flush
- Propofol at a dose of 1000mg IV over 5 minutes to induce coma
- If allergic to propofol, the alternative is phenobarbital at a dose of 3000mg IV over 5 minutes
- 10mL of 0.9% sodium chloride flush
- 30mg of cisatracurium after coma induction
- If cisatracurium is not available, 200mg of rocuronium IV is administered.
- 10mL of 0.9% sodium chloride flush

Ontario

There is no standardized protocol in Ontario. Sampling of a few protocols across the province revealed the use of standard medications at varying doses and timings of administration:

- The anxiolytic midazolam in doses from 2.5-20mg as either IV push or over 1 minute
- The local anesthetic lidocaine 2% in doses ranging between 40-60mg IV over 30 seconds
- If allergic to lidocaine, magnesium sulfate 1000mg IV over 5 minutes is used in some protocols
- Propofol at 1000mg IV over 2-5 minutes or as IV push OR phenobarbital 3000mg IV over 5 minutes to induce coma
- The neuromuscular blocking agent cisatracurium 30-40mg IV over 10-30 seconds OR rocuronium 200mg

In addition to the standard drugs opioids were included on several protocols. Some of the

suggested or recommended opioids and dosages include:

- Morphine 5-10mg IV every 10 minutes as needed for analgesia or respiratory distress
- Fentanyl 100mcg IV over 5-10 seconds
- Fentanyl 200-500mcg IV
- Hydromorphone 4-10mg IV push or every 10 minutes as needed

Another aspect of one of the protocols in Ontario was the use of optional bupivacaine 400mg IV over 1 minute to induce asystole.

Manitoba

Manitoba has a standardized prescription for MAiD via intravenous administration:

- The anxiolytic midazolam at a dosage of 10mg via IV push
- 10mL of 0.9% sodium chloride flush
- 100mg of 2% lidocaine via IV push (if allergic to lidocaine use: magnesium sulphate 1000mg diluted to 10ml with normal saline slow IV push over 5 minutes)
- Propofol 500mg administered via IV push to induce coma (if allergic to propofol use: phenobarbital 300mg diluted to 50ml with normal saline slow IV push over 5 minutes)
- 10mL of 0.9% sodium chloride flush
- 300mg of rocuronium IV after coma induction (if allergic to rocuronium use: pancuronium 16mg rapid IV push)
- 10mL of 0.9% sodium chloride flush
- A second dose of propofol 500 mg IV over the course of 10 minutes (unless allergic as above)
- 10mL of 0.9% sodium chloride flush
- A third dose of propofol 500mg IV can be utilized if deemed necessary by the health care provider (unless allergic as above)

Saskatchewan

The protocol for IV administration of MAiD in Saskatchewan is as follow (Saskatchewan Health Authority, 2019):

- Midazolam at a dosage of 10mg IV over 30 seconds
- 40mg of 2% lidocaine over 30 seconds
- 10mL of 0.9% sodium chloride flush
- 1000mg of propofol slowly administered
- 10mL of 0.9% sodium chloride flush
- 200mg rocuronium via rapid administration
- 10mL of 0.9% sodium chloride flush
- 400mg IV Bupivacaine is given on a PRN basis for risk of delayed cardiac arrest

Alberta

There is a MAiD Medication protocol in place in Alberta (Alberta College of Pharmacy, 2017):

- Midazolam at a dosage of 2.5-10mg over 2 minutes
- 40mg of 1% or 2% lidocaine IV over 30 seconds
- If allergic to lidocaine, 1000mg of magnesium sulfate is administered over 5 minutes
- Propofol over 2.5 minutes at a dose of 1000mg two minutes after the administration of lidocaine or magnesium
- 10mL of 0.9% sodium chloride flush
- A second dose of propofol 500mg IV can be administered if required. If allergic to propofol, phenobarbital is injected at a dose of 3000mg IV over 5 minutes. An additional dose of 3000mg of phenobarbital can be given if required
- 10mL of 0.9% sodium chloride flush
- 200mg of rocuronium IV via rapid injection
- If unavailable, 30mg of cisatracurium via rapid IV injection

Opioids are optional in the protocol. Listed options for premedication include fentanyl at 25-500mcg IV over 1-2 minutes, sufentanil at 10-50mcg IV over 1-2 minutes, or remifentanil at 10-1000mcg IV over 1-2 minutes.

British Columbia

In British Columbia, a standardized provincial protocol is used. The intravenous administration of MAiD utilizes an anxiolytic, a local anesthetic, a coma-inducing agent, and a neuromuscular blocking agent in sequence as IV push doses (Daws & Reggler, 2016):

- Midazolam at a dosage of 2.5-10mg over 2 minutes
- 10mL of 0.9% sodium chloride flush
- 40mg of lidocaine over 30 seconds
- No alternative to lidocaine is given. A second dose of midazolam 2.5-10mg can be administered prior to the lidocaine if necessary. In practice, providers have given both midazolam and lidocaine as IV push
- 10mL of 0.9% sodium chloride flush
- Propofol at a dosage of 1000mg
- A second dose of 1000mg propofol can be administered if the first dose was not sufficient to induce a medical coma. The alternative to propofol, although rarely used, is phenobarbital 3000mg in 30mL of saline over 5 minutes
- 10mL of 0.9% sodium chloride flush
- 200mg of rocuronium
- 10mL of 0.9% sodium chloride flush
- In 2019, bupivacaine was added as an optional add-on medication for the British Columbia protocols at a dose of 400mg over 30-60 seconds (College of Physicians and Surgeons of British Columbia, 2019).

Yukon, Northwest Territories, Nunavut

In the Yukon, the protocol consists of:

- Midazolam IV 2.5-10mg over 2 minutes

- 40mg lidocaine IV over 30 seconds
- If allergic to lidocaine, 1000mg of magnesium sulfate is administered over 5 minutes
- 10mL of 0.9% sodium chloride flush
- Propofol at a dose of 1000mg IV via slow injection over 5 minutes.
- If coma cannot be confirmed, an additional dosage of 500mg can be administered via slow injection over 5 minutes. If an allergy to propofol exists, phenobarbital is injected at a dose of 3000mg IV over 5 minutes. An additional dose of 3000mg of phenobarbital can be given if required.
- 10mL of 0.9% sodium chloride flush
- 200mg of rocuronium via rapid injection.
- If rocuronium is unavailable, 30mg of cisatracurium can be injected rapidly.
- 10mL of 0.9% sodium chloride flush

The Northwest Territories recognize the Medical Assistance in Dying Interim Medication Protocols for the Northwest Territories as the standard for all medications used in MAiD (Government of Northwest Territories, 2018). This protocol in currently available for practitioners involved in administration of MAiD as well as approved pharmacies:

- The anxiolytic midazolam at a dosage of 2.5-10mg IV push over 2 minutes, with an option of a repeat dose
- Lidocaine 40mg IV over 30 seconds, with an option of a repeat OR if allergic, magnesium sulfate 1000mg (diluted with normal saline) IV over 5 minutes
- 10mL of 0.9% sodium chloride flush
- Propofol 1000mg IV over 5 minutes, with an additional dose of 500mg IV over
- 2.5 minutes OR if allergic, phenobarbital 3000mg (diluted with normal saline) IV over 5 minutes, with an option of a repeat dose
- 10mL of 0.9% sodium chloride flush
- Rocuronium 200mg via rapid IV injection, with an option of a repeat dose OR if allergic, cisatracurium 30mg via rapid IV injection, with an option of a repeat dose
- 10mL of 0.9% sodium chloride flush

For Nunavut, several protocols were reviewed and then adapted to Nunavut needs, according to Donna Mulvey, territorial director of pharmacy for the Department of Health (personal communication, October 2, 2019):

- The anxiolytic midazolam at a dosage of 10mg IV push over 5-10 seconds
- After having waited 3-5 minutes, 60mg of lidocaine as IV push over 5-10 seconds
- After waiting for 10-15 seconds, 1000mg of propofol as IV push over 2-3 minutes
- 200mg of rocuronium given as IV push over 30 seconds
- 400mg Bupivacaine 0.5% can be administered as IV push over 30-60 seconds as well but is listed as optional.

Pharmacology and Physiology

Common medications include an anxiolytic (midazolam), a local anesthetic (lidocaine), a coma-inducing agent (propofol or barbiturate), and a neuromuscular blocking agent (rocuronium, cisatracurium, atracurium, vecuronium). Adjuncts used include opioids (morphine, fentanyl, hydromorphone) for sedation and respiratory depression. Other medications utilized include bupivacaine for induction of asystole and metoclopramide for nausea.

For these pharmacologic agents, mechanism of action, physiologic effects, therapeutic dosing and speed of injection, MAiD dosing, and side effects will be discussed.

<u>Common Medications</u>

1. Coma-inducting Agents

   Propofol
   Propofol is a short-acting intravenous general anesthetic. Proposed mechanism of action is widespread CNS depression resulting from GABAA receptor agonism and potentially inhibition of NDMA receptors (Kotani, Shimazawa, Yoshimura, Iwama, & Hara, 2008).

   Its effects can be summarized as follows (Abola, Geralemou, Szafran, & Gan, 2017):

   a. *Central Nervous System*
      As discussed above, propofol results in widespread CNS depression. It has neuroprotective and anticonvulsant properties. It decreases cerebral blood flow, intracranial pressure, and the rate of oxygen consumption by the brain. Propofol also results in EEG burst suppression.
   b. *Cardiovascular*
      Propofol significantly decreases systemic vascular resistance, cardiac output, as well as stroke volume.
   c. *Respiratory*
      Propofol leads to dose-dependent respiratory depression (ranging from decreased tidal volume and increased respiratory rate to apnea) and is a potent bronchodilator. Propofol also blunts the body's response to hypoxia and hypercarbia.

   Propofol is a very versatile drug which can be used as a sedative for the induction of anesthesia as well as the induction of coma in critically ill patients. Dosage used is dependent on context. For the induction of general anesthesia, suggested therapeutic dosing in the routine clinical setting is
   2-2.5mg/kg for healthy adults with an ASA score of 1-2 and patients below the age of 55 (Pharmascience, 2017). The suggested speed of injection is 40mg of propofol every 10 seconds with an onset of action of one arm-brain circulation time, on average

approximately 40 seconds (Pharmascience, 2017; Liew, Joffe, & Coursin, 2012). The pharmacokinetic profile of propofol is characterized by a rapid onset and a predictable context-sensitive half-time (Abola, Geralemou, Szafran, & Gan, 2017). The ED95 (the dose required to achieve the desired effect in 95% of the population) for propofol is approximately 2.56mg/kg calculated based on lean tissue mass (Leslie & Crankshaw, 1990). MAiD dosing is 5-10 times the normal dose for induction of general anesthesia.

Common adverse effects include pain on injection in approximately 60-70% of patients (if propofol is the only peripherally administered drug), dose- dependent hypotension, apnea, and involuntary body movements (Jalota et al, 2011; Marik, 2004; (Pharmascience, 2017). Another adverse effect is the development of propofol-induced seizure-like phenomena, which are estimated at an incidence of 1 in 47,000 (Hickey, Martin, & Chuidian, 2005).

A rare adverse effect of propofol is anaphylaxis. This has been mostly noted with formulations containing metabisulfite (Marik, 2004). An adverse effect associated with allergy to metabisulfite or the administration of high propofol doses is a collection of clinical findings referred to as “gasping syndrome”. The syndrome includes central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites in urine and blood (Liew, Joffe, & Coursin, 2012). The gasping respirations may be concerning to the patient’s family and are thus an adverse effect that clinicians should be familiar with.

Another rare adverse effect of propofol administration is the development of propofol infusion syndrome (PRIS), which is not relevant in the MAiD setting (Abola, Geralemou, Szafran, & Gan, 2017).

Barbiturates (Phenobarbital, Thiopental)
Effects of barbiturates include sedation, hypnosis, and prevention of seizures (Sandoz Canada, 2015). Barbiturates act on the GABAA receptor resulting in widespread CNS depression (Lewis & Adams, 2019).

Its effects can be summarized as follows (Abola, Geralemou, Szafran, & Gan, 2017):

a. *Central Nervous System*
   As discussed above, barbiturates result in widespread CNS depression. They also have anticonvulsant properties and are neuroprotective. They decrease cerebral blood flow, intracranial pressure, and the rate of oxygen consumption by the brain. Thiopental is also noted to result in EEG burst suppression.
b. *Cardiovascular*
   Barbiturates decrease mean arterial pressures, venous vascular tone, and cardiac output.
c. *Respiratory*

Barbiturates lead to dose-dependent respiratory depression.

The therapeutic dose for sedation for the long-acting barbiturate phenobarbital is 30-120mg/day in 2-3 divided doses with a maximum of 400mg/day (Gennaro, 1995, as cited in World Health Organization, 2001). Onset of action for IV administration is 5 minutes with peak effect occurring after 15 minutes (West- Ward Pharmaceuticals Corp., 2018). MAiD dosing in Canada for phenobarbital is anywhere between 1000-3000mg IV, administered over the course of 5 minutes.

Thiopental is currently not available in North America. Thiopental is an analog of thiobarbital. Therapeutic dosing for general anesthesia induction for thiopental is 3-6 mg/kg (Yoo et al., 2015). Patient variability will affect the required induction dose. MAiD dosing in the Netherlands is 2000mg IV administered over the course of 5 minutes or in Colombia 30mg/kg over 30-45 seconds (Ministro de Salud y Protección Social, 2015). Thiobarbital is currently only used in Belgium for MAiD at a dose of 2000mg of thiobarbital diluted in 20mL of normal saline (De Laat, De Coninck, Derycke, Huysmans, & Coupez, 2018).

Adverse effects for all barbiturates utilized in the setting of MAiD include hypotension, drowsiness, depressed respiratory drive and coma (Lewis & Adams, 2019). Accidental administration of thiopental into an artery can lead to formation of crystals and subsequent vasospasm, thrombus formation, pain, and tissue necrosis (Abola, Geralemou, Szafran, & Gan, 2017). Although thiopental is not currently available in North America, it is important to note that all barbiturates can form a precipitate with the neuromuscular blocking agent, if inadequate flushing of the intravenous line with saline has occurred (KNMP & KNMG, 2012). The Dutch guidelines for MAiD mention pain with injection with barbiturates as another adverse effect of barbiturates. According to Abola, Geralemou, Szafran, & Gan (2017), methohexital commonly induces pain, whereas thiopental is mainly painful if injected outside the vein into subcutaneous tissue.

2. Local Anesthetics – lidocaine

   Lidocaine is an amide local anesthetic and inhibits the initiation and conduction of nerve impulses by blocking voltage-gated sodium channels on neuronal membranes (Lin & Liu, 2017).

   Its effects can be summarized as follows (Lin & Liu, 2017):

   a. *Central Nervous System*
      Local anesthetics readily cross the blood brain barrier. Effects on the CNS are determined by the plasma concentration of the local anesthetic. Mild sensory disturbances can occur at low plasma concentrations.
   b. *Cardiovascular*

Cardiovascular effects can include hypotension, dysrhythmias, and myocardial depression. All local anesthetics affect the conduction system of the heart via a dose-dependent inhibition of sodium channels.

c. *Respiratory*
Increasing local anesthetic concentration can result in pulmonary artery hypertension. This only occurs at toxic doses and is not relevant at routine clinical dosing or in the setting of MAiD.

At the low doses used adverse effects of local anesthetics are incredibly rare. Local anesthetic toxicity is dose-dependent and manifests itself from light- headedness, tinnitus, and perioral numbness to seizures, excessive sedation, coma, as well as respiratory and cardiac arrest (Yin & Liu, 2017).

Lidocaine is often used to reduce the pain associated with injection of agents such as propofol or phenobarbital, although a systematic review in 2011 by Joleta et al. stated that one of the most efficacious methods of decreasing pain on injection was to use a larger vein or to pre-treat with lidocaine only in combination with a modified Bier block for smaller hand veins. A subsequent Cochrane meta-analysis by Euasobhon et al. in 2016, comprising of over 10 000 patients, confirmed that providing lidocaine by any means to reduce or prevent propofol-induced pain is better than not providing lidocaine. 20-100mg of lidocaine is given either as IV push or over 30 seconds as part of MAiD dosing in Canada.

3. Neuromuscular blocking agents

Neuromuscular blocking agents of choice are non-depolarizing muscle relaxants, effectively inhibiting acetylcholine receptors on the postsynaptic membrane to paralyze skeletal muscle (Naguib, Lien, & Meistelman, 2014).

Their effects can be summarized as follows (Brull, 2017; Cheong & Wong, 2000):

a. *Central Nervous System*
No effects on CNS are reported.

b. *Cardiovascular*
Rocuronium and cisatracurium, both used in MAiD, have minimal cardiovascular effect. Vagolytic and direct sympathomimetic effects are only exhibited by pancuronium.

c. *Respiratory*
All neuromuscular blocking agents paralyze skeletal muscles, effectively causing apnea.

d. *Other*
Rocuronium is associated with pain on injection.

All of the neuromuscular blocking agents used in MAiD are considered intermediate acting with 20-50 minutes in duration (Naguib & Lien, 2004). Therapeutic doses in mg/kg are 0.6-1 for rocuronium and 0.15-0.2 for cisatracurium. Most commonly, rocuronium or cisatracurium are utilized for MAiD in North America. The ED95 for rocuronium is 0.305mg/kg and for cisatracurium 0.04mg/kg (Naguib, Lien, & Meistelman, 2014).

Suggested doses for MAiD are roughly 10 times ED95 for a 70kg person or 200mg of rocuronium, 30mg of cisatracurium, and 100mg of atracurium. Colombia utilizes vecuronium, with therapeutic dose of 0.1-0.2mg/kg, at 1 mg/kg over 90 seconds for MAiD (Naguib, Lien, & Meistelman, 2014; Ministro de Salud y Protección Social, 2015). Belgium also makes use of the short-acting mivacurium as an alternative to the more common neuromuscular blocking agents, with therapeutic dose of 0.2-0.25 mg/kg, at 20 mg for MAiD (Naguib, Lien, & Meistelman, 2014; De Laat, De Coninck, Derycke, Huysmans, & Coupez, 2018).

Adverse effects or neuromuscular blocking agents are dependent on agent of choice (Naguib, Lien, & Meistelman, 2014):

a. Hypotension with administration of atracurium and mivacurium related to histamine release
b. Bradycardia or rarely asystole after administration of vecuronium or atracurium
c. Rare risk of anaphylaxis with rocuronium and atracurium

Adjuncts

1. Anxiolytics

Although the Dutch guidelines do not recommend the use of benzodiazepines to induce unconsciousness in MAiD, they discuss their use as anxiolytics and as a premedication in intravenous MAiD (KNMP & KNMG, 2012). The most commonly used medication for this purpose is midazolam, a short acting benzodiazepine. Benzodiazepines bind to stereospecific receptors on the postsynaptic GABA neuron within the CNS and lead to the enhancement of the inhibitory effect of GABA (Abola, Geralemou, Szafran, & Gan, 2017).

Their effects can be summarized as follows (Abola, Geralemou, Szafran, & Gan, 2017):

a. *Central Nervous System*
   Benzodiazepines produce several clinically desirable effects in the context of MAiD including sedation and anxiolysis. The CNS depressant effect of benzodiazepines is dose-dependent, with 30-50% receptor occupancy required for sedation while a 20% receptor occupancy is sufficient for anxiolysis. Due to the ceiling effect of benzodiazepines, burst suppression or an isoelectric EEG cannot be achieved. Benzodiazepines also have anti- convulsant properties.

b. *Cardiovascular*
   Benzodiazepines result in a minimal decrease in systemic vascular resistance. This effect is minor, as homeostatic reflexes are preserved with benzodiazepine administration.
c. *Respiratory*
   Benzodiazepines depress the central respiratory drive and decrease upper airway reflexes.

The usual dose of midazolam for the purpose of anxiolysis is 0.5-2mg IV over 2 minutes with slow titration to effect (Waring et al., 2003). At this dosage, midazolam rarely leads to respiratory depression. In MAiD, dosage across protocols ranged from 2.5-20mg IV. In those instances, midazolam IV is to be administered anywhere from IV push to over the course of 2 minutes. Onset of action, when administered intravenously, is rapid with time to peak effect is 2-3 minutes (Abola, Geralemou, Szafran, & Gan, 2017).

Adverse effects include bradypnea due to depressed central respiratory drive, somnolence, and decreased tidal volume. This effect can be complementary to propofol in the context of MAiD, and unlikely to adversely affect the patient in MAiD when medications are administered in rapid succession. Despite its water- solubility, midazolam may also result in pain with injection due to its acidic formulation (Abola, Geralemou, Szafran, & Gan, 2017). Rare adverse effects include anaphylaxis.

2. Opioids

   Opioids include morphine, fentanyl, hydromorphone, sufentanil and remifentanil. Opioids act on the opioid-specific receptors in the CNS and peripheral tissues to produce analgesic effects. Pure opioid agonists, such as morphine, fentanyl, and hydromorphone stimulate mu receptors and have the strongest analgesic effects (Trescot, Datta, Lee, & Hansen, 2008).

   Opioid effects can be summarized as follows (Dahan, Niesters, Smith, & Overdyk, 2017):
   a. *Central Nervous System*
      Opioids can result in diffuse CNS effects, including dizziness, euphoria or dysphoria, sedation, drowsiness, hallucinations, and cognitive dysfunction (memory loss, inability to focus or concentrate).
   b. *Cardiovascular*
      Opioids affect the cardiovascular system both centrally and peripherally. Centrally, this effect relates to the activation of vagal nuclei and the depression of vasomotor areas in the brainstem. Peripherally, opioids can result in orthostatic hypotension, mild bradycardia, and a reduction in systemic and pulmonary resistance when given at routine clinical dosing. If administered at supra-clinical

doses, opioids can lead to direct myocardial depression and arterial as well as venous dilation.

c. *Respiratory*
   Opioids result in central respiratory depression and decreased muscle tone in the upper airways due to suppression of involved neurons in the brainstem (Dahan, Niesters, Smith, & Overdyk, 2017). Furthermore, opioids depress chemo- and arousal reflexes leading to a delayed and weaker response to upper airway obstruction. Giving potent opioids at high doses rapidly in the context of anesthesia can also result in skeletal muscle rigidity, which can contribute to respiratory insufficiency.

For IV opioids, therapeutic dosing depends on indication. Onset of action for IV morphine occurs within 5 minutes with a time to peak of 20 minutes (Aubrun, Mazoit, & Riou, 2012). For IV fentanyl, onset is immediate with effects lasting between 0.5-1 hour (Sandoz Canada Inc., 2018). IV hydromorphone takes 5 minutes for onset of action with time to peak of 10-15 minutes (Ganzberg & Haas, 2017). IV remifentanil has an onset of action of 1-2 minutes with blood concentrations of remifentanil decreasing by 50% in 3-6 minutes (Abbott, 2001). Sufentanil has a rapid onset of action with rapid recovery when compared to fentanyl (Akorn Inc, 1995). Dosages used in MAiD are varied with morphine being used at 5-10mg IV push or 5-10mg IV every 10 minutes as needed, fentanyl being used at 25-500mcg IV over seconds or minutes, sufentanil at 10-50mcg IV over 1-2 minutes, or remifentanil at 10-1000mcg IV over 1-2 minutes (in Canada) or at 25mcg/kg of fentanyl over 30-45 seconds (in Colombia as per the 2015 publication by the Ministro de Salud y Protección Social), and hydromorphone at 4-10mg IV push or 4-10mg IV every 10 minutes as needed.

Adverse effects include respiratory depression, sedation, and nausea/vomiting. For the purposes of MAiD, clinicians use these drugs for their sedative effects and effects on respiratory depression. Administration of opioids also affect the smooth muscle layers of the GI tract leading to delayed gastric emptying, constipation, bowel distention, and paralytic ileus. Furthermore, they can cause acute urinary retention (Dahan, Niesters, Smith, & Overdyk, 2017). Neither GI nor urological adverse effects are a concern in the MAiD setting.

Other medications

1. Anti-emetic agents

   Metoclopramide inhibits dopamine and serotonin receptors in the CNS chemoreceptor trigger zone and enhances response to acetylcholine in the tissue of the upper GI tract (Zabirowicz & Gan, 2019).

Metoclopramide effects can be summarized as follows (Zabirowicz & Gan, 2019):

a. *Central Nervous System*
   Metoclopramide can lead to drowsiness and restlessness.
b. *Gastrointestinal*
   Metoclopramide prevents and treats nausea and vomiting. It also enhances gastrointestinal motility and accelerates gastric emptying.

In the Dutch protocol, it is included as the anti-emetic of choice (KNMP & KNMG, 2012). Metoclopramide was only mentioned in one protocol from Ontario, as an agent to administer prior to opioids, arguably to decrease opioid side effects. Therapeutic dosage is 10-20mg IV once with onset of action being 1-3 minutes, time to peak 1-2 hours for adults, and duration of action of 1-2 hours (Baxter Healthcare Corporation, 2009). However, several studies have shown no clinically significant anti-emetic effect with 10mg. A study published in the BMJ in 2003 argued the effective use of metoclopramide at a dosage of 25-50mg with minimal side effects, which include extrapyramidal effects, such as dystonia (Wallenborn et al., 2006; Zabirowicz & Gan, 2019).

2. Cardiac arrest-inducing agents – bupivacaine

   In some protocols in Ontario, the local anesthetic bupivacaine is optionally used to induce asystole. In 2019, it was added as an optional add-on in the British Columbia protocol at the discretion of the prescriber as a Cardiac Arrest-inducing agent at a dose of 400mg. Bupivacaine is an amide local anesthetic and inhibits the initiation and conduction of nerve impulses by blocking voltage-gated sodium channels on neuronal membranes (Lin & Liu, 2017). Bupivacaine is used extensively for both local and regional anesthesia in routine practice.

   The effects of local anesthetics are previously summarized in the section on lidocaine and will not be reiterated. However, it is important to note that bupivacaine has several features that can potentiate its cardiotoxicity and predispose to arrhythmias and cardiovascular collapse. Bupivacaine cardiotoxicity is potentiated by the greater affinity for binding sodium channels in comparison to lidocaine and its slow dissociation from sodium channels during diastole. It also has a greater direct myocardial depressant effect (Lin & Liu, 2017).

   Bupivacaine has also been associated with CNS complications (e.g. anxiety, dizziness, seizures). In routine clinical use, intravenous use of bupivacaine is contraindicated due to reports of cardiac arrest and/or death (Pfizer Canada, 2019); however, this effect is the reason this medication is utilized in some protocols used in MAiD at a dose of 400mg IV delivered over 30-60 seconds.

Recommendations

As MAiD in Canada is and will continue to be provided by a variety of clinicians, an evidence-based national guideline that is easy to use and that reliably results in the rapid death of the patient is of utmost importance. Before discussing our recommendations for medication protocols, there follows a discussion on medication safety and drug administration.

Medication Safety

Wahr et al. (2017) in an article in the British Journal of Anesthesia stated that in 5.3% of medication administrations during surgery, medication errors occur - with over 70% being deemed preventable. Common medication errors include wrong dose as a result of miscalculation of dose or concentration as well as substitution of drugs due to syringe or vial swaps. There are few randomized controlled trials demonstrating that a specific technique is more effective than another in reducing medication errors. This 2017 paper made 35 recommendations based on their systematic review, which also looked at a Canadian guideline by the Institute for Safe Medication Practices (Institute for Safe Medication Practices, 2015). These recommendations included but were not limited to:

1. labelling every medication with name, date, and concentration
2. discarding unlabelled syringes immediately
3. preferably using single-use vials
4. utilizing high alert labels for concentrated or high-risk drugs
5. provider-prepared syringes from manufacturer vials with aforementioned best practice is the safest way to mitigate against a medication error but should only be considered when routinely practiced. Manufacturer or pharmacy prepared syringes are an appropriate alternative for providers not used to this practice
6. having a policy for unused drugs

Although these recommendations were made for the operating room environment, best practice would dictate incorporating some of the more applicable recommendations to out-of-OR environments. We recommend clear labelling of syringes to avoid scenarios such as administering a neuromuscular blocking agent prior to giving sedation in the context of MAiD. Additionally, a high-alert label for the neuromuscular blocking agent will facilitate medication safety. Prefilled and labelled syringes by pharmacy would decrease provider error and decrease the potential administration of wrong and potentially ineffective dosages. If pre-filled syringes are provided as part of the MAiD kits, we would encourage the taping of empty vials of clear medications to their respective syringes for additional identification and safety. From expert experience, we also recommend differently sized syringes for different medications in the protocol in order to have a second visual cue in addition to drug labelling for keeping all drugs apart.

In most provinces, it is recommended that an additional supply of all IV medication is available at the time of administration, thus often 2 MAiD kits are released to the clinician. In addition, unused medication is to be returned to a pharmacy or discarded and not reused. We encourage this practice for safety reasons. Where possible, the second kit should not be drawn up to avoid potential waste if a second kit is not required. In addition, this protocol is designed to provide clear and direct messaging on which drugs to use, and how, in order to facilitate ease of usage for all MAiD providers in Canada. As such, we have eliminated drug dose ranges and splitting of drugs into several doses.

Drug Administration

Good intravenous access is essential in the MAiD context. Unless a patient has central venous access (ie. PICC line), two larger bore intravenous catheter sites are strongly recommended (i.e. avoid 24 gauge IVs and butterfly needle sets). Both intravenous catheters should be checked for proper position inside the lumen of the vein prior to providing MAiD. This can be done with a one-time saline flush or the use of a straight line IV solution “drip” to gravity.

In any circumstances, where an essential medication is not eliciting a desired/ therapeutic effect, it is most likely that the intravenous has migrated interstitial.
The same recommended doses from the second kit should be administered in the same order through a different intravenous. Alternatives and deviation from essential medications is unnecessary and introduces significant risk. Refer to CAMAP guidelines on “Failed MAiD in the Community in Canada” for an approach to loss of vascular access.

Most protocols advocate flushing of peripheral IV lines, extension tubing, or adaptors with 10mL of normal saline after each medication with particular emphasis on flushing between the coma-inducing agent and the neuromuscular blocking agent. Flushing has the purpose of preventing the mixture of incompatible solutions or cleaning the catheter lumen of blood buildup (RNAO, 2005). In the MAiD context, the latter concern is not relevant. Although it is known that precipitation of barbiturates and neuromuscular blocking agents occurs due to acid-base interactions, it is important to note that this does not hold true for propofol and neuromuscular blocking agents (Vuyk, Sitsen, & Reekers, 2014). It thus follows that flushing in between the different medications advocated in these recommendations for this purpose is not necessary.

It appears that flushing prior to and post medication administration also has its roots in published nursing guidelines. The flush prior to medication administration confirms patency and provides a clean intraluminal surface while flushing after medication administration to prevent drug deposits in the peripheral line (Goossens, 2015). In anesthesia settings, the administration of drugs for induction through peripheral intravenous lines requires an open line but does not utilize normal saline flush between each medication. For a one-time use of tubing/adaptors for MAiD, flushing for the discussed purposes in nursing guidelines does not apply and adds additional unnecessary steps. If not utilizing a straight line, a saline flush may be considered

following the administration of all medications when IV tubing of significant length and volume is employed.

The Institute for Safe Medication Practices in their guidelines for IV push medications (2015) state that IV push medications are to be administered as “recommended by the manufacturer, supported by evidence in peer-reviewed biomedical literature, or in accordance with approved institutional guidelines”. As all the recommendations and guidelines were made for the clinical setting and not in the context of MAiD, for simplification and ease of protocol use, we recommend all drugs to be administered as IV push.

Essential medications

Essential aspects of MAiD include coma, then respiratory arrest followed by cardiac arrest. According to KNMP & KNMG (2012), the time between respiratory arrest and cardiac arrest may extend to up to 20 minutes. To avoid this lag time, medications for the intravenous administration of MAiD should address both respiratory and cardiac systems and thus include a coma-inducing agent as well as potentially an agent to induce cardiac arrest.

1. Coma Induction

   To achieve a medically induced coma, it is of utmost important to select an agent (and a dosage) that will significantly reduce consciousness. The characteristics for a medically induced coma are as previously described by KNMP & KNMG (2012):
   - No response to verbal stimuli
   - Circulatory depression (slow, weak pulse)
   - Ventilatory depression (slow, shallow breaths)
   - Lack of protective reflexes (i.e. eyelash reflex)

   The most common agents for coma induction include propofol or barbiturates. Both propofol and barbiturates may cause pain when injected (KNMP & KNMG, 2012). Barbiturates can also form a precipitate with the neuromuscular blocking agent if inadequate flushing of the intravenous line with saline has occurred (KNMP & KNMG, 2012). In addition, according to KNMP & KNMG (2012), a lethal effect cannot be guaranteed with thiopental. This is in contrast to the reliability of utilizing propofol to induce coma. The time to recovery from respiratory depression was also much shorter with thiopental than with propofol (Abola, Geralemou, Szafran, Gan, 2017). The coma inducing effects of propofol are dose dependent, and at the recommended doses for MAiD, coma should persist through respiratory and circulatory arrest.

   According to Graham, Myles, Leslie, Chan, Paech, Peyton, & Dawlatly (2011), propofol was also much more economical than thiopental, but once again no comparisons to other barbiturates were made. Propofol does seem to be the drug most

anesthesiologists, emergency and critical care clinicians will be more familiar with than barbiturates, with the reverse being true for general practitioners.
Nonetheless, barbiturates are considered controlled substances, requiring additional documentation, administrative work, and safe storage.

As such, we recommend that propofol should be the first-line drug of choice and the only option for inducing coma in an intravenous protocol for MAiD administration. The debate around a true propofol allergy being a contraindication and the reason to divert to a barbiturate can be challenged by two reasons: 1) True propofol allergy is incredibly rare with 1:60 000 incident cases (Asserhøj, Mosbech, Krøigaard, & Garvey, 2016) and 2) In the rare cases an allergy were to occur, the patient would arguably already be either heavily sedated and/or amnestic post-midazolam administration.

Adjuncts with potential benefit

1. Neuromuscular blocking agent

   The addition of a neuromuscular blocking agent could be debated. A neuromuscular blocking agent can only be administered once a patient is already in a medically induced coma. There is a variety of non-depolarizing agents utilized in MAiD, including rocuronium and cisatracurium. If MAiD is administered by an anesthesiologist or a critical care clinician, the preference of one over the other seems to be related to which neuromuscular blocking agent is most commonly administered and thus with which drug the medical professionals are most comfortable (KNMP & KNMG, 2012).
   The administration of vecuronium in the Colombian protocol is based on expert opinion stated in a paper by Lossignol (2008). The full text of this paper is not available and thus cannot be further discussed. However, the choice for rocuronium or cisatracurium over vecuronium in Canada is certainly informed by the availability of these drugs.

   At the doses for both propofol and barbiturates utilized in MAiD, respiratory arrest will likely occur even without the administration of a neuromuscular blocking agent. Some patients will have no effective circulation before the administration of a neuromuscular blocking agent. It can also be argued that the delay between respiratory and cardiac arrest (even with neuromuscular blocking agents) is approximately 20 minutes, thus making an agent to induce cardiac arrest more important than a neuromuscular blocking agent. Having said that, there may be a benefit and safety in the redundancy of including a neuromuscular blocking agent to confirm and maintain respiratory arrest beyond 20 minutes. While the return of respiration prior to cardiac arrest is almost non-existent, it cannot ethically be studied to justify the deletion of this well-established drug in most protocols.

2. Benzodiazepines

   As previously discussed, the Dutch guidelines do not recommend using benzodiazepines to induce unconsciousness in MAiD. However, benzodiazepines can be used as anxiolytics and as a premedication in intravenous MAiD (KNMP & KNMG, 2012). Midazolam is the most common used benzodiazepine for this purpose. We would challenge the notion of limiting the use of midazolam to its anxiolytic properties, especially at the dosages utilized in some Canadian protocols being much higher than in the Dutch guidelines. Nonetheless, consideration of patient population and previous use of benzodiazepines will influence this decision in light of a paper by Morita, Tei, & Inoue published in 2016 discussing the development of tolerance to midazolam in palliative care with prolonged administration.
   The ED90 for midazolam for sedation purposes is currently under investigation but is still in the recruitment phase, as indicated by a registered clinical trial on ClinicalTrials.gov (ClinicalTrials.gov, 2019). The ED95 for midazolam for amnesia purposes is approximately 0.044 mg/kg (Yan, Gao, & Yue, 2016). The ED95 for midazolam required to erase the memory of propofol-induced pain on injection was 0.061mg/kg in patients from the age of 30-40, 0.049mg/kg in patients from the age of 40-50, 0.033mg/kg in patients from the age of 50-60, and 0.033mg/kg in patients from the age of 60-70 (Boku et al., 2016). As one of the main arguments of this paper is to include midazolam for sedation and amnestic effects and the great majority of patients is over the age of 50, the ED95 utilized hereafter is 0.033mg/kg.

3. Local Anesthetics (pre-coma inducing agent)

   As stated by KNMP & KNMG (2012), both propofol and barbiturates may cause pain when injected. Rocuronium can also lead to significant pain on injection (Zhang, Wang, Wang, & Wang). The most common local anesthetic used for ameliorating pain on injection is lidocaine.

   As previously discussed, a systematic review by Jalota et al. (2011) noted that utilizing a larger diameter vein, such as the antecubital vein, was one of the most efficacious methods to decrease pain on injection of propofol. According to a subsequent Cochrane meta-analysis by Euasobhon et al. in 2016, there was no difference between low (≤ 20mg or ≤ 0.2mg/kg) or high dose (>20mg or >0.2mg/kg) lidocaine as pre-treatment alone, pre-treatment with venous occlusion, or as a propofol-lidocaine admixture. However, looking at their subgroup analysis, there was a statistical difference for the pre-treatment groups (low/high dose and with/without venous occlusion) with a suggestion that low dose lidocaine (≤ 20mg or ≤ 0.2mg/kg) pre-treatment alone appeared to provide the least efficacy. Although the difference in their subgroup analysis was statistically significant for the pre-treatment subgroups, the heterogeneity for this particular calculation was quite high and thus no real conclusion could be drawn from it,

supporting the author's conclusions. No significant adverse effects were found at doses less than 1mg/kg.

Since the conclusion drawn is that providing lidocaine by any means to reduce or prevent propofol-induced pain is better than not providing lidocaine, lidocaine will continue as an optional component of our proposed national guideline. Although venous occlusion has shown great benefit, the comfort for patients undergoing MAiD should be at the forefront. Admixing it with propofol may be challenging for providers in the community. In addition to that, there was an in vitro report of dose- and time- dependent oil droplet coalescence 30 minutes after the addition of 40mg of lidocaine to propofol with the potential to cause pulmonary embolism. Furthermore, there was a concern of potentially decreasing the concentration of propofol concentration after 3 hours post-admixture with 40mg of lidocaine (Masaki, Tanaka, & Nishikawa, 2003).
Given these drawbacks, we would recommend lidocaine as a pre-treatment rather than as an admixture. As the high dose seems to have minimal side effects when not utilized with venous occlusion, we do recommend using a high dose of lidocaine if used at all. The suggested dosing in a paper by Xing et al. (2018) is 40mg.
Furthermore, use of a larger-diameter vein will further reduce propofol-induced pain.

4. Local Anesthetics (Cardiac arrest)

   Bupivacaine, despite its contraindication as an IV medication in routine clinical use, is utilized in MAiD at a dose of 500mg IV over 1 minute for the purpose of inducing cardiac arrest. As discussed above, bupivacaine would also decrease the lag time between respiratory and cardiac arrest. El-Boghdadly, Pawa, and Chin (2018) state that doses as low as 1.6mg/kg of bupivacaine when intended as intravenous regional anesthesia or Bier block result in cardiac arrest if bupivacaine enters the central circulation. This would mean that potentially a dose as low as 112mg could result in cardiac arrest for an average 70kg person. As doses of at least 4-5 times the ED95 for the desired effect are generally used in MAiD practice, then this would mean a minimum dose of 560mg. As the concentration of bupivacaine available is often 5mg/ mL, this would require a total volume of 100mL for a 500mg injection. It is important to consider the challenges associated with administering such a large volume.

Adjuncts with no potential benefit

1. Opioids

   The protocol from the Netherlands has advised against the use of opioids in both oral and IV MAiD regimens due to the uncertainty regarding opioid use and reliable induction of coma. The concern is that terminally ill patients are often tolerant of opioids and the associated respiratory depressant effects (KNMP & KNMG, 2012). In addition, there is a concern regarding significant side effects including nausea/ vomiting (KNMP & KNMG,

2012). Furthermore, opioids are not required in MAiD for their analgesic properties. Opioids should further be avoided due to risk of diversion and need for secure storage, especially considering the already existing opioid crisis, as well as regulatory and administrative challenges.

2. Anti-emetic agents

   As discussed, metoclopramide has mainly been included in protocols which also include opioids to treat opioid-induced nausea or vomiting. In the intravenous protocol, as all medications are recommended to be administered as IV push, the patient will be unconscious before developing any significant nausea or vomiting symptoms.

Adjuncts with potential harm

1. Insulin

   Sufficiently high doses of insulin can result in death through induction of a hypoglycemic coma. However, the depth of coma as well as time to death is highly variable and depends on the patient's health status (KNMP & KNMG, 2012). During shallow periods of coma, the patient may become agitated and suffer cramps. We recommend against the use of insulin during MAiD.

2. Potassium Chloride

   Although potassium chloride can induce cardiac arrest in high doses, the administration of potassium chloride through a peripheral vein is very painful if used as a sole agent. In addition, potassium chloride can result in muscle spasms that are not relieved by neuromuscular blocking agents (KNMP & KNMG, 2012). High-dose potassium chloride is considered a 'high-risk' drug and is therefore only available in a limited fashion.

   We recommend against the use of potassium chloride during MAiD in our protocol. Although not part of this particular paper, organ donation after MAiD has become an important topic of discussion in Canada over the past few years (Downar et al., 2019). Given the strict rules and limitations with organ donation surrounding viability of organs and the dead-donor rule in the context of MAiD (Downar et al., 2019), the use of potassium chloride can be considered to shorten the time to circulatory arrest. As already discussed, bupivacaine could alternatively be used for its cardiac arrest-inducing effects but comes with significant challenges due to the volume required to achieve an adequate dose.

Protocol Recommendation

Below is a summary table of the protocol recommended by CAMAP for IV MAiD medications in the order of administration. The essential medications and dosages to induce death are recommended based on 4 to 10 times the ED95 of each drug for a 70kg individual to ensure therapeutic effect and prolonged duration of action across a wide population of patients (ie. different ages and weights). ED95 is the dose required to achieve the desired effect in 95% of the population Suggested dosing has been adjusted against those goals with consideration of dose per vial provided by the pharmaceutical to avoid unnecessary wasting of any medication. It is important to note that propofol ED95 is based on lean body mass, which for a 70kg individual would mean a lean body mass of 50kg for females and 54kg for males based on the Boer equation as discussed in Boer, 1984.

All medications are stable at room temperature. Although rocuronium should be stored under refrigeration, the unopened vials can be stored up to 90 days at room temperature. If the vial is punctured, rocuronium should be utilized within 30 days (Sandoz Canada, 2015). It is also important to note that patients are not required to be NPO prior to MAiD.

Administration Order	**Agent**	**Purpose**	**ED95 (mg/kg)**	**Suggested dosing for MAiD**
#1	Midazolam	Anxiolysis/Sedation/ Amnesia to Propofol-induced Pain	0.033	10 mg
#2	Propofol	Coma Induction	2.56	1000mg
#3	Rocuronium **OR**	Neuromuscular blocking agent	0.305	200mg
	Cisatracurium		0.04	40mg

Optional medications

Lidocaine dosing is based on 0.2mg/kg for a 70kg individual and convenient dosing. Bupivacaine at a dose of 1.6mg/kg resulted in cardiac arrest when intended as intravenous regional anesthesia or Bier block, if bupivacaine entered the central circulation.

Agent	Purpose	Suggested dosing for MAiD
Lidocaine	Reduction propofol-induced pain on injection	40mg
Bupivacaine	Cardiac Arrest	500mg

About the Commissioned Authors

Franziska Miller MD: Dr. Miller completed her undergraduate and medical degree at McMaster University. She is a trainee in the anesthesiology residency program at Dalhousie University and is also currently completing a Master of Education at the University of Dundee.

Janice Chisholm MD FRCPC: Dr. Chisholm is an Associate Professor at Dalhousie University in the Department of Anesthesiology, Pain Management and Perioperative Medicine. Involved with MAiD since its legalization, she has helped lead the development of MAiD care in Nova Scotia. She is currently a member of the NSHA MAiD Advisory Committee and a Board Member with CAMAP.

Alan Chaput BScPhm PharmD MD MSc FRCPC CCPE: Dr. Chaput is an Associate Professor of Anesthesiology and Pain Medicine at the University of Ottawa and has been involved in MAiD as an assessor and provider since 2016. Prior to entering medicine, he worked as both a community pharmacist and hospital pharmacist and was involved in pharmacoeconomic research in the pharmaceutical industry.

Bill I. Wong MD FRCPC: Dr. Wong is the Program Chief and Medical Director of Anesthesiology at Trillium Health Partners in Mississauga, Ontario. He has been involved with MAiD since the inception of the legislation and is the Co-chair and Medical Director of the Assistance in Dying Team at THP, providing MAiD across the GTA. He is an Assistant Professor with the University of Toronto Department of Anesthesiology and Pain Medicine.

Viren N. Naik MD MEd MBA FRCPC: Dr. Naik is a Professor of Anesthesiology and Pain Medicine and the R.S. McLaughlin Professor of Medical Education at the University of Ottawa. He is the Medical Lead for MAiD across eastern Ontario, which has been recognized as a practice leader by Accreditation Canada and Health Standards Organization, and a CAMAP Board Member.

References

Abbot. (2001). Remifentanil. Retrieved November 12, 2019, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/20630se5-005_ultiva_lbl.pdf

Abola, R., Geralemou, S., Szafran, M., Gan, T.J. (2017). Intravenous Anesthetics. In: Barash, P., Cullen, B., Stoelting, R., Cahalan, M., Stock, C., Ortega, R., … Holt, N., Clinical Anesthesia (8th ed., pp. 751-778). Philadelphia: Lippincott Williams & Wilkins.

Akorn Inc. (1995). Sufentanil Citrate Injection. Retrieved November 12, 2019, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019050s032lbl.pdf

Alberta College of Pharmacy. (2017, February 15). Updated MAiD Medication Protocol available online. Retrieved September 26, 2019, from https://abpharmacy.ca/articles/updated-maid-medication-protocol-available-online

Asserhøj, L. L., Mosbech, H., Krøigaard, M., & Garvey, L. H. (2016). No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut. British Journal of Anaesthesia, 116(1), 77–82.

Association des pharmaciens des établissements de santé du Québec. (2017). Medical assistance in dying (MAID): the Quebec Experience. Presented at Banff Seminar, Banff, Alberta, Canada. Retrieved September 26, 2019, from https://www.cshp.ca/sites/default/files/files/Events/Banff%202017/MAID-Quebec%20Banff%20Seminar%202017-final.pdf

Aubrun, F., Mazoit, J.-X., & Riou, B. (2012). Postoperative intravenous morphine titration. British Journal of Anaesthesia, 108(2), 193–201.

Baxter Healthcare Administration. (2009). Metoclopramide injection. Retrieved November 11, 2019, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017862s061lbl.pdf

Boer, P. (1984). Estimated lean body mass as an index for normalization of body fluid volumes in man. American Journal of Physiology, 247. 632-635.

Boku, A., Inoue, M., Hanamoto, H., Oyamaguchi, A., Kudo, C., Sugimura, M., & Niwa, H. (2016). Effective Dosage of Midazolam to Erase the Memory of Vascular Pain During Propofol Administration. Anesthesia Progress, 63(3), 147–155.

Brull, S. (2017). Neuromuscular Blocking Agents. In: Barash, P., Cullen, B., Stoelting, R., Cahalan, M., Stock, C., Ortega, R., … Holt, N., Clinical Anesthesia (8th ed., pp. 811-858). Philadelphia: Lippincott Williams & Wilkins.

Brussels Federation for Palliative and Continuing Care. (n.d.) Organisation of Palliative Care in Belgium. Retrieved September 27, 2019, from https://www.fbsp-bfpz.org/palliative-care-in-belgium

Cheong, K. F., & Wong, W. H. (2000). Pain on injection of rocuronium: Influence of two doses of lidocaine pretreatment. British Journal of Anaesthesia, 84(1), 106– 107.

ClinicalTrials.gov. (2019). The 90% Effective Sedation Dose Of Midazolam. Retrieved January 13, 2020, from https://clinicaltrials.gov/ct2/show/NCT03813043

Cohen-Almagor, R. (2009). Euthanasia Policy and Practice in Belgium: Critical Observations and Suggestions for Improvement. Issues in Law & Medicine, 24(3), 32.

College of Physicians and Surgeons of British Columbia. (2019). Minor updates made to MAiD. Retrieved November 11, 2019, from https://www.cpsbc.ca/for-physicians/college-connector/2019-V07-02/05

Commission Nationale de Contrôle et d'Évaluation. (2019). Commission Nationale de Contrôle et d'Évaluation de l'application de la loi du 16 mars 2009 sur l'euthanasie etl'assistanceau suicide -Cinquième rapport à l'attention de la Chambre des Députés.

Commission sur les soins de fin de vie. (2019). Rapport su la situation des soins de fin de vie au Québec. Retrieved September 26, 2019, from http://www.assnat.qc.ca/Media/Process.aspx?MediaId=ANQ.Vigie.Bll.DocumentGenerique_144177&process=Original&token=ZyMoxNwUn8ikQ+TRKYwPCjWrKwg+vIv9rjij7p3xLGTZDmLVSmJLoqe/vG7/YWzz

Dahan, A., Niesters, M., Smith, T., & Overdyk, F. (2017). Opioids. In: Barash, P., Cullen, B., Stoelting, R., Cahalan, M., Stock, C., Ortega, R., … Holt, N., Clinical Anesthesia (8th ed., pp. 779-810). Philadelphia: Lippincott Williams & Wilkins.

Daws, T., & Reggler, J. (2016). Medical Assistance in Dying (MAiD). Retrieved September 26, 2019, from https://divisionsbc.ca/sites/default/files/ljennings/Medical%20Assistance%20in%20Dying%20-%20Protocols%20and%20Procedures%20Version%209%20-%2020160920.pdf

De Laat, M., De Coninck, C., Derycke, N., Huysmans, G., & Coupez, V. (2018). Richtlijn Uitvoering Euthanasie. Retrieved August 25, 2019 from www.pallialine.be.

Dierickx, S., Deliens, L., Cohen, J., & Chambaere, K. (2016). Euthanasia in Belgium: Trends in reported cases between 2003 and 2013. CMAJ, 188(16), E407–E414.

Downar, J., Shemie, S. D., Gillrie, C., Fortin, M.-C., Appleby, A., Buchman, D. Z., Shoesmith, C., Goldberg, A., Gruben, V., Lalani, J., Ysebaert, D., Wilson, L., & Sharpe, M. D. (2019). Deceased organ and tissue donation after medical assistance in dying and other conscious and competent donors: Guidance for policy. CMAJ, 191(22), E604–E613.

Emanuel, E. J., Onwuteaka-Philipsen, B. D., Urwin, J. W., & Cohen, J. (2016). Attitudes and Practices of Euthanasia and Physician-Assisted Suicide in the United States, Canada, and Europe. JAMA, 316(1), 79–90.

Euasobhon, P., Dej-arkom, S., Siriussawakul, A., Muangman, S., Sriraj, W., Pattanittum, P., Lumbiganon, P. (2016). Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults. Cochrane Database of Systematic Reviews, (2). https://doi.org/10.1002/14651858.CD007874.pub2

Ganzberg, S. I., & Haas, D. A. (2017). General Anesthesia. In: Dowd, F.J., Johnson, B. S., & Mariotti, A. J. (Eds.), Pharmacology and Therapeutics for Dentistry (Seventh Edition) (pp. 221–240).

Goossens, G. A. (2015). Flushing and Locking of Venous Catheters: Available Evidence and Evidence Deficit. Nursing Research and Practice, 2015, 15.

Government of Canada. (2016). About Medical Assistance in Dying. Retrieved November 11, 2019, from https://www.justice.gc.ca/eng/cj-jp/ad-am/about- apropos.html

Government of Canada (2019). Medical assistance in dying. Retrieved September 26, 2019, from https://www.canada.ca/en/health-canada/services/medical- assistance-dying.html

Government of Northwest Territories (2018, November). Medical Assistance in Dying Interim Guidelines for the Northwest Territories. Retrieved September 26, 2019, from https://www.hss.gov.nt.ca/sites/hss/files/maid_interim_guidelines_-_in_force_november_1_2018_-_english.pdf

Graham, A. M., Myles, P. S., Leslie, K., Chan, M. T. V., Paech, M. J., Peyton, P., & Dawlatly, A. A. E. (2011). A Cost-Benefit Analysis of the ENIGMA Trial. Anesthesiology: The Journal of the American Society of Anesthesiologists, 115(2), 265–272.

Health PEI. (2016). Medical Assistance in Dying Guidance Document.

Hickey, K. S., Martin, D. F., & Chuidian, F. X. (2005). Propofol-induced seizure-like phenomena. The Journal of Emergency Medicine, 29(4), 447–449.

Horizon Health Network. (2017). Prescription for Medical Assistance in Dying. Institute for Safe Medication Practices (ISMP). (2015). Safe Practice Guidelines for Adult IV push medications. Retrieved December 8, 2019, from https:// www.ismp.org/guidelines/iv-push

Jalota, L., Kalira, V., George, E., Shi, Y.-Y., Hornuss, C., Radke, O., … Apfel, C. C. (2011). Prevention of pain on injection of propofol: Systematic review and meta- analysis. BMJ, 342, d1110. https://doi.org/10.1136/bmj.d1110

KNMP & KNMG. (2012). Guidelines for the Practice of Euthanasia and Physician- assisted Suicide. Retrieved August 28, 2019, from https://www.knmg.nl/web/file?uuid=bc11990b-d37a-4fa9-9e36-69d34bd229db&owner=5c945405-d6ca-4deb- aa16-7af2088aa173&contentid=223&elementid=2003770

Kotani, Y., Shimazawa, M., Yoshimura, S., Iwama, T., & Hara, H. (2008). The Experimental and Clinical Pharmacology of Propofol, an Anesthetic Agent with Neuroprotective Properties. CNS Neuroscience & Therapeutics, 14(2), 95–106.

Kouwenhoven, P. S. C., Thiel, G. J. M. W. van, Raijmakers, N. J. H., Rietjens, J. A. C., Heide, A. van der, & Delden, J. J. M. van. (2014). Euthanasia or physician- assisted suicide? A survey from the Netherlands. European Journal of General Practice, 20(1), 25–31.

Leslie, K., & Crankshaw, D. P. (1990). Potency of Propofol for loss of consciousness after a single dose. British Journal of Anaesthesia, 64(6), 734–736.

Lewis, C. B., & Adams, N. (2019). Phenobarbital. StatPearls. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK532277/

Liew, E. C.-L., Joffe, A. M., & Coursin, D. B. (2012). Propofol. In J.-L. Vincent & J. B. Hall (Eds.), Encyclopedia of Intensive Care Medicine (pp. 1854–1858). Springer.

Lin, Y, & Liu, S. (2017). Local Anesthetics. In: Barash, P., Cullen, B., Stoelting, R., Cahalan, M., Stock, C., Ortega, R., … Holt, N., Clinical Anesthesia (8th ed., pp. 859-886). Philadelphia: Lippincott Williams & Wilkins.

Lossignol, D. (2008). [Euthanasia: Medications and medical procedures]. Revue Medicale De Bruxelles, 29(4), 435–440.

Marik, P. E. (2004). Propofol: Therapeutic indications and side-effects. Current Pharmaceutical Design, 10(29), 3639–3649.

McKim, A. (2018, April). MAiD in Newfoundland [online presentation]. Retrieved September 26, 2019, from https://arnnl.ca/sites/default/files/MAiD%20in%20Newfoundland-%20ARNNL%202.0%20April%2011%202018%20teleconference.pdf

Masaki, Y., Tanaka, M., & Nishikawa, T. (2003). Physicochemical Compatibility of Propofol-Lidocaine Mixture: Anesthesia & Analgesia, 97(6), 1646–1651.

Ministère de la Santé & Ministère de la Sécurite sociale. (2010). L'euthanasie et l'assistance au suicide. Retrieved September 27, 2019, from http://sante.public.lu/fr/publications/e/euthanasie-assistance-suicide-questions-reponses-fr-de-pt-en/euthanasie-assistance-suicide-questions-fr.pdf

Ministro de Salud y Protección Social. (2015). Protocolo para la aplicacíon del procedimiento de euthanasia en Colombia. Retrieved September 26, 2019, from https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/DE/CA/Protocolo-aplicacion-procedimiento-eutanasia-colombia.pdf

Morita, T., Tei, Y., & Inoue, S. (2003). Correlation of the Dose of Midazolam for Symptom Control with Administration Periods: The Possibility of Tolerance. Journal of Pain and Symptom Management, 25(4), 369–375.

Naguib, M., Lien, C., & Meistelman, C. (2014). Chapter 34 – Pharmacology of Blocking Drugs. In: R. Miller (Eds.), Miller's Anesthesia (8th ed., pp. 958-994). London: Elsevier Health Sciences.

Nova Scotia Health Authority. (2016). Pre-printed order Medical Assisted Dying – Physician Administered IV Protocol.

Patients Rights Council. (n.d.). Colombia. Retrieved September 26, 2019, from http://www.patientsrightscouncil.org/site/colombia/

Pfizer Canada. (2019). Product Monograph – Marcaine. Retrieved November 11, 2019, from https://www.pfizer.ca/sites/default/files/201908/Marcaine_and_Marcaine_Spinal_PM_E_L3_04Feb2019.pdf

Pharmascience. (2017). Propofol – Product Monograph. Retrieved November 11, 2019, from https://pdf.hres.ca/dpd_pm/00041122.PDF

Regionale Toetsingscommissies Euthanasie. (2018). Jaarverslag 2018. Retrieved September 26, 2019, from https://derechoamorir.org/wp-content/uploads/2019/04/2019-informe-anual-NL-2018-neer.pdf

RNAO. (2005). Nursing Best Practice Guideline – Care and Maintenance to reduce vascular access complications. Retrieved December 8, 2019, from https://rnao.ca/sites/rnao-ca/files/Care_and_Maintenance_to_Reduce_Vascular_Access_Complications.pdf

Sandoz Canada Inc. (2014). Product monograph – metoclopramide. Retrieved November 11, 2019, from https://www.sandoz.ca/sites/www.sandoz.ca/files/Metoclopramide%20HCl%20PMe%2020141118.pdf

Sandoz Canada Inc. (2015). Product monograph – rocuronium bromide. Retrieved January 20, 2020, from https://www.sandoz.ca/sites/www.sandoz.ca/files/Rocuronium_INJ_Product_Monograph.pdf

Sandoz Canada Inc. (2018). Product monograph – fentanyl citrate injection. Retrieved November 11, 2019, from https://www.sandoz.ca/sites/www.sandoz.ca/files/Fentanyl%20Citrate%20Product%20Monograph.pdf

Saskatchewan Health Authority. (2019). Provincial Medical Assistance In Dying (MAID) Program Intravenous Prescription Protocol.

Smith, P. (2017). State of Victoria will allow voluntary euthanasia from mid 2019. BMJ, 359.

Trescot, A. M., Datta, S., Lee, M., & Hansen, H. (2008). Opioid pharmacology. Pain Physician, 11(2 Suppl), S133-153.

Vuyk, J., Sitsen, E., & Reekers, M. (2014). Chapter 30 – Intravenous Drugs. In: R. Miller (Eds.), Miller's Anesthesia (8th ed., pp. 821-863). London: Elsevier Health Sciences

Wahr, J. A., Abernathy, J. H., Lazarra, E. H., Keebler, J. R., Wall, M. H., Lynch, I., … Cooper, R. L. (2017). Medication safety in the operating room: Literature and expert-based recommendations. BJA: British Journal of Anaesthesia, 118(1), 32– 43.

Wallenborn, J., Gelbrich, G., Bulst, D., Behrends, K., Wallenborn, H., Rohrbach, A., … Olthoff, D. (2006). Prevention of postoperative nausea and vomiting by metoclopramide combined with dexamethasone: Randomised double blind multicentre trial. BMJ, 333(7563), 324.

Waring, J. P., Baron, T. H., Hirota, W. K., Goldstein, J. L., Jacobson, B. C., Leighton, J. A., … American Society for Gastrointestinal Endoscopy, Standards of Practice Committee. (2003). Guidelines for conscious sedation and monitoring during gastrointestinal endoscopy. Gastrointestinal Endoscopy, 58(3), 317–322.

West-Ward Pharmaceuticals Corporation. (2018). PHENOBARBITAL SODIUM- phenobarbital sodium injection. Retrieved November 11, 2019, from https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=ffcaa218-ed6a-4557-9645-b9a91128a214&type=display

World Health Organization. (2001). Phenobarbital and its sodium salt. In: World Health Organization (Eds.), IARC Monographs on the evaluation of carcinogenic risks to humans (pp. 161-289). Lyon: IARC.

Xing, J., Liang, L., Zhou, S., Luo, C., Cai, J., & Hei, Z. (2018). Intravenous Lidocaine Alleviates the Pain of Propofol Injection by Local Anesthetic and Central Analgesic Effects. Pain Medicine, 19(3), 598–607.

Yan, J., Gao, C., & Yue, Y. (2016). Abstract PR636: Ed50 For Intravenous Midazolam- Induced Amnesia And Its Duration in Surgical Patients. Anesthesia & Analgesia, 123(3S), 819.

Yoo, K. Y., Jeong, C. W., Jeong, H. J., Lee, S. H., Na, J. H., Kim, S. J., … Lee, J. (2012). Thiopental dose requirements for induction of anesthesia and subsequent endotracheal intubation in patients with complete spinal cord injuries. Acta Anaesthesiologica Scandinavica, 56(6), 770–776.

Zabirowicz, E. S., & Gan, T. J. (2019). Pharmacology of Postoperative Nausea and Vomiting. In: Hemmings, H.C, & Egan, T.D. (Eds.), Pharmacology and Physiology for Anesthesia (Second Edition) (pp. 671–692).