

MEDICAL CARE IN THE LAST DAYS OF LIFE



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PRACTICE
GUIDELINES

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Note: In this publication, the masculine gender is used without prejudice and solely to facilitate reading.

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INTRODUCTION

The Collège des médecins du Québec's discussion paper on appropriate end-of-life care and the issue of euthanasia, made public on November 3, 2009, triggered many reactions, especially from physicians. The creation of the Select Committee on Dying with Dignity by the National Assembly of Québec allowed many testimonies and opinions to be heard. Some of these concerned the medications used in the last days of life without making a clear distinction between palliative care and aid in dying (which is covered in a separate document).

The Collège therefore felt it would be helpful to produce these practice guidelines in order to better inform and equip physicians with respect to the proper use and effects of medications commonly used in the last days of life. These guidelines are not meant to be a detailed document on all types of palliative care, which covers the entire period of life when the patient is known to be incurable; they address only medical care and prescriptions in the very last stage of life, when death is imminent, to relieve the suffering of dying

patients. A good knowledge of drug therapies that can be offered to these patients will improve the quality of medical services provided to patients who have reached the end of their life. Specific palliative care syndromes such as obstruction, cachexia, hypercalcemia, etc. will not be addressed here. Nor will these guidelines address nursing and the care provided by other professionals involved in end-of-life care (mouth care, constipation, spiritual and psychological needs, etc.). Physicians who would like to learn more about palliative sedation are invited to consult the guidelines *Palliative sedation at the end of life*, a joint publication of the Société québécoise des médecins de soins palliatifs and the Collège des médecins du Québec.

WHAT IS MEANT BY "THE LAST DAYS OF LIFE"?

When it is time to provide support and relief to the dying, the final days and hours are often critical. In an arbitrary manner and for the purposes of this document, we agree that this period called "the last days of life" starts when the dying person is no longer able to swallow his medication or when the agony phase seems imminent. In most cases, the patient will die within hours or days of diminished consciousness or inability to drink.

These guidelines will discuss the notion of a peaceful death but also that of a distressing death, which is sometimes preceded by suffering or distress. In these guidelines, the physician will find the main competencies he must possess to provide appropriate care in the last days of life. A succinct reminder of the medication required to relieve a dying person is presented. We will address the major premortem syndromes. We will talk about special considerations when treating patients in a facility and at home.

There is more than one way to die and more than one care model that can be used and prescribed in the last days of life. The purpose of this document is to present the basic knowledge and tools needed to relieve the vast majority of patients in the last days of their life.

Most of the treatments presented in this document are not evidence based; however, they were proposed by recognized experts.

CARE IN THE LAST DAYS OF LIFE IN RELATION TO PALLIATIVE CARE

In Quebec, all patients, including those in the last days of their life, should have access to the care required by their condition. There are palliative care teams in most regions in Quebec. They have expertise in providing relief and support to end-of-life patients, irrespective of the diagnosis; their services are not limited to caring for cancer patients. Their expertise is not exclusive; every attending physician, family physician or other specialist has a duty to provide effective relief to patients under their care in the last days of their life and to consult experts in their region if necessary. In Quebec, every dying person must be able to obtain quality end-of-life care.

“Every attending physician, family physician or other specialist has a duty to provide effective relief to patients under their care in the last days of their life.”

MYTHS SURROUNDING OPIOIDS

AN OBSTACLE TO PROVIDING RELIEF TO PATIENTS IN THE LAST DAYS OF THEIR LIFE

It is important to discuss the main myths surrounding the use of opioids with patients and their family.

Myths surrounding the use of opioids that lead to suboptimal pain relief [1]

| | |
|--|--------------|
| There is a maximum safe dose | False |
| Tolerance is inevitable | False |
| Opioids control all types of pain | False |
| Increasing the doses inevitably causes respiratory depression | False |
| The subcutaneous (SC) route is more effective than the oral (PO) route | False |
| The intravenous (IV) route is more effective than the SC route | False |
| Using opioids always causes confusion and drowsiness | False |
| A patient who asks for his doses too often is a narcotic addict | False |

Source: Association des pharmaciens des établissements de santé du Québec (2008).
Adapted with the permission of APES.

Chapter 1/ Prerequisites to the administration of care in the last days of life

1.1 COMPETENCIES REQUIRED BY A PHYSICIAN WHO PROVIDES COMFORT CARE TO A PATIENT IN THE LAST DAYS OF LIFE

The physician must be able to:

- › Assess the pain (location, severity, quality, chronology, radiation, aggravating and alleviating factors) and other symptoms (nausea/vomiting, anxiety, insomnia and dyspnea) as well as the consequences of these symptoms for the patient and his family.
- › Explain the objectives of comfort care in relieving pain and other symptoms to the patient and the family.
- › Use an appropriate style of communication for the circumstances and the people concerned to ensure they understand the treatment plan properly.
- › Know which medications to prescribe for analgesia and to relieve other symptoms.
- › Detect any adverse drug effects and intervene appropriately to counteract them.
- › Personalize the treatment plan while using, to the extent possible, a simple treatment protocol.
- › Review the treatment plan regularly.
- › Provide for and ensure that a supply of medication is kept readily available at the patient's bedside for a pain crisis or distress.
- › Work in an interdisciplinary approach.

1.2 GOLDEN RULES FOR PAIN RELIEF IN THE LAST DAYS OF LIFE [1]

1.2.1 PRESCRIBE THE REQUIRED ANALGESIA

- › Choose an appropriate analgesic based on the severity of the pain, using recommended agents at adjusted doses;
- › Know the pharmacology of the chosen medication (class, onset of analgesia, peak effect, duration of analgesia, available preparations, etc.);
- › Provide for a route of administration other than the oral route;
- › Administer analgesics at appropriate intervals based on their duration of action;
- › Know the main opioid analgesics but also non-opioid analgesics that can be used alone or in combination with opioids.

1.2.2 SWITCH OPIOID OR ROUTE OF ADMINISTRATION

INDICATIONS

- › Switch from the oral route to the subcutaneous route.
- › Switch from the oral route to the transdermal route.
- › Switch opioid if pain is not relieved (significant increase in doses, overdosing or intolerable adverse effects for the patient).
- › Switch opioid if opioid-induced hyperalgesia is suspected in a given patient (consider doing so in the presence of generalized pain exacerbated by an increase in opioid doses).

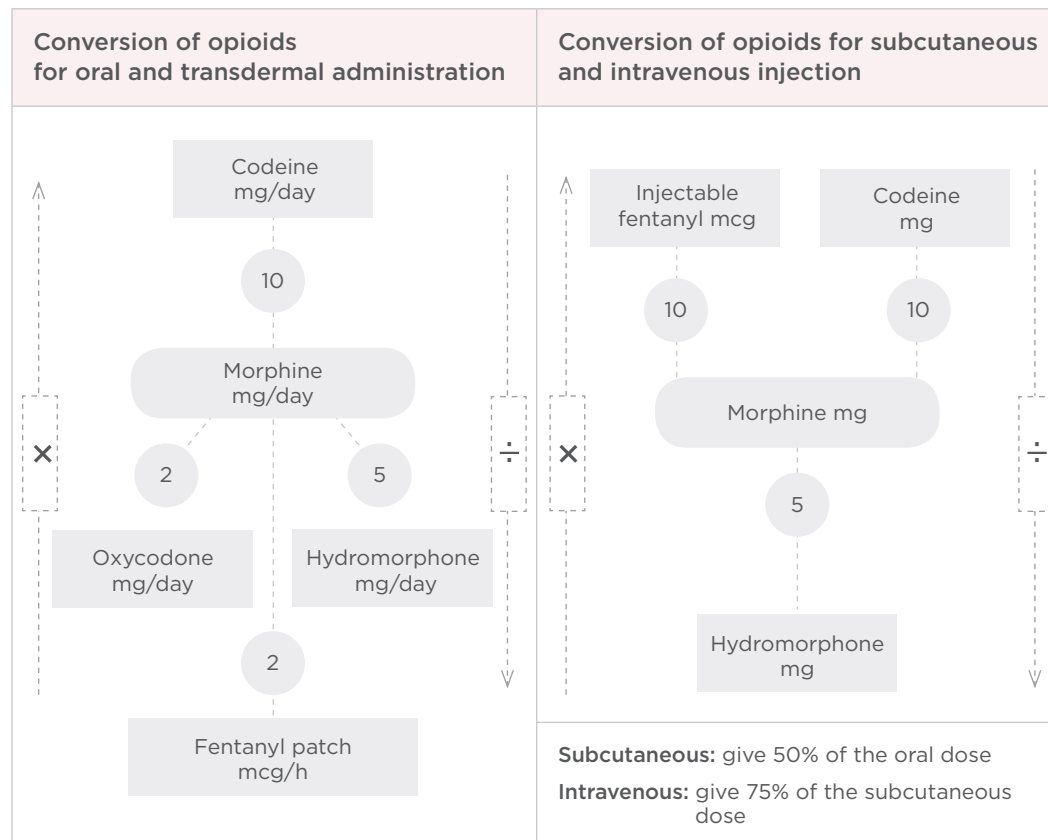
SUGGESTED PROCEDURE

- › If the patient was effectively relieved by the previous oral opioid and the physician would like to switch to the subcutaneous route because the agony phase is imminent, determine the subcutaneous dose of the same opioid, i.e., 50% of the oral dose (Table 1).
- › If the patient was effectively relieved by the previous opioid, but the physician would like to switch opioid because of adverse effects, for example, determine the equianalgesic dose of the new opioid (Figure 1, Table 1). Then reduce the dose of the new agent by 25 to 50% for the first doses to allow for incomplete cross-tolerance between the opioids and thus minimize the risk of overdosing. The goal is to provide effective relief for the patient without causing excessive drowsiness.

- › If the patient is not effectively relieved, increase the dose of the new opioid according to the schedule established based on the pharmacokinetic parameters of the molecule used (Table 1).
- › Be especially cautious if a non-opioid analgesic is added when making the switch.
- › Provide for breakthrough doses of this opioid, usually 10 to 15% of the daily dose, to be given every hour, as needed, for the oral route and every 30 minutes, as needed, for the injectable route.
- › If for specific conditions, the opioid chosen for breakthrough doses is a brand-name fentanyl preparation for sublingual or buccal administration: follow the manufacturer's recommended adjustment schedule or ask the palliative care team for assistance.
- › Except in specific situations (presence of fentanyl or buprenorphine patches, cough relief, methadone use) and despite some anecdotal evidence of therapeutic success, combining two opioid agents to relieve baseline pain is not recommended.
- › Always keep in mind that the conversion ratios suggested in this document are taken from general guidelines. The relief obtained and the side effects vary widely between individuals. The dosage must therefore be adjusted rapidly based on the patient's clinical response.

1.2.3 KNOW THE ANALGESIC EQUIVALENTS OF VARIOUS OPIOIDS

Figure 1
Analgesic equivalents of various opioids



- › The 2 charts are useful for converting between 2 molecules with the same route of administration (PO with PO, IV with IV, SC with SC).
- › The numbers are the conversion factor between opioid molecules.
- › Multiply or divide the dose to be converted by the conversion factor in the direction of the arrow.
- › Reduce the converted dose by 25% if the patient has been taking the opioid for more than one month to account for tolerance.
- › The fentanyl patch is usually changed every 3 days. A 25 mcg/h patch is the equivalent of around 50 mg of morphine PO/day (or 25 mg SC/day).
- › Breakthrough doses: give 10 to 15% of the total daily dose.

Adapted from Dechêne, G., et al. (2000). *Précis pratique de soins médicaux à domicile*, Saint-Hyacinthe/ Montréal, Edisem/FMOQ, 533 p.; Aline Boulanger, M.D., CHUM Pain Clinic and Hôpital du Sacré-Coeur de Montréal; Geneviève Dechêne, M.D., GMF du Sud-Ouest, Verdun.

- › If for specific conditions, the opioid chosen for breakthrough doses is a brand-name fentanyl preparation for sublingual or buccal administration: follow the manufacturer's recommended adjustment schedule or ask the palliative care team for assistance.

Table 1
Pharmacokinetic parameters of short-acting oral or parenteral opioids [2-4]

| Agent | Equivalents | Onset of analgesic effect | Peak analgesic effect | Duration of analgesic effect |
|-----------------------------|---------------------------------|---|------------------------------------|--------------------------------|
| Morphine | PO 20 mg SC 10 mg IV 8 mg | PO 45-60 min. SC 10-20 min. IV 2-5 min. | PO 1 h SC 0.5-1 h IV 15 min. | PO 4-6 h SC 4-6 h IV 2 h |
| Hydromorphone | PO 4 mg SC 2 mg IV 1.5 mg | PO 30 min. SC 10-20 min. IV 5 min. | PO 1 h SC 0.5-1 h IV 15 min. | PO 3-5 h SC 3-5 h IV 2 h |
| Oxycodone | PO 10-15 mg | PO 15-30 min. | PO 0.5-1 h | PO 4-6 h |
| Injectable fentanyl* | SC 100 mcg IV 80 mcg | IV 1-2 min. | IV 10-15 min. | IV 1-2 h |
| Codeine** | PO 200 mg SC 120 mg | PO 30-60 min. SC 10-20 min. | PO 1-1.5 h SC 0.5-1 h | PO 4-6 h SC 4-6 h |

* Injectable fentanyl accumulates and its effect is sustained with repeated dosing.

** We suggest avoiding the use of codeine at the end of life. It has little or no analgesic effect.

1.2.4 PRESCRIBE SUBCUTANEOUS OPIOIDS

INTERMITTENT INJECTIONS EVERY 4 HOURS

Determine the dose for SC injection:

- › calculate the total dose of oral opioid the patient has been given in the previous 24 hours (regular and breakthrough doses);
- › calculate the equianalgesic dose if switching opioid;
- › convert to the SC route by dividing this dose by two;
- › divide this value by 24 hours to obtain the hourly dose of opioid (mg/h):

- › multiply the hourly dose by 4 to obtain the dose of opioid that will be injected regularly every 4 hours;
- › adjust this dose every 12 to 24 hours based on the relief obtained;
- › if the patient is not relieved after the conversion, the dose can be increased by 25, 50 or even 100% per 24 hours based on the severity of the pain and the imminence of the end of life; a patient must not be allowed to suffer needlessly in the last days of his life.

Determine the breakthrough dose:

- › 10 to 15% of the total daily dose;
- › or 50% of the 4-hourly dose;
- › inject every 30 minutes as needed if the patient is not relieved;
- › if injectable fentanyl is the agent used for breakthrough doses, take possible accumulation into account.

Take the volume for SC injection into account when choosing the opioid concentration:

- › generally less than 2.5 mL per intermittent injection; preferably less than 1 mL per injection.

Example

MS Contin 40 mg bid + 4 BTDs of morphine 5 mg per day
= 100 mg total/day.

This is the equivalent of 50 mg of morphine SC/day.

Morphine 8 mg SC q 4 h regularly will be prescribed,
with morphine 5 mg SC every 30 min PRN if discomfort.

CONTINUOUS SC INFUSION (CSCI)**Determine the dose for SC infusion:**

- › calculate the total dose of oral opioid the patient has been given in the previous 24 hours (regular and breakthrough doses);
- › calculate the equianalgesic dose if switching opioid;
- › convert to the SC route by dividing this dose by two;
- › divide this value by 24 hours to obtain the hourly dose of opioid (mg/h):

- › analgesic blood levels are reached in a few hours. Start the infusion with a bolus that is 2 to 4 times the hourly dose;
- › adjust the infusion every 12 to 24 hours based on the relief obtained;
- › if the patient was being given a sustained-release preparation, start the continuous infusion no more than 6 to 9 hours after the last tablet or suppository was taken (Appendix I);
- › if the patient is suffering, the infusion may be started earlier and adjusted rapidly based on response.

Determine the breakthrough dose:

- › 10 to 15% of the total daily dose or once or twice the hourly dose;
- › inject every 30 minutes as needed if the patient is not relieved.

Administer the SC infusion:

- › take the volume for SC infusion into account: generally less than 5 mL/h (the volume is higher than with intermittent injections because the injection is continuous);
- › this prescription should be discussed with the pharmacist; pumps and syringe drivers are available in some local community service centres (CLSCs), hospitals and private or specialized pharmacies.

Example

MS Contin 40 mg bid + 4 BTDs of morphine 5 mg per day
= 100 mg total/day.

This is the equivalent of 50 mg of morphine SC/day.

The infusion will be started with a bolus of 4 to 8 mg in 1 min., followed by a continuous infusion of morphine 2 mg/h.

The breakthrough dose will be 5 mg SC every 30 min. as needed.

Chapter 2/ Treatment of the major syndromes encountered in the last days of life [5-10]

2.1 PAIN

Pain is the most troubling manifestation in the last days of life [11]. Patients are often heard to say: “So long as there’s no pain!”

The main questions regarding pain relief are:

- › Can pain be prevented?
- › How can the patient be relieved?
- › Do opioids have to be used?
- › Can opioids harm the patient?

2.1.1 PATIENT WHO IS ALREADY RELIEVED BY AN OPIOID AND IS UNABLE TO SWALLOW

For patients who are already relieved by their opioids, the analgesic medication simply has to be administered by a route other than the oral route: a switch is usually made to the subcutaneous route (Appendices I and II). However, for patients already on fentanyl patches, the transdermal patch will be left in place and additional doses of opioids will be administered subcutaneously.

Medication must then be adjusted every 12 to 24 hours based on the relief obtained and possible drowsiness (acceptable or not); this adverse effect varies between patients. The other potential adverse effects of opioids, mainly constipation (universal and dose independent), nausea and confusion, must be treated so that the opioid doses are not reduced unduly: everything possible must be done to relieve a patient in the last days of his life.

There are no sufficiently reliable pain tests or scales to determine the dose of opioid a patient might need. Constant reassessment of the patient is still the best way to monitor analgesic treatment. Numerical or visual analog pain scales can, at best, be used to compare the patient with himself.

End-of-life patients may experience increased suffering in the final days before death; this can be explained, among other things, by ankylosis secondary to immobility. This phenomenon must be provided for in end-of-life prescriptions (Table 3).

Opioid analgesic medication is usually administered transdermally and/or subcutaneously in the last days of life. However, it can also be administered by other routes, mainly the oral transmucosal route and, occasionally, the rectal route, used primarily in pediatrics but sometimes also in adult medicine, at home, for example.

Opioids can be given by these routes of administration intermittently (as needed) or regularly. Thus, concentrated injectable opioid formulations can be placed drop by drop in the buccal cavity between the gum and cheek. For patients who are already on methadone, the medication will continue to be administered by the oral transmucosal route; a concentrated methadone solution can be placed in the buccal cavity.

Concentrated injectable opioid solutions (morphine or hydromorphone), suppositories of certain opioids (morphine, oxycodone or hydromorphone) or non-opioid-coated tablets (methadone, morphine, oxycodone or hydromorphone) can be administered rectally. Make sure the rectal ampulla is empty prior to administration.

2.1.2 PATIENT WHO IS UNCONSCIOUS OR UNABLE TO COMMUNICATE

Although unconscious patients will be unable to communicate their suffering clearly, a number of standardized tools can be used to assess pain in patients who are confused or unable to express themselves [12]. The family's and caregivers' opinions as to the quality of the patient's relief are very helpful in this context. A routine analgesic and/or anxiolytic medication can be administered to these patients when they are in the last days of their life. Many experts propose administering small subcutaneous doses of opioid and midazolam and adjusting them based on clinical response (Appendix II).

2.1.3 PATIENT WHO IS EXPERIENCING LITTLE OR NO SUFFERING

The final days before death are peaceful for most patients, with little pain, agitation or terminal respiratory rates. Care must be taken to ensure that this seeming peace is indeed the expression of genuine well-being. The dying person may be too weak to show that he is suffering.

For patients who experience little suffering, the family and caregivers must nonetheless keep an opioid, a benzodiazepine and an anticholinergic on hand so that they can provide rapid relief for the patient should the situation deteriorate (Table 3). It is also recommended that the family and caregivers have the necessary training to immediately administer the medications required in the event of severe suffering or distress (Appendix III).

2.1.4 ACUTE PAIN EXACERBATION

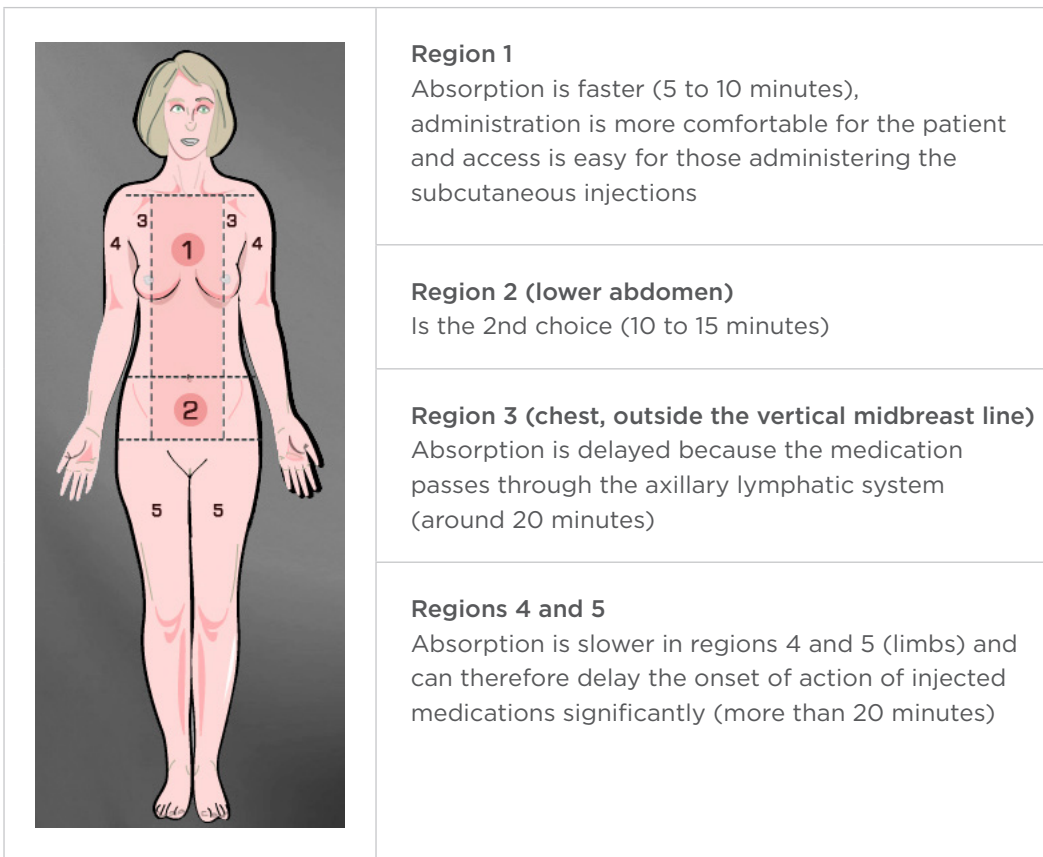
When a patient is seen for an acute exacerbation of his pain, irrespective of the care setting (emergency department, home, long-term care facility, etc.), the patient must be given immediate relief if he is dying. If not, the time can be taken to determine the cause of the pain exacerbation in order to decide on the therapeutic approach, while also taking the patient's wishes into account.

The physician's pain assessment must be completed by that of the patient and his family [13, 14]. Simply having the patient assess the severity of the pain himself makes the treatment more effective [15].

For patients who are unable to swallow and who are not in very severe pain, the subcutaneous route is preferred, for after the first 24 hours it is just as effective as the intravenous route yet has fewer adverse effects [16-17].

The subcutaneous administration site can influence the rate of absorption of medications [18-20]. Due to its faster rate of absorption (5 to 10 minutes), the anatomical site recommended for the subcutaneous administration of medications in the last days of life is located between the vertical midbreast line, in a rectangle extending from the top of the sternum to the navel, i.e., in the chest and upper abdominal region. Furthermore, this area is easy to access and means that the patient is not bothered by the device when he moves.

Figure 2
Injection sites and estimated time to onset of action of medication injected subcutaneously by site (5 regions) [1, 19, 20]



Reproduced with the permission of Palli-Science.

When the injection is given more laterally, outside the vertical midbreast line, the medication has to pass through the axillary lymphatic system, slowing its absorption. The second site to consider is therefore the lower abdomen. Injecting into the shoulders and arms can delay the onset of action of medications. The thighs are the last choice for the subcutaneous administration of molecules.

Scarred skin may absorb medication poorly and must be avoided. Nor must irradiated areas, even those that appear to be intact, be used. Obviously, edematous areas cannot be used, since they are already unable to absorb the fluid present.

For very severe pain, the onset of the effect is faster with the intravenous route. A number of studies have shown that rapidly adjusting intravenous morphine was effective and had few adverse effects when the physician titrated the morphine every 5 minutes (Appendix II).

2.1.5 WHAT SHOULD BE DONE WITH A PATIENT WHO DOES NOT OBTAIN RELIEF DESPITE TREATMENT?

It is troubling to see a patient continue to suffer when the standard medication is used properly, even after the SC administration of a combination of an opioid, midazolam and an anticholinergic (Appendix III).

There are many possible causes for this incomplete response to analgic therapy and they must be identified immediately:

- › Ensure subcutaneous injections are not being given at cutaneous sites where the rate of absorption is slower (edema, scarring, marked subcutaneous tissue atrophy, thighs); in the presence of anasarca, other routes of administration will have to be used.
- › Some patients in the last days of their life may develop tolerance (reduced analgesic effect with repeated administration of the molecule) to the analgesic effects of opioids and need significantly higher doses.
- › In some patients, opioids can increase pain and even cause a phenomenon of hyperalgesia (opioid-induced heightened sensitivity to pain). This hyperalgesia is mainly seen in patients who are being given high doses of opioids, the equivalent of more than 200 mg of oral morphine per day.

If hyperalgesia occurs or if an escalating dose of opioids fails to provide relief, opioids can be rotated (see 1.2.2). Caution must be exercised when using the intravenous route, for tachyphylaxis (rapid tolerance) can develop in the very short term when this route of administration is used and would mean that doses would have to be given at shorter intervals to maintain adequate analgesia. The phenomenon of tachyphylaxis seems to be less pronounced when the subcutaneous route is used (although this phenomenon is poorly documented).

Refractory cancer pain may sometimes respond to the oral or subcutaneous administration of dexamethasone due to the possible reduction of peritumoral edema and the mass effect.

When the source of refractory pain is localized (a limb, a plexus, a nerve root), regional anesthesia techniques can be tried to relieve some patients who are in severe pain. These techniques are not usually part of the therapeutic arsenal proposed to patients in the last days of their life due to their complexity, the length of time it takes to obtain them in some settings, the need for continuous infusion and the possibility of failure in cases of complex pain. If a patient is in severe pain, the physician must not hesitate to discuss refractory cases with the anesthesiologist.

In practice, it may become difficult to identify the exact cause of loss of pain control in the final moments of life. Furthermore, in the final hours of life, many patients may become agitated. Is this agitation the expression of uncontrolled pain or generalized discomfort due to immobility? Or is it associated with anxiety or delirium? A distended bladder? Fecal impaction? These questions often go unanswered, since the patient's diminished level of consciousness often means that he is no longer able to communicate properly. It is suggested that this agitation be controlled (see 2.5 and Appendix II) using benzodiazepines and/or sedative neuroleptics while optimizing the use of analgesics. Methotrimeprazine is a potent sedative neuroleptic at the end of life for patients who require a sedative and possibly analgesic effect (Appendix II). Given its potential adverse effects (orthostatic hypotension, delirium and anticholinergic effects), methotrimeprazine is mainly reserved for the last days of life for agitated patients and exhausted patients with uncontrolled pain despite optimal analgesic use. Note that this molecule can cause simple redness and warmth of the skin at the subcutaneous injection site for which no intervention is necessary.

Barbiturates are a class of drugs that are useful in the last days of life for relieving seizures [21], refractory anxiety and agitation (Appendix II). They do not have any analgesic activity as such but produce a feeling of well-being. Barbiturates have anxiolytic, anticonvulsant and sedative properties that are useful in cases of refractory pain. Phenobarbital is the only barbiturate administered subcutaneously.

Ketamine is a general anesthetic that is rarely used in the last days of life: it should be used only by experienced physicians.

2.1.6 WHAT SHOULD BE DONE IF RELIEF-ORIENTED INTERVENTIONS CAUSE SEDATION?

In the very last moments of life, when the dying person is experiencing severe suffering that is difficult to control (significant pain, acute severe pain, dyspnea, nausea/vomiting, agitation, anxiety, etc.), the Collège des médecins urges physicians to provide immediate relief to the patient. It is unacceptable to allow a patient to suffer in the last days of his life.

“It is unacceptable to allow a patient to suffer in the last days of his life.”

“The physician must not withhold relief from a dying patient for fear of causing secondary sedation if all other therapeutic options have failed.”

The physician’s interventions must always be directed at providing the best possible relief in situations of severe suffering that require analgesics, anxiolytics or neuroleptics. The attending physician must not hesitate to rapidly consult a colleague who is an expert in end-of-life symptom relief if the treatments given fail to produce the desired outcome. The physician must not withhold relief from a dying patient for fear of causing secondary sedation if all other therapeutic options have failed.

2.2 NAUSEA AND VOMITING

Nausea and vomiting are common symptoms at the end of life due to the widespread use of opioids but also due to possible gastrointestinal tract involvement. However, these symptoms are less common in the last days of life and especially during the agony phase, when the patient is no longer eating or drinking. If present, relieving these symptoms is just as important as pain relief [22].

With a relatively simple medication such as haloperidol (Haldol®), most nauseous patients obtain relief; this molecule can be administered subcutaneously (Appendix II).

In cases of severe refractory nausea and/or vomiting, fast-dissolving olanzapine (Zyprexa Zydis®) and dexamethasone may be effective.

Dimenhydrinate (Gravol®) is rarely used in the last days of life; it is mainly used for cases of nausea associated with movement or nausea of vestibular origin. Likewise for metoclopramide (Maxeran®), which is mainly useful for patients with gastric stasis (gastric fullness, projectile vomiting that is not preceded by nausea).

2.3 DYSPNEA

One of patients' greatest fears in the last days of life is of "suffocating" to death. Dyspnea causes genuine suffering for the patient and those who witness it, the patient's family and caregivers [23]. Dyspnea in the last days of life is complex, in most cases the result of a combination of a number of problems such as extreme muscle weakness, hypoxemia, anemia, infection, pulmonary edema, pulmonary embolism, bronchospasm.

Directing a simple fan at the patient's face can help. It is recommended to administer opioids such as morphine, hydromorphone or fentanyl (Appendix II) and/or a benzodiazepine such as lorazepam or midazolam to dyspneic patients [24, 25, 31]. This drug combination has been found to be more effective than oxygen in relieving dyspnea [26-28].

According to the findings of studies on cancer patients at the end of life, oxygen should not be used to relieve dyspnea unless the patient is very hypoxic (oxygen saturation below 88%), has severe dyspnea at rest or decompensated cor pulmonale with edema: oxygen is therefore not the first-line treatment for dyspneic patients in the last days of their life [29].

This recommendation is consistent with the reference framework of the Programme national d'oxygénothérapie à domicile [National home oxygen therapy program] [30] which indicates that for patients with a neoplastic disease:

- › Oxygen therapy is not the first-line treatment for dyspneic users in the palliative phase. In the absence of severe hypoxemia, oxygen therapy is not recommended for the dyspneic user with advanced cancer.
- › Comfort oxygen therapy may be considered in the presence of severe hypoxemia (saturation at rest < 88%) for a user with primary lung cancer or a pulmonary condition associated with any other type of cancer if the prognosis of survival is believed to be less than 3 months.

For patients with non-neoplastic diseases in the terminal phase:

- › Comfort oxygen therapy may be considered in the presence of severe hypoxemia or decompensated cor pulmonale with edema.

It is normal to see oxygen saturation decrease just before death. Therefore measuring oxygen saturation is not recommended, nor is doing an arterial blood gas in the very last moments of life or putting oxygen on a dying patient.

However, oxygen should not be denied to a patient who is already on it and finds it beneficial: oxygen must then be seen as a comfort treatment to be continued for as long as the patient finds it beneficial in the last moments of his life. Due to the relief felt by some patients, but also sometimes the insistence of worried family members, especially in the home setting, a therapeutic trial of oxygen may be acceptable for some dyspneic patients for whom drug therapy does not seem to be sufficient, irrespective of oxygen saturation. Evidence appears to show that patients stop using oxygen when they feel it is of no benefit.

2.4 TERMINAL RESPIRATORY RALES

Terminal respiratory rales in the last days of life can be caused by increased bronchial secretions (which the patient is too weak to clear), pulmonary edema or a respiratory tract infection. It is hard to distinguish between these conditions in the last moments of life in a patient who presents with rales [32]. It is helpful to know that these conditions affect around one third of patients in the last days of their life and that treatment with subcutaneous anticholinergics is usually effective in most patients in the agony phase (Appendix II).

Anticholinergics inhibit the production of bronchial secretions [33] but they do not reduce the amount of secretions already present in the respiratory tree: this is why a patient who is well hydrated immediately before the agony phase may have more secretions than a patient who stopped drinking and hydration several hours before the agony phase. Subcutaneous scopolamine is fast acting but causes significant sedation and may cause agitation with repeated doses. The other anticholinergics used in the last days of life have fewer sedative effects than SC scopolamine (Appendix II).

Should anticholinergics fail and if pulmonary edema is suspected, the administration of furosemide 20 mg SC, to be repeated after one hour as needed, may be considered. This provides relief for some obstructed patients.

Anticholinergics will have little effect on pulmonary and bronchial infections in the last days of life. There are no other treatment options for this type of bronchial condition.

Terminal respiratory rales do not have to be treated if the patient is peaceful, unconscious and has no ciliary reflex, since it is probably not causing him any discomfort. It is mainly distressing to family members, since breathing is sometimes very noisy and often irregular at the end of life. Once the condition has been explained to them, family members will understand that the patient is not suffering and that medication cannot always reduce the secretions.

Tracheal suctioning, an invasive and ineffective technique, is not appropriate in the last days of life. At best, a rigid suction catheter could be used to remove copious secretions in the mouth.

2.5 TERMINAL AGITATION AND DELIRIUM

In the last days before death, many patients will be agitated. Some even speak of delirium. This condition is very distressing to the patient, his family and caregivers. The physician should not hesitate to control this agitation. Is it anxiety? Is it poorly controlled pain or dyspnea that is making the patient anxious? Is the patient suffering from alcohol or benzodiazepine withdrawal? Is it fecal impaction, a distended bladder? Agitation caused by urinary retention can be relieved rapidly by urinary catheterization or by removing the impacted stool in cases of fecal impaction, but terminal agitation is relieved by drug therapy. The ultimate goal of our interventions is to relieve the agitation.

“... most medications that relieve agitation may cause secondary sedation.”

“... it is more helpful from a clinical standpoint to simply direct our interventions toward the relief of suffering and accept that sedation might be a side effect in some patients.”

We must be aware that most medications that relieve agitation may cause secondary sedation. Some speak of “palliative sedation”, but it is more helpful from a clinical standpoint to simply direct our interventions toward the relief of suffering and accept that sedation might be a side effect in some patients (Table 3, Appendix II). This should be explained to family members.

2.6 TERMINAL DISTRESS

Distress is a widely used term to describe any extremely painful or intolerable, mostly acute, situation at the end of life. There are many potential underlying causes: acute pulmonary edema, acute respiratory failure, massive pulmonary emboli, acute myocardial infarction, massive mesenteric ischemia, massive hemorrhage, epileptic status, refractory pain, severe delirium accompanied by agitation, fear/panic in the face of imminent death, etc.

In these critical situations, the cause of the patient's sudden suffering is not always obvious and attempting to identify the cause would result in unacceptable delays in providing relief for the patient.

The treatments proposed here come from clinical observations; they are therefore based on expert opinion [34]. The simultaneous subcutaneous administration of a trio of medications (opioid, midazolam and scopolamine), referred to by some as a "distress protocol", is intended to provide rapid relief from pain, anxiety, dyspnea and terminal respiratory rales (Appendix III). The doses of the three medications must be adjusted based on the patient's current medication and condition. The simultaneous administration of three molecules is an exception and is not a basic method of treatment for end-of-life patients. However, it is to be expected that most patients will need an opioid, an anticholinergic and a benzodiazepine in the last days of their life. It is important that caregivers, including family members at home, have immediate access to these three molecules, that they be kept on hand and that they know how to use them. These three molecules should be prescribed at the outset to all patients in the last days of their life (advance prescriptions) before the agony phase and above all before a situation of distress arises (Table 3, Appendix III).

Of course, in cases of significant distress, if a venous line is already in place or venous access is easy, the physician must not hesitate to administer the medication intravenously to provide relief as quickly as possible.

"Adjusting the medication as the patient's condition deteriorates ensures effective symptom relief and minimizes the risk of distress."

Chapter 3/ Frequently asked questions regarding medical care in the last days of life

3.1 WHY AND HOW TO USE THE SUBCUTANEOUS ROUTE IN THE LAST DAYS OF LIFE

The subcutaneous route is effective: it is widely used in palliative care. Injecting medications in the subcutaneous space is less invasive and less painful than the intramuscular route.

A number of variables, such as the viscosity of the medication, its pH, its solubility and the injection site, will affect the rate of medication absorption. The needle does not have to be inserted at a particular angle, since the injection is given in the subcutaneous tissue which acts like a "sponge" (Figure 2).

To avoid accidental needlesticks, it is best to use a system where no needle is left at the injection site: standard 24- or 27-gauge intravenous cannulae can simply be used, which will be inserted under the skin and left in place. There are also more expensive "butterfly" catheters with retractable needles as well as BD Insyte™ or Insuflon® catheters. The medication will be injected in these devices by continuous infusion or intermittent injection.

3.2 IS IT APPROPRIATE TO USE THE INTRAVENOUS ROUTE IN THE LAST DAYS OF LIFE?

When there is an acute pain exacerbation, severe pain will be relieved more quickly by the intravenous route. An intravenous route is believed to probably be more effective than the subcutaneous route, especially in cases where lymphatic drainage might be reduced: local edema, anasarca, radiation therapy site or heavy scarring [19, 20].

3.3 DOES MORPHINE HASTEN DEATH? [35-39]

It is often said that morphine can "hasten death", that it shortens the life of a person in the terminal phase. We often hear things like "They put him on morphine... he doesn't have long left." If we hesitate to use morphine to relieve patients and only use it in the very last moments of life, only a few hours or a few minutes before death, this coincidence can reinforce the notion that morphine is associated with death.

Opioids have more benefits than harms and it is important to explain this to patients and their family. Countless Quebecers are given opioids every day for the relief of moderate to severe pain, for the common problems of acute and chronic pain (cancer, surgery, low back pain, etc.), without reducing their life expectancy.

Many studies show that opioids do not shorten life when prescribed correctly. On the other hand, various reports indicate that people who experience suffering stop eating or even commit suicide when their suffering becomes intolerable. We must not be afraid to use morphine or other opioids to provide effective relief for patients in the last days of their life.

"We must not be afraid to use morphine or other opioids to provide effective relief for patients in the last days of their life."

3.4 HOW SHOULD MEDICATIONS THAT ARE NO LONGER USEFUL IN THE LAST DAYS OF LIFE BE DISCONTINUED?

Once it has been agreed that only comfort care will be provided, after discussing the matter with the patient and his family members and obtaining their agreement, the administration of all preventive medications and all medications that do not contribute to the patient's well-being must be discontinued. To begin with, the administration of aspirin and lipid-lowering agents must be discontinued. The administration of antihypertensives must also be discontinued gradually or rapidly, depending on the patient's prognosis, since many analgesics, including opioids, cause hypotension and blood pressure drops at the end of life in most patients long before the agony phase, due, among other things, to weight loss. Likewise for hypoglycemics, which are likely to cause hypoglycemic episodes in a patient who has lost weight or who hardly eats anymore.

The same is true of cholinesterase inhibitors used in dementia as well as antidepressants which should have been discontinued gradually long before the last days of life. There are few benefits to continuing these molecules. They must be tapered rapidly (but not abruptly) before the agony phase so that only medication that is essential and of benefit to the patient is continued.

It is preferable to discontinue prophylactic anticoagulation therapy, if any. However, if the anticoagulant was started after a thromboembolism or a specific heart condition such as atrial fibrillation, anticoagulation therapy may be continued. Oral warfarin sodium should be discontinued and replaced with low molecular weight heparins because they are simple to adjust. Irrespective of the situation, oral anticoagulation therapy should be discontinued as soon as the patient is no longer able to swallow.

For patients with a history of seizures, especially multiple seizures, anticonvulsants will be continued until death and will be replaced, when the patient is no longer able to swallow, with subcutaneous benzodiazepines or phenobarbital. Another solution is to administer diazepam, valproic acid or levetiracetam rectally (Appendix II).

The administration of steroids prescribed less than two weeks previously can be discontinued without tapering, irrespective of the dose. If they increase the patient's comfort or if he has been taking them for several months, they will be maintained for as long as the patient is able to swallow them. Once the patient is no longer able to swallow, dexamethasone can be administered subcutaneously in the same doses, where appropriate.

Laxatives that are being administered to a patient who is on opioids must be discontinued once he is no longer able to swallow, except in the presence of symptomatic fecal impaction, where suppositories, enemas and, as needed, removal of the impacted stool will then be prescribed selectively.

The relief of symptoms associated with heart failure requires the administration of diuretics such as furosemide. The reduction or discontinuation of diuretics must take the patient's comfort into account, since dyspnea caused by fluid overload can be relieved by subcutaneous opioids. For patients with severe heart failure that is well controlled with diuretics but who are bothered by frequent voiding, a urinary catheter can be inserted and the medication maintained.

Any antibiotics the patient is on should be discontinued unless they contribute to the patient's well-being, for example by suppressing fever.

Some people will ask the physician to stop all their medications, except for those that provide relief, to avoid prolonging life. This is a legitimate patient request and derives from the principle of consent to medical care or refusal of such care. The physician must ensure that the patient clearly understands the consequences of this decision and must not refuse a clear request in this regard [1].

Chapter 4/ Specific situations

4.1 CONSIDERATIONS FOR A HOME DEATH AND FAVOURABLE CONDITIONS [40]

Many patients would prefer to stay at home for the last days of their life but, for various reasons, only a minority of Quebecers, around 10%, currently die at home [41, 42]. In Quebec, this choice is considered a valid alternative to dying in hospital. Home care services are seeing an increasing number of requests to this effect [43]; Quebecers can receive safe, high-quality palliative care at home [41, 44-46].

For a physician, keeping a patient at home in the last days of his life calls for a different model of patient care organization than in hospital, where medication and professionals are on hand. At home, most care and treatments are provided by family members under the home care nurse's periodic supervision and the physician's telemonitoring by telephone (Table 2). In collaboration with the nurse, the physician must prepare the medication in the patient's home in advance, in anticipation of the various symptoms and complications that might arise in the last days of life (Table 3). Most difficult situations that arise in the last days of life can be managed effectively at home.

Favourable conditions for a home death, mainly organizational, are presented in Table 2. They reduce hospitalizations and repeated emergency room visits. It should be noted that the organization of care in the last days of life at home is similar to that in other living environments such as long-term care facilities, for example. Irrespective of the patient's living environment, he should receive comprehensive palliative care, with the same treatment options as those offered in hospital. Medical services in the last days of life must be available in the patient's living environment if he so wishes.

“Irrespective of the patient's living environment, he should receive comprehensive palliative care, with the same treatment options as those offered in hospital.

Medical services in the last days of life must be available in the patient's living environment if he so wishes.”

Table 2**Keeping a patient at home in the last days of his life*****Favourable conditions and organization of medical practice [43]***

| Favourable condition | Organization of medical practice |
|--|---|
| <p>The physician makes home visits.</p> | <p>A home visit by the physician is recommended when caring for a patient in the last days of life, but also when a new problem arises, when symptoms are poorly controlled or when the end of life is near. A group practice with colleagues who also make home visits makes it easier to provide follow-up for these cases.</p> <p>The home nurse is the key person in home-based palliative care. The physician will often provide follow-up to the patient remotely after having met him at least once. A high degree of telephone availability on the part of the physician and a home-based palliative care nurse navigator (nurse who is responsible for the patient outside of the hospital) is crucial.</p> |
| <p>The physician brings the medical record with him when he makes home visits. The referring physician should provide relevant information immediately (imaging, latest laboratory tests and medical consultations).</p> | <p>If the patient's medical record is in a public institution where the <i>Archives Act</i> prohibits a person from taking a record out of the institution, it should be pointed out that this Act is in conflict with the <i>Code of ethics of physicians</i> and the <i>Regulation respecting records, places of practice and the cessation of practice by a physician</i>. Furthermore, if a physician is prosecuted under the <i>Criminal Code</i> (code that takes precedence over the <i>Archives Act</i> in a trial), great importance will be given to the requirement that the physician have all the information needed before making a decision regarding the patient.</p> <p>Any physician who makes a home visit must therefore have the medical record in his possession, i.e., the medical notes, imaging and laboratory results as well as the medical summaries and consultation reports. These items from the original institution record could be duplicated to create a "secondary" institution record that the physician can take with him on his visits. An electronic medical record will facilitate the development of medical home care.</p> |

| | |
|---|---|
| <p>Follow-up of unstable cases at home requires unrestricted access to the attending physician.</p> | <p>Medical office staff must be trained to ensure that urgent messages are passed on to the attending physician; the physician must return calls (pharmacists, nurses and family caregivers) concerning a home-based patient in the last days of his life promptly, just as he would do for a hospitalized patient, and make home visits when necessary.</p> |
| <p>The attending physician works closely with CLSC home care nurses in an interdisciplinary approach.</p> | <p>The patient's nurse navigator and the attending physician must know one another and regularly discuss changes in the patient's condition, just as they do for hospitalized patients (interdisciplinary approach).</p> <p>The professionals responsible for the patient do not always work in the same institution and are not always responsible for the same record; they must be able to communicate with one another quickly, for instance by pager, cellphone and fax, in the event of decompensations or a deterioration in the patient's condition.</p> <p>Several CLSCs leave bedside charts ("home record") in the home of a severely ill patient where the main care to be provided to the patient is noted along with the vital signs and any recent changes in his condition. This valuable communication tool reduces the risk of errors and ensures rigorous, quality patient follow-up, just as in a hospital setting.</p> |
| <p>24-hour nursing and medical telephone availability</p> | <p>24-hour telephone access allows patients who wish to stay at home to do so up to the time of death and ensures family carers receive appropriate support. On-call nurses should be able to reach a physician quickly in an emergency.</p> <p>Group family medicine practice makes it easier to establish 24-hour medical telephone service for vulnerable home-based patients. Failing this, a regional hospital palliative care unit's on-call service can be contacted.</p> |

| | |
|-------------------------------------|--|
| Prescription of follow-up by nurses | The nurse's use of individual and collective prescriptions for home follow-up of patients facilitates patient care and reduces the number of medical visits. With the nurse, the physician must determine the factors to monitor (vital signs, symptoms) and the parameters above which the physician should be called. |
| Prescription of treatment by nurses | As in the hospital setting, CLSC home care nurses can, using individual and collective prescriptions, perform a number of helpful and necessary procedures to keep patients at home, such as select and change dressings, administer parenteral therapy (SC, IM and IV), make dose adjustments for certain molecules (insulin and warfarin sodium), provide ostomy or drain care, etc. |
| Delegation to family caregivers | <p>Unlike the approach in hospitals, family caregivers are the main care providers in home care, since they are present. They administer medication by the oral, transdermal or subcutaneous route in accordance with the physician's prescription and the nurse's teaching.</p> <p>They perform basic monitoring of symptoms and contact the nurse if there are any problems, while the nurse is, in turn, in contact with the physician as much as necessary.</p> <p>They are present when the patient dies and notify the health care team.</p> <p>Trust and teamwork with family caregivers are fundamental to keeping a patient at home in the last days of his life.</p> |
| Do not resuscitate | A "Do not resuscitate" form (or document indicating the level of care) will be left at the patient's home, duly signed by the patient: this will prevent unwanted and unnecessary resuscitation when the patient dies. To the extent possible, the necessary and most comprehensive information possible about the procedure to follow after a home death will be left for the family. |

The goal of home-based care in the last days of life is to relieve the patient's terminal suffering, just as in a hospital setting. The molecules administered and their routes of administration are essentially the same as in hospital (Appendix II). A basic supply of medications, common to most types of care in the last days of life, should already be at the patient's home if a rapid deterioration or complication is feared as well as for those who wish to die at home (Table 3). This supply of medications will allow visiting nurses or family members to deal with difficult or urgent situations.

In the last days of life, a switch to the subcutaneous route for certain molecules essential to the patient's well-being must be anticipated (Appendices I and II). Table 3 proposes a basic supply of medications to be kept at the home of a patient who is in the last days of his life or to be left at the long-term care facility. Needless to say, this list is not exhaustive but can serve as a basic guide that can be adapted to the clinical situation.

Table 3
Last days of life at home or in a long-term care facility
Basic supply of medications to be kept on hand

| Drug class | Suggested molecule (doses in Appendix II) | Target symptoms |
|--|--|--|
| Benzodiazepines SL and SC | | |
| | Lorazepam (Ativan®)* | Anxiety, insomnia, dyspnea, seizures |
| | Midazolam (Versed®) | Anxiety, insomnia, dyspnea, seizures, before a painful procedure |
| Parenteral opioids | | |
| <p>Injectable opioids:</p> <p>The opioid that is already being administered is usually chosen, halving the 4-hourly dose to obtain the subcutaneous 4-hourly dose.</p> <p>For patients on transdermal fentanyl, the TD medication that is already being administered is continued, with morphine or hydromorphone SC.</p> | <p>Morphine SC</p> <p>Hydromorphone SC</p> <p>Fentanyl TD</p> | <p>Pain, dyspnea, distress, discomfort in the last days of life</p> |
| Injectable neuroleptics SC | | |
| | <p>Methotrimeprazine (Nozinan®)*</p> <p>Marked sedative effect</p> | <p>Severe agitation or insomnia that does not respond to benzodiazepines; refractory pain; nausea and vomiting</p> |

* Or any molecule in the same class.

| Anticholinergics SC | | |
|---------------------|--------------------------------|---|
| | Scopolamine, glycopyrrolate | Reduces bronchial rales in the last days of life that may be distressing to the family Scopolamine's sedative effect is potentiated when combined with an opioid |

4.2 PEDIATRIC PALLIATIVE CARE

BECAUSE CHILDREN DIE TOO...

In Quebec, 800 children die annually, 50% of those before 1 year of age [47]. It is extremely important to provide support to the dying child and his family, for the loss of a child is a tragedy and even an absurdity for his family unit. The emotional shock caused by his death is felt by his family and by caregivers.

A SIMILAR APPROACH TO ADULT PALLIATIVE CARE...

Pediatric palliative care is active, comprehensive care, encompassing the physical, psychological, social and spiritual dimensions. The goal is to maintain the best possible quality of life for the child and to support his family; this includes symptom relief for the child, respite services for the family and care up to the time of death and during the bereavement period. While the approach in pediatric palliative care draws on experience acquired with adults, it differs in a number of respects.

DIFFERENT DISEASES...

While oncology is most prominent in adult palliative care, the most common diseases in children are neuromuscular, neurodegenerative and metabolic. Many deaths are also caused by accidents or neonatal complications, mostly sudden and unexpected. This patient group can be divided into six groups of children and families, as defined by the *Normes en matière de soins palliatifs pédiatriques* [Pediatric palliative care standards]. A palliative approach should be taken with any child who has a medical condition that might prevent him from reaching 18 years of age and should start as soon as the diagnosis is announced. The palliative phase can therefore be very long, even lasting years. The goal of interventions is always to improve quality of life and comfort in order to allow the child to live life and develop to the fullest.

THE CHALLENGES INVOLVED...

The first major challenge in pediatrics is a proper pain and symptom assessment, for the child's stage of cognitive and emotional development influences his experience and interpretation of his pain. A number of assessment tools are tailored to a child's age and ability to communicate. These scales can be used by both care providers and parents; this means that the latter become the main spokespeople and the main assessors of their child's symptoms and pain. Including family members in the health care team is fundamental and imperative.

When medication cannot be administered orally, the transmucosal route is an excellent solution because it is fast acting. Most palliative medication (opioids, benzodiazepines, ketamine and scopolamine) can be administered by this route using the most concentrated formulation possible (a volume of less than 0.1 cc is ideal to avoid stimulating swallowing). In children, the transdermal route using low-dose fentanyl patches reduces the need for injectables.

The rectal route may be an option, especially for the continued administration of certain anticonvulsants, using a concentrated solution with a small Fr5 feeding catheter. The intramuscular and intravenous routes must be avoided even if the patient has an indwelling central venous catheter. The subcutaneous administration of intermittent doses can be simplified by placement of an Insuflon® catheter, which is very small, comfortable and has no dead space. It can be used to administer several compatible medications, without any need for flushing. The volume per dose to administer that is tolerated by tissues varies with age; we try to limit the volume to 0.2 mL in premature infants, 0.5 mL in children and 1 mL in adolescents. Continuous subcutaneous infusion sets, such as Comfort Soft® or Inset II®, used in diabetes, ensure mobility, comfort and quality of life for children both in hospital and at home.

Documentation and studies on pediatric drug therapy are more limited than in adult palliative care. Treatments are based on clinical experience adapted from both pediatric and adult medicine. In general, pediatric doses are calculated in mg/kg and do not exceed regular adult doses. In addition to medication, non-pharmacological measures and distraction such as massage therapy, pet therapy, visualization and music therapy must be encouraged, for children are particularly receptive to them.

In recent years, research and expertise in pediatric palliative care have made it possible to better meet the needs of children and their families. More attention is paid to understanding what the child is going through, his disease and his death, the special needs of siblings, parents and grandparents as well as to relieving the distress experienced by caregivers, thus improving care. Creating a legacy is now recognized as essential to alleviate the existential suffering of the child and his family. Since one of the dying child's greatest fears is that he will be forgotten, many activities can be carried out to help him create mementos (photography, hand sculpture, album, journal, etc.).

TEAMWORK...

For a caregiver, taking care of a child with a limited life expectancy may seem extremely challenging and anxiety inducing both emotionally and in terms of organization. Despite the sadness of such situations, these experiences are always rewarding and the positives largely outweigh the initial fears. There's no need to be an expert. Every caregiver must know that they can always turn to interdisciplinary palliative care teams in Quebec's pediatric centres for support.

CONCLUSION

We hope that these guidelines will be helpful to clinicians caring for patients who are in the last days of their life. They are not meant to be a detailed palliative care handbook but to present recognized basic medical care for this final stage of a person's life. We decided not to address complex moral and ethical issues here, but instead to present treatments the clinician can use to provide effective relief for his patients in the last days of their life. The treatments described in these guidelines, whose goal is to relieve the suffering of dying patients, must be accessible across Quebec in hospital centres, palliative care hospices, at home and in long-term care facilities alike.

— Appendices

APPENDIX I - SUGGESTED TRANSITION TIMES WHEN SWITCHING OPIOID FORMULATIONS OR ROUTES OF ADMINISTRATION [1]

| Initial formulation | New formulation | Important |
|-----------------------|-------------------|---|
| Short acting PO q 4 h | ISC q 4 h | Start SC at the scheduled time of the next dose |
| Short acting PO q 4 h | CSCI | Start the infusion at the same time as the last short-acting dose |
| Long acting PO q 12 h | ISC q 4 h or CSCI | Start SCI or CSCI 6 to 9 h after the last long-acting dose |
| ISC q 4 h | CSCI | Start CSCI at the same time as the last short-acting SCI dose |
| CSCI | ISC | Start ISC + continue CSCI x 1 h, then discontinue Total daily dose divided by 6 injected q 4 h |

— Appendices

APPENDIX II - INJECTABLE MEDICATION FOR SYMPTOM RELIEF IN THE LAST DAYS OF LIFE

| PAIN | |
|--------------------------|--|
| Opioid analgesics | |
| Opioid-naive patient | <p>a) Usual starting injectable dose</p> <ul style="list-style-type: none"> ➤ Morphine ISC/IIV: 5 mg (1 to 5 mg) q 4 h CSCI/CIVI: 1 mg/h (0.5 to 1 mg/h) ➤ Hydromorphone ISC/IIV: 1 mg (0.25 to 1 mg) q 4 h CSCI/CIVI: 0.25 mg/h (0.1 to 0.25 mg/h) <p>b) Rapid adjustment if severe pain</p> <ul style="list-style-type: none"> ➤ Morphine ISC/IIV: 1 mg (1 to 3 mg) q 5 to 10 min. (q 15 min. if ISC) max. 10 mg or <i>ad</i> relief or undue sedation ISC/IIV: the dose that provides relief is given 2 h later, then q 4 h CSCI/CIVI: the total dose that relieves the patient is divided by 4, then administered immediately |
| Non-opioid-naive patient | <ul style="list-style-type: none"> ➤ Switch from PO to SC ➤ Patient is in pain: ↑ usual dose by 25 to 50% ➤ Patient is in severe pain: ↑ usual dose by 100% ➤ Severe pain - rapid adjustment IIV: 10 to 20% of the total daily dose q 5 to 10 min. or <i>ad</i> relief / undue sedation (max. 4 to 5 doses) ISC: idem q 15 min. |
| Opioid breakthrough dose | <ul style="list-style-type: none"> ➤ ISC: 10 to 15% of the daily dose q 30 min. PRN ➤ CSCI: once or twice the hourly dose q 30 min. PRN ➤ CIVI: idem q 10 min. PRN |

APPENDIX II - INJECTABLE MEDICATION FOR SYMPTOM RELIEF IN THE LAST DAYS OF LIFE

| Non-opioid analgesics | |
|---------------------------------|--|
| Methotrimeprazine (Nozinan®) | ISC*, IIV: 10 mg (2.5 to 50 mg) q 6 h (max. 300 mg/day) → To relieve refractory pain with or without nausea and vomiting, or agitation |
| Dexamethasone (Decadron®) | ICI, IIV: 4 mg (4 to 20 mg), then 4 mg (2 to 8 mg) qd (qd to qid) |

* Route of administration not recognized in the product monograph.

| OTHER SYMPTOMS | |
|--|---|
| Terminal respiratory rates | |
| Glycopyrrolate (Robinul®) | ISC: 0.4 mg (0.2 to 0.6 mg) q 4 h PRN → Does not cause sedation |
| Scopolamine/ hyoscine hydrobromide | ISC: 0.4 mg (0.2 to 0.8 mg) q 4 h PRN → Amnesiac and highly sedative → May cause hallucinations, delirium, agitation |
| Hyoscine (Buscopan®) | ISC, IIV: 20 mg, then 10 mg (10 to 20 mg) q 4 h PRN → Does not cause sedation |
| Transdermal scopolamine (Transderm-V®) | 1 to 3 patches (1.5 mg/patch releasing 1 mg in 3 days) → Several hours before clinical effect is obtained → Causes little sedation → May cause hallucinations, delirium, agitation |

APPENDIX II - INJECTABLE MEDICATION FOR SYMPTOM RELIEF IN THE LAST DAYS OF LIFE

| Nausea and vomiting | |
|---------------------------------------|--|
| Haloperidol (Haldol®) | ISC, IIV*: 1 mg (0.5 to 1 mg) q 8 h (suggested max.: 3 mg/day to avoid extrapyramidal reactions) |
| Metoclopramide (Maxeran®, Reglan®) | IIV, ISC*: 10 mg (5 to 10 mg) q 4 h (suggested max.: 40 mg/day) → Do not administer if bowel obstruction |
| Dexamethasone (Decadron®) | ISC, IIV: 4 mg (4 to 20 mg) stat, then 4 mg (2 to 8 mg) qd <i>ad qid</i> |
| Olanzapine (Zyprexa Zydis®) | Fast-dissolving PO: 5 mg qd to bid (max.: 10 mg/day) |
| Methotrimeprazine (Nozinan®) | SC, IIV*: 5 mg (2.5 to 25 mg) q 6 h |

| Agitation - delirium | |
|--------------------------------------|--|
| Lorazepam (Ativan®) | ISC*, IV, SL, IR: 0.5 mg (0.5 to 4 mg) q 6 h (4 to 6 h) CSCI*, CIVI: 0.5 to 1 mg/h (max. 4 mg/h) |
| Midazolam** (Versed®) | ISC, IIV: 1 to 10 mg q 4 h (2 to 4 h) (max. 10 mg/h or 240 mg/day) CSCI, CIVI: 2 mg (1 to 5 mg) stat, then 0.5 to 5 mg/h (max. 10 mg/h or 240 mg/day) |
| Methotrimeprazine (Nozinan®) [48] | ISC*, IIV: 5 mg (5 to 50 mg) q 6 h (max. 300 mg/day) CSCI, CIVI: 1 to 10 mg/h |

* Route of administration not recognized in the product monograph.

** Doses *ad* 1200 mg/24 h have been administered in complex, refractory cases or in the presence of tachyphylaxis.

APPENDIX II - INJECTABLE MEDICATION FOR SYMPTOM RELIEF IN THE LAST DAYS OF LIFE

| | |
|-----------------------|--|
| Phenobarbital | ISC*, IIV, IR: 30 mg (15 to 60 mg) q 6-12 h → For agitated patients, suggested loading dose: 120 mg (120 to 480 mg), then 120 mg (60 to 360 mg) q 6 h → In exceptional cases, up to 2500 mg/day can be prescribed |
| Haloperidol (Haldol®) | ISC, IIV: 1 mg (0.5 to 5 mg) q 1 h PRN or fixed doses q 8 h (max. 25 mg/day) |

| Seizures | |
|------------------------------|---|
| Midazolam (Versed®) | Seizure or status epilepticus ISC, IIV: 5 mg (5 to 10 mg), q 10-15 min. x 1-2 doses → May also be given by the intranasal or transmucosal route Prophylaxis CSCI: 1 mg/h (1 to 4 mg/h) ISC: idem (total 24 h dose divided by 6) q 4 h → Fast acting (less than 15 min.) even when administered SC |
| Lorazepam (Ativan®) | Seizure or status epilepticus IV, IR, SL, ISC*: 4 mg (4 to 8 mg) or (0.05 to 0.1 mg/kg) q 10-15 min. x 1-2 doses Prophylaxis ISC*, IIV: 1 mg (0.5 to 4 mg) q 4 h |
| Diazepam (Diastat®, Valium®) | Prophylaxis IR: 10 mg x 1, then 20 mg qd to bid thereafter |
| Valproic acid (Depakene®) | Prophylaxis IR: 15 mg/kg/day in 2 to 3 divided doses (max. 60 mg/kg/day) → Takes ± 3 days for the medication to be effective |

* Route of administration not recognized in the product monograph.

APPENDIX II - INJECTABLE MEDICATION FOR SYMPTOM RELIEF IN THE LAST DAYS OF LIFE

| | |
|---------------|--|
| Phenobarbital | <p>Prophylaxis ISC*, IIV: 60 mg (60 to 150 mg) q 8-12 h → Redness at the SC injection site → Causes drowsiness</p> <p>Seizure (1st episode) Bolus of 60 to 100 mg then maintenance dose: 60 mg (60 to 150 mg) SC q 8-12 h <i>ad</i> 400 mg/day in divided doses (usual dose 3-5 mg/kg/day) → If patient is already on anticonvulsivants, higher initial dose; adjust based on clinical condition (assess the risk of seizures secondary to the abrupt discontinuation of oral agents)</p> <p>Status epilepticus ISC*, IV: loading dose 10 mg/kg (max. 600 mg) Start with half the dose calculated, then give the remainder of the dose after 30 to 60 min. if status epilepticus persists (reaches peak plasma concentration in 2 to 4 hours) → The clinical effect takes 30 minutes if phenobarbital is given IV or 60 minutes if it is given SC*</p> |
|---------------|--|

* Route of administration not recognized in the product monograph.

APPENDIX II - INJECTABLE MEDICATION FOR SYMPTOM RELIEF IN THE LAST DAYS OF LIFE

| DYSPNEA | |
|---|---|
| Opioid | |
| Morphine SC (or equivalent: hydromorphone SC; fentanyl patch TD) | <p>Opioid-naïve patient 1 to 2.5 mg ISC q 4 h</p> <p>Non-opioid-naïve patient ↑ usual dose by ≈ 25 to 50% based on the severity of the dyspnea</p> <ul style="list-style-type: none"> ➤ Provide for breakthrough doses ➤ Adjust dose q 24 h ➤ ↑ by 25 to 100% based on clinical response and tolerance |
| Benzodiazepines | |
| Lorazepam (Ativan®) | SL, IR, ISC*, IV: 0.5 mg (0.5 to 2 mg) q 4 h CSCI*, CIVI: 0.1 to 0.5 mg/h |
| Midazolam (Versed®) | ISC, IIV: 1 to 10 mg q 2-4 h CSCI, CIVI: initial dose of 2 mg (1 to 5 mg), then 0.5 to 5 mg/h SC, IV → Little sedative effect at less than 1 mg/h → Tolerance develops quickly |

* Route of administration not recognized in the product monograph.

— Appendices

APPENDIX III - SAMPLE PRESCRIPTION FOR DISTRESS IN PALLIATIVE CARE

| | | |
|---|------------------------------|-----------------------------------|
| Patient identification | | |
| A. PRESCRIPTION FOR DISTRESS | | |
| Medications, dose, dosage, route of administration | Nurse | Space reserved for the pharmacist |
| 1. In the first syringe: Midazolam (Versed®) (5 mg/mL) 5 mg SC stat or ____ mg | | |
| 2. In the second syringe, mix: Scopolamine (0.4 mg/mL) 0.4 mg SC stat or ____ mg or $\left\{ \begin{array}{l} \text{Morphine} \\ \text{Hydromorphone (Dilaudid®)} \end{array} \right.$ 10 mg SC stat or ____ mg 2 mg SC stat or ____ mg | | |
| This prescription indicates the minimum doses suggested for all distressed adults | | |
| <ul style="list-style-type: none"> › Inject the contents of the first syringe in the upper chest, near the sternum, then inject the contents of the second syringe next to the site of the first injection. › If the medication is injected intravenously, dilute the contents of each syringe in a solution of NaCl 0.9% until a total volume of 10 mL per syringe is obtained. Slowly inject the contents of each syringe over 2 minutes. › The three (3) medications can be repeated once, after 20 minutes, while waiting to speak to the physician, if the distress persists. | | |
| <p>Midazolam: The dose can be increased to 10 mg if the patient was being given 3 to 12 mg of lorazepam per 24 hours or the equivalent. Give 15 mg of midazolam if the patient was being given more than 12 mg of lorazepam per 24 hours or the equivalent.</p> <p>Opioid: The dose can be increased to up to 100% of the regular 4-hourly opioid dose or up to a maximum of 50 mg of morphine or 10 mg of hydromorphone.</p> | | |
| B. ISOLATED TERMINAL SECRETIONS | | |
| For all patients in the last days of life, make sure medication is prescribed to relieve isolated terminal secretions. | Nurse | Space reserved for the pharmacist |
| 1st choice <input type="radio"/> Glycopyrrolate (Robinul®) 0.4 mg SC every 4 hours PRN or ____ mg every ____ hours PRN | | |
| 2nd choice <input type="radio"/> Scopolamine 0.4 mg SC every 4 hours PRN or ____ mg every ____ hours PRN | | |
| _____ | _____ | |
| Date/time | Authorized medical signature | |

— Appendices

APPENDIX IV - LIST OF ABBREVIATIONS

| | |
|------|---------------------------------------|
| bid | Twice a day |
| BTD | Breakthrough dose |
| CIVI | Continuous intravenous infusion |
| CSCI | Continuous subcutaneous infusion |
| IIV | Intermittent intravenous |
| IM | Intramuscular |
| IR | Intrarectal |
| ISC | Intermittent subcutaneous |
| IV | Intravenous |
| PO | Oral |
| PRN | As needed |
| q | Every (e.g., q 3-4 h: every 3 to 4 h) |
| qd | Once a day |
| qid | Four times a day |
| SC | Subcutaneous |
| SL | Sublingual |
| stat | Immediately |
| TD | Transdermal |

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