Institut national d'excellence en santé et en services sociaux
Québec

QUEBEC'S NATIONAL MEDICAL PROTOCOL

No. 888028

Administration of Continuous Palliative Sedation (CPS) in Adults at the End of Life

Developed in collaboration with an advisory committee consisting of Quebec clinicians and experts

CLINICAL SITUATION OR TARGET POPULATION

A person 18 years of age and older at the end of life who receives palliative care that is intended exclusively to ensure his or her comfort[1]

AND

Who has at least one intolerable and refractory symptom, i.e., a symptom that causes intolerable suffering to the person, and when no other treatment option is available or considered acceptable in the situation, after discussion with the person or his or her legal representative (see principal symptoms in Section 1.3)

AND

Whose vital prognosis is limited or compromised (in accordance with the ethical and clinical elements, and the decision-making process described in the *Palliative Sedation at the End of Life: Practice Guidelines*, published by the CMQ-SQMDSP).

CONTRAINDICATIONS TO THE APPLICATION OF THIS PROTOCOL

No contraindications.

INSTRUCTIONS

Throughout the document, the term "continuous palliative sedation" (CPS) refers to the use of a pharmacological treatment for refractory symptom relief by inducing a state of deep sedation that will be maintained until the person's death.

When CPS is being considered:

- Consultation with a specialized palliative care team should be considered throughout the process.
- Ensure compliance with the ethical, clinical and decision-making elements described in *Palliative Sedation at the End of Life: Practice Guidelines*, published by the CMQ-SQMDSP, including, in particular:
  - Written documentation of the free and informed consent of the person (or his or her legal representative) according to the specific requirements prescribed in *An Act respecting end-of-life care* (Chapter IV, Section I). A specific consent form is available (MSSS website).
  - The assessment of the person's vital prognosis based on clinical judgment and in conjunction with members of the interprofessional team, taking into account, among other things, the extent of the disease, its rate of progression, the rapidity of functional decline, the person's ability to hydrate and eat.
- Discuss the decision to initiate CPS with the person and the choice of care setting in which it will be administered. If applicable, involve the informal caregiver as soon as possible in these discussions.
- If the person wishes to receive palliative sedation in a living environment[2]:
  - Ensure that the required resources (professional, material and technical) together with medical/nursing telephone support are available at all times and able to intervene in a timely manner if the situation deteriorates.
  - Take into account any limitations relating to the accessibility of certain molecules (supply, preparation, delivery times).
  - Ensure that the informal caregiver has been informed of the responsibilities associated with his or her role (see Information to be Transmitted in Section 3).
  - Verify that other people will be available to support the informal caregiver or to take over for this caregiver with the person receiving CPS, especially in a home setting.

[1] Usually corresponds to a level of care D if documented.

[2] Throughout this document, the term "living environment" includes all environments that lack direct access to a technical platform, e.g., a person's home, a long-term care centre (CHSLD), a palliative care hospice.

1. HEALTH STATUS ASSESSMENT

1.1 Health history

Inquire about the presence of any of the following concomitant medical conditions (to guide the choice of pharmacological treatment or mode of administration):

- hepatic impairment (see Precautions section of Table 2.4);
- risk of convulsions (history of convulsions or brain metastases) (see section on Major Adverse Reactions in Table 2.4);
- anasarca (see Principles of Treatment in Section 2.2);
- severe thrombocytopenia (see Principles of Treatment in Section 2.2);
- clinical Parkinsonism (see Precautions section in Table 2.4).

Look for the presence of an implantable cardiac defibrillator (ICD).

1.2 Lifestyle habits

Inquire about:

- any history of alcohol use disorder[3];
- regular and concurrent use of other psychoactive substances (e.g., cannabis, opioids).

1.3 Signs and symptoms

Look for at least one of the following symptoms:

- Pain
- Dyspnea
- Abundant bronchial secretions
- Respiratory or hemorrhagic distress
- Delirium
- Agitation
- Nausea
- Vomiting
- Convulsions
- Psychological or existential distress[4]
- Other refractory condition

Describe any such symptom(s), as well as the intensity and tolerability of the suffering caused.

1.4 Treatment history

Assess the refractory nature of the symptom(s) identified in Section 1.3 (involve interprofessional team members as needed):

- Verify that previous treatment trials were carried out under appropriate conditions;
- Verify that no other treatment options are available or considered acceptable in the situation, after discussion with the person or his or her legal representative (i.e., no other treatment options will be able to provide adequate relief, in a timely manner, without unacceptable side effects or complications for the person being treated).

[3] Benzodiazepine tolerance may be a consequence of regular benzodiazepine use or an alcohol use disorder.

[4] Exercise caution in assessing the refractory nature of psychological or existential distress. To be considered refractory, existential distress must resist special attention and a well-conducted multidimensional therapeutic approach (listening, spiritual and religious support, psychotherapy, pharmacotherapy, etc.) involving contributions from several care providers.

For guidance on the choice of pharmacological treatment, inquire about:

- Regular and concurrent use of benzodiazepines[5];
- Regular and concurrent use of other psychoactive substances (e.g., opioids, antipsychotics, antidepressants, medical cannabis);
- A history of a severe allergic reaction or significant intolerance to the administration of one of the drugs (or other ingredients in the injectable formulation) suggested in Section 2.

2. THERAPEUTIC APPROACH

2.1 Treatment goal

- To **quickly and completely** relieve the refractory symptom(s) identified by inducing **deep and continuous** sedation, which will be maintained until the person's death:
  - Unlike medical assistance in dying, palliative sedation does not have the goal or effect of causing the person's death.

2.2 Treatment principles

- **Dose adjustments should be made as soon as possible**, taking into account the properties of the drugs being administered (see Table 2.4) in order to relieve suffering quickly and completely. Additional doses of sedative agents should generally be provided so that the healthcare team can quickly manage inadequate sedation while waiting to contact the prescriber to adjust the regular medication.
- Drugs should preferably be administered subcutaneously, with IV administration reserved for situations where the efficacy of the SC route may be in doubt (e.g., partial or absent response, anasarca or severe thrombocytopenia).
- Two agents of the same therapeutic class should not be combined.
- When administering a combination of several agents, each agent should preferably be administered in a separate infusion in order to titrate them independently, thereby maximizing sedation and reducing adverse effects. If several agents are combined in the same infusion, verify compatibility and stability of the drug combinations with the pharmacist.
- Scopolamine monotherapy is not indicated to induce deep sedation. However, it can be administered in conjunction with other sedative agents in the presence of bronchial rales, respiratory embarrassment, significant secretions or if sedation is inadequate.
- Opioids are not sedative agents *per se* and are therefore not indicated to induce deep sedation. However, they should be considered in conjunction with a sedative agent when pain and dyspnea are among the symptoms identified.

2.3 Prerequisites, depending on clinical situations

- If an ICD is being used, deactivate the "defibrillator" function. In a living environment, consider the various deactivation options for the ICD model by asking the manufacturer[6] or the facility's cardiac department.
- Discontinue all procedures that are not intended to maintain or improve the person's sense of comfort and continue treatments that contribute to symptom relief. For more details on continuing hydration and nutrition, see *Palliative Sedation at the End of Life: Practice Guidelines*.

[5] Benzodiazepine tolerance may be a consequence of regular benzodiazepine use or an alcohol use disorder.

[6] In some cases, the device could be disabled remotely.

2.4 General information on pharmacological treatment

The general information on pharmacological treatments presented below is not exhaustive.

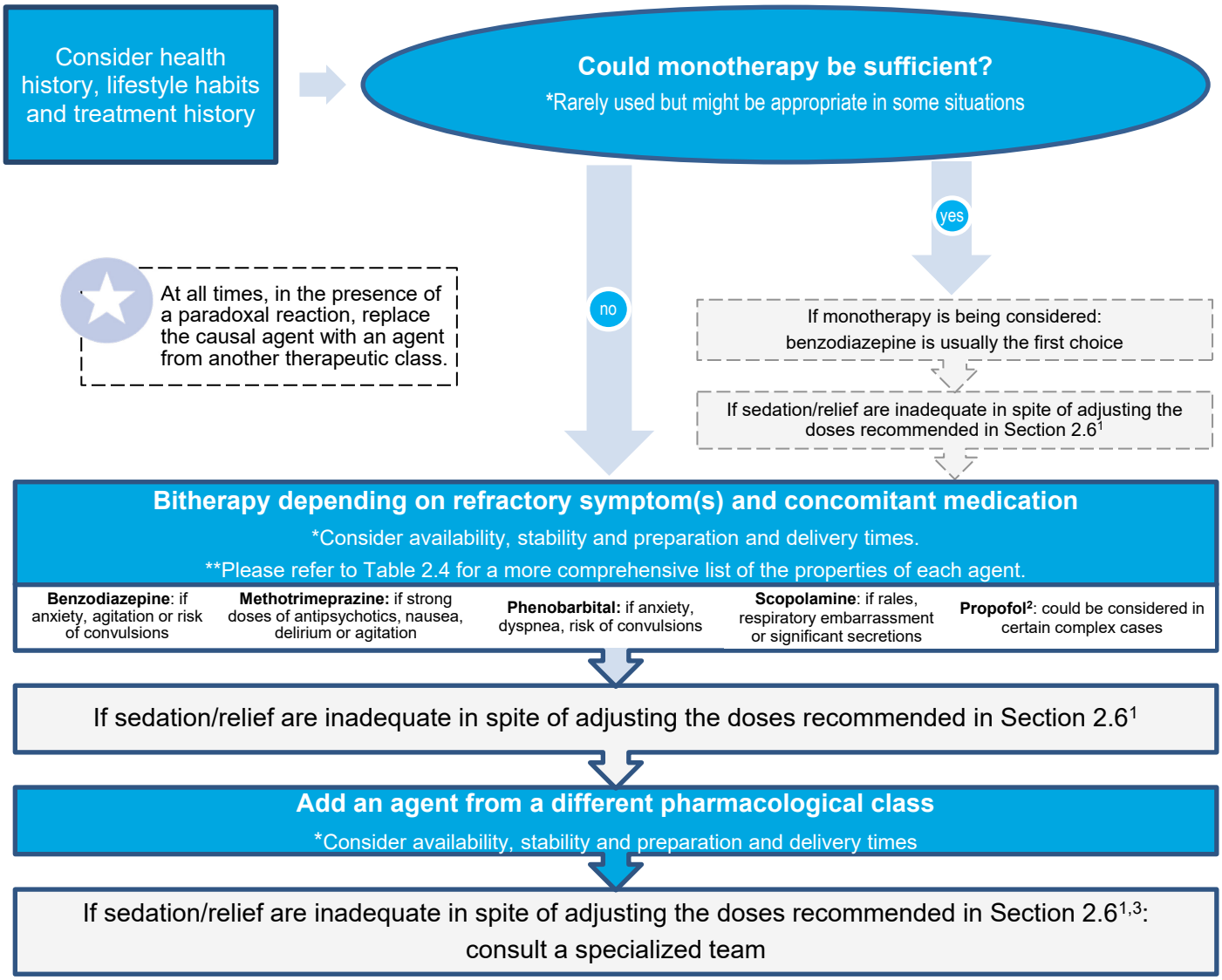
Class	Benzodiazepines		Antipsychotics	Barbiturates	Anaesthetics	Anticholinergics
Molecule and possible route of administration	**Midazolam (IV or SC)**	**Lorazepam (IV or SC)**	**Methotrimeprazine (IV or SC)**	**Phenobarbital (IV or SC)**	**Propofol (IV)**	**Scopolamine (IV or SC)**
Properties	Sedative Hypnotic Anxiolytic Amnesic Anticonvulsant		Sedative Antipsychotic Anxiolytic Antinausea	Sedative Hypnotic Anticonvulsant	Sedative Hypnotic Anticonvulsant Antinausea	Sedative Anticholinergic Antinausea
Main refractory symptoms to consider when choosing a molecule	Agitation Anxiety Convulsions Delirium Dyspnea		Delirium accompanied by pre-terminal confusion or agitation Hallucinations Nausea and/or vomiting	Agitation Convulsions	Agitation Convulsions Delirium Nausea and/or vomiting	Respiratory embarrassment Bronchial rales Significant secretions
Onset of action	1-5 min. (IV)	6-10 min. (IV)	–	5 min. (IV)	30-60 seconds	–
	5-15 min. (SC*)	15-30 min. (SC*)	20-40 min. (SC*)	20-60 min. (SC*)	–	45 min. (SC*)
Duration of action	30-80 min.	6-8 hours	4 hours (SC*)	10-12 hours	3-10 min.	3-6 hours (SC*)
Half-life	3-4 hours	10-20 hours	15-30 hours	53-118 hours	0.5-7 hours	9.5 hours
Contra-indications	A history of allergic reaction or intolerance to the product or other ingredients in the injectable formulation					
Administration precautions	–		• Potentially irritating drug if administered SC • Very severe hepatic impairment: reduced doses could be considered • Clinical Parkinsonism	Very severe hepatic impairment: reduced doses could be considered	Administration possible only in an institutional or specialized setting	–
Main adverse effects	Tolerance (increased doses may be required over time) Paradoxical reaction (agitation, behavioural disorder, aggressiveness) Respiratory depression		Extrapyramidal effect Anticholinergic effects† Lowering of the seizure threshold in an overdose situation	Paradoxical reaction Respiratory depression	Respiratory depression Negative inotropic effect Injection site pain	Anticholinergic effects with secondary agitation†

* The pharmacokinetics of the subcutaneous route is extrapolated from the intramuscular route.

† The most common adverse effects related to anticholinergics are as follows: dry mouth, urinary retention, confusion, exacerbated delirium.

2.5 Choice of pharmacological treatment

! The following algorithm was developed to support decision-making regarding the choice of treatment. However, it does not replace clinical judgment.



[1] Dose adjustments should be made as soon as possible, taking into account the properties of the medication used (Table 2.4).

[2] Propofol should be administered only in an institutional or specialized setting.

[3] If no other option is available, a hospital transfer may ultimately be necessary for people who receive continuous palliative sedation in a living environment.

2.6 Dosage

Reminder: Health history, lifestyle habits and treatment history should be considered when selecting the initial dosage. For example, a patient naïve to these agents could receive doses near the lower end of the range while a patient who was already receiving them on a regular basis could be given doses closer to the higher end.

Intermittent administration	Continuous administration	Consider adding a sedative agent starting from a dose of[1]	Maximum dose[2]
Midazolam (IV or SC)			
5 mg regularly every 2 hours[3]	Loading dose: 5 to 10 mg Initial rate: 2 to 5 mg/h Titrate from 1 to 2 mg/h as needed	10 mg every 2 hours or 5 mg/h	480 mg/24 hours
Lorazepam (IV or SC)			
1 to 2 mg regularly every 4 hours Upon initiation, the dose may be repeated after 30 to 60 minutes as needed.	⚠[4]	2 mg every 4 hours	48 mg/24 hours
Methotrimeprazine (IV or SC)			
12.5 to 25 mg regularly every 4 hours Re-assess after 45 to 90 minutes and repeat dose as needed. Use the sum of the two doses to establish the new regular dose.	Loading dose: 12.5 to 25 mg Initial rate: 3 to 6 mg/h Titrate in increments of 1 mg/h as needed	25 mg every 4 hours or 6 mg/h	300 mg/24 hours (max. 50 mg/dose)
Phenobarbital (IV or SC)			
30 to 60 mg regularly every 6 to 8 hours Upon initiation, the dose may be completed one hour later as needed.	⚠	120 mg every 6 hours	720 mg/24 hours
Propofol (IV) **_It is recommended that less experienced professionals consult a specialized team_**			
–	Initial rate: 1 to 3 mg/kg/h (17 to 50 mcg/kg/min.) Titrate 1 mg/kg/h every 10 to 15 minutes (17 mcg/kg/min.)	Consult a specialized team	
Scopolamine (IV or SC)			
0.4 mg every 4 hours	0.1 mg/h[5]	0.8 mg SC every 4 hours or 0.2 mg/h	9.6 mg/24 hours

⚠ Intermittent administration is preferred. However, continuous administration can be considered but with caution.

[1] If the initial dose chosen is the same as the dose at which an additional agent should be considered, then a combination of agents may be appropriate.

[2] Maximum doses are indicated for informational purposes. The use of higher doses may be necessary and acceptable in some situations, based on clinical judgment.

[3] Given the short half-life of midazolam, continuous administration is preferred. However, intermittent administration of midazolam may be relevant, particularly when end of life is imminent or in an urgent situation while waiting to access an infusion.

[4] IV infusion of lorazepam is not recommended because of its long half-life and the risk of complications associated with the accumulation of its solvent (e.g., tubular necrosis, lactic acidosis).

[5] Although no contraindications have been identified for continuous IV administration of scopolamine, data on this subject are limited.

3. INFORMATION TO BE TRANSMITTED

Discuss the following with the person, his or her loved ones and the healthcare team:

BEFORE STARTING CPS

- Information about the person's health status and what loved ones should expect, including:
  - the natural course of the disease and the end-of-life process;
  - the treatment goal (**quick** attainment of sustained **deep** sedation until death);
  - the expected results and duration of treatment**;**
  - the monitoring procedures established.
- Information on the responsibilities associated with the informal caregiver role, including the minimum presence required with the person receiving CPS, particularly in the living environment, as well as the physical and emotional burden associated with care.
- With the progression of the disease and the approach of death, it is normal to feel many changing emotions (both for the loved ones and for the person being treated). It is therefore possible to:
  - feel growing fear, impatience, anxiety, irritability and sadness or even guilt and regret;
  - have a feeling of helplessness, confusion and loss of control over the situation;
  - experience mood swings between periods of denial, acceptance, hope and despair;
  - be worried and not always know what to do.
- If necessary, please consult the following information resources:
  - *Palliative and End-of-Life Care: A Guide for Caregivers*;
  - tools for loved ones;
  - videos for informal caregivers[7]**.**

AS SOON AS CPS IS STARTED AND THROUGHOUT THE PROCESS

- Information needed to reach the care team at any time, as well as situations for which the care team should be contacted.
- Available resources (e.g., system navigators, nurses, social workers, case managers, spiritual care providers) to support the informal caregiver in his or her role, if applicable, and facilitate the organization of services.
- Information about drug administration.
- Information on what to watch for:
  - signs of discomfort (e.g., agitation, awakening); it is important to remember that movements are possible and acceptable in CPS if no signs of discomfort are observed, as well as rales that are not a sign of discomfort;
  - main adverse drug reactions (see Section 2.4).
- Information on whether or not to continue certain forms of comfort care (e.g., hydration and nutrition, mouth care, hygiene care and more specific care such as for urinary catheters, drains, wound care and mobilization of bedridden individuals) and detailed information on how and when to provide such care.
- Information concerning the attestation of death in the home

[7] These videos are only available in French.

4. FOLLOW-UP

** The importance of interprofessional collaboration in this process should be emphasized.*

- In conjunction with the interprofessional team, ensure optimal management of the psychological and spiritual aspects of the person receiving CPS (and his or her informal caregiver, if applicable).

- Ensure that the person receiving CPS is regularly monitored by the interprofessional team or informal caregivers, depending on the setting, in order to quickly identify any change in his or her condition (e.g., adverse drug effects, signs of discomfort or awakening or complications).

  *In a home setting, ensure that experienced medical/nursing personnel are reachable for support by phone at all times (24 hours a day, 7 days a week) and are able to intervene on site if necessary.

- Regardless of the care setting, have the interprofessional team carry out the assessment of the person receiving CPS as described below.

Minimum frequency: to be adjusted based on changes in the condition of the person receiving CPS	
Until adequate relief and sedation are achieved	Every 30 minutes
And then	At least 2 times a day * When continuous palliative sedation is given in a living environment, telephone follow-up could be used in place of the second daily assessment for individuals in stable condition. Follow-up frequency should also take into account the needs of the informal caregiver, if applicable.

Required assessments

- The person's sedation level ideally determined using the Richmond Agitation-Sedation Scale (RASS) (see Appendix I): the target score for achieving deep sedation is -4 or -5.
- Adverse drug reactions (see Section 2.4).
- Respiratory frequency (in the presence of bradypnea or heavy snoring, it may be necessary to adjust the medication).
- Level of relief from pain and other symptoms identified in Section 1.3, observing in particular the person's facial features and any signs of discomfort such as restlessness or moaning. Assessment grids can be used, as needed, to help evaluate pain relief. For example:
  - the CPOT scale (see Appendix II): the target score is 2 or less (a score greater than or equal to 3 is a sign of significant discomfort);
  - the Nociception Coma Scale (see Appendix III)*:* the target score is 10 or less (a score greater than 10 is a sign of significant discomfort).
- If necessary, a sample monitoring form for documenting these assessments is available in the appendix of Palliative Sedation at the End of Life: Practice Guidelines.

! CPS administration must be reported using the CPS report form to the following officials, in accordance with the provisions of ***An Act respecting end-of-life care***:

- Prescribers practising in an institution report to the facility's CPDP;
- Prescribers practising outside the facility report to the CMQ.

5. SITUATIONS REQUIRING SPECIAL ATTENTION, REASSESSMENT OR FURTHER INVESTIGATION

- Inadequate sedation or relief in spite of administering the doses recommended in Section 2.6.
- Adverse effects or hypersensitivity (see Section 2.4).
- Death of the person in a complex family situation or any situation that would require psychological follow-up:
  - Supporting the family, loved ones and interprofessional team members during the bereavement period;
  - If necessary, referring family members to another resource such as their local community service centre (CLSC) or a community group that offers bereavement follow-up.

REFERENCES

This protocol is based on the latest scientific data and best practice recommendations which were enhanced with contextual information and experiential knowledge provided by Quebec clinicians, experts and patients. For further details on the process used to develop this medical protocol and to consult the references, see the report in support of this protocol.

APPENDIX I RICHMOND AGITATION-SEDATION SCALE (RASS)

Adapted from the Richmond Agitation-Sedation Scale (RASS)

Source: *Palliative Sedation at the End of Life: PRACTICE GUIDELINES*. Société Québécoise des Médecins en Soins Palliatifs (SQMDSP) and Collège des Médecins du Québec (CMQ), 2016.

Level	Description	Definition
+ 4	Combative	Combative, violent, immediate danger to the team
+ 3	Very agitated	Pulls to remove tubes and catheters and/or aggressive behaviour towards the team
+ 2	Agitated	Frequent non-purposeful movements and/or fights the ventilator
+ 1	Restless	Anxious or apprehensive, but movements purposeful, infrequent, non-vigorous, non-aggressive
0	Alert and calm	
- 1	Drowsy	Not fully alert but sustained awakening to voice (eye contact > 10 s)
- 2	Light sedation	Briefly awakens with eye contact to voice (eye contact < 10 s)
- 3	Moderate sedation	Any movement (e.g., eye opening) to voice but no eye contact
- 4	Deep sedation	No response/movement to voice, but any movement to physical stimulation (non-nociceptive shaking/rubbing of shoulder or sternum)
5	Unrousable	No response/movement to either voice or physical stimulation (non-nociceptive shaking/rubbing of shoulder or sternum)

APPENDIX II CRITICAL-CARE PAIN OBSERVATION TOOL (CPOT)

Indicator	Score (0 to 8)		Description
Facial expression	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Brow lowering Mild nasolabial folds Narrowed eyes Or any other change in facial expression (e.g., suddenly opens eyes, tears flow when mobilized)
	Grimacing	2	Brow lowering, nasolabial folds Eyes closed and narrowed Mouth may be open Patient may bite endotracheal tube
Body movements	Absence of movements or normal position	0	Immobile, does not move (this does not necessarily mean absence of pain) Normal position (movements not directed towards pain or not performed to protect from pain)
	Protective movements	1	Slow, cautious movements Touches or rubs pain site Extends hand to reach pain site, tubes Touches tubes Tries to attract attention by tapping foot or hands Decortication, decerebration
	Agitation	2	Pulls at tubes Tries to sit up in bed Constantly moves Does not cooperate Pushes staff away Attempts to crawl over the bed rails
Interaction with ventilator (intubated patients)[8] or **Vocalization**	Tolerates ventilation or movements	0	Alarms not activated, patient is calm
	Coughs but tolerates mechanical ventilation	1	Coughs but remains calm; alarms may go off but stop spontaneously
	Fights mechanical ventilator	2	Asynchrony: blocks his or her breathing, constantly triggers alarms
	Expresses himself or herself normally or remains silent	0	Expresses himself or herself normally or remains silent
	Moans, sighs	1	Moans, sighs
	Screams, cries	2	Screams, cries
Muscle tension Assessment by passive flexion and extension of upper limbs at rest or assessment when patient is mobilized	Relaxed	0	No resistance to movements, normal muscle tone
	Tense, rigid	1	Resistance to movements
	Very tense or rigid	2	Difficulty completing movements or inability to do so Clenches his or her fists

Source: GÉLINAS *et al.*, 2015, *Le CPOT Évaluer la douleur de patients adultes inconscients [Assessing pain in unconscious adult patients]*

[8] This indicator is not relevant to CPS.

APPENDIX III PAIN RELIEF SCALE

Adapted from the *Nociception Coma Scale* (NCS)

Source: VINAY *et al*. *Médecine Palliative: Soins de support – Accompagnement – Éthique*, 2012. 11: p. 102-109. [Palliative Medicine: Supportive Care – Guidance – Ethics]

Observations	State	Points
Face	Relaxed	1
	Tense	2
	Strained	3
	Grimacing	4
Tears	Absent	1
	Present	2
Moaning	Absent	1
	Present	2
Limbs	Relaxed	1
	Stiff	2
	Rigid	3
Movements	Calm	1
	Fidgeting	2
	Agitated	3
	Very agitated	4
	Combative	5
Respiration	< 19	1
	≥ 19	2
Pulse	< 110	1
	≥ 110	2