THE CHAMPLAIN REGION
PALLIATIVE SEDATION THERAPY
CLINICAL PRACTICE GUIDELINES AND PROTOCOLS

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Committee responsible for developing guidelines:

Co-chairs: Dr. José Pereira MD (University of Ottawa, Bruyere and TOH)
Ms. Debbie Gravelle APN (Bruyere and Palliative Community Consult Service)
Members: Ms. Sally Tierny (Pharmacist, Bruyere)
Ms. Lynn Kachuik APN (TOH)
Dr. Louise Coulombe MD (Community Palliative Care Team)
Dr Shirley Bush, MD (Bruyere)

External Review committee:
Dr. A Dick Hospice Renfrew
Dr.M J Randlatt- Cornwall Hospice
Dr. K Bmiji – Palliative care division
Dr. A Borduas- Hawkesbury Hospital
Dr. R Leiva- Bruyere Continuing care
Mr. A Lauzon- Palliative Care Cordinator- Cornwall Hospital
Dr. J Scott- Palliative Care Division
Dr. P Lawlor- Palliative Care Division
Dr. M Chasen- Palliative Care division
Dr. R Gilbert- Family Physician- Pembroke
Ms. E Brine- PPSMCS Renfrew County
Dr. R Mahtani- Palliative Care Division
Dr. P Hall- Palliative Care Division
Dr. T Tucker- Palliative Care Division

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Persons responsible for revisions: Champlain Palliative and End-of-Life Network

IMPORTANT NOTE

Palliative Sedation Therapy (PST) is to be considered only as a last resort option when all other treatments have failed. The gravity of the decision to sedate is emphasized. It should not be confused with sedation that results as an adverse effect from treatment of a symptom or problem such as delirium. PST begins when the intention or goal of treatment is to achieve sedation in a patient who is at the end of life (terminal phase) and has a symptom that cannot be controlled. A specialist palliative care team needs to be involved in the decision-making process prior to initiating PST.

Process to revise guidelines:
The Champlain Palliative and End-of-Life Network provided the mandate to develop the clinical guidelines on PST for the region and approved the process. The guidelines are based on a consensus process involving representatives from various disciplines and settings, including palliative care specialists and non-specialists with significant experience in palliative care. The initial drafts were prepared by an interprofessional committee representing various disciplines and settings. Key articles were identified in the international peer reviewed literature related to the topic. Local, national and international guidelines were also reviewed. These provided valuable input into the development of these guidelines. The committee met on five occasions in 2009 and discussed in detail the various aspects of PST and drew up, by consensus, the current version of the guidelines.

An advisory regional council on PST is being established and the initial draft developed by the core committee is being sent to council members for their review and further input. Once further input is received from this group, the core committee will meet to review the suggestions from the advisory council and discuss the incorporation of these suggestions in a final version of the guidelines.

INTRODUCTION

The interprofessional community of palliative care professionals in Ottawa and the Champlain Region recognizes the importance of palliative sedation therapy-related clinical guidelines in order to ensure that this therapy is applied appropriately and effectively. The clinical practice guidelines are divided into two sections:

A. **Palliative Sedation Therapy: General Guidelines**
   The general guidelines define palliative sedation therapy (PST) and describe the indications for PST and the criteria that need to be in place before PST is initiated in a particular patient. They also highlight some key ethical considerations and provide guidelines for monitoring patients receiving PST . The guidelines apply to a variety of settings of care, including in-patient medical and surgical units, in-patient palliative care units, hospices, patient homes and nursing homes.

B. **Palliative Sedation Therapy: Medication Protocols**
   This section of the Guidelines relates specifically to the medications used for achieving palliative sedation therapy. These include methotrimeprazine, midazolam, phenobarbital (or phenobarbitone), and propofol. It is recognized that some of these drugs may be used in palliative care for indications other than PST; methotrimeprazine for controlling the symptoms of delirium and midazolam and phenobarbital (or phenobarbitone) for controlling seizures. In the context of PST, they are used with the intent of inducing sedation indefinitely where the symptom is deemed to be intractable and irreversible. It is also recognized that the realities of different settings (e.g. in-patient palliative care unit versus patient's home) influence the medication and protocol used.

Goal of the Guidelines

The primary goal of the guidelines, including the medication protocols, is to ensure effective, safe and appropriate use of palliative sedation therapy in the Champlain region. They also aim to enhance standardization of practice, as it relates to PST, in the region. It is recognized that there exists considerable literature on PST. The goal of these Champlain Guidelines is not to reflect the many varying points of views pertinent to this topic, but rather to provide only the essential elements as identified through the consensus process for the region. It is anticipated that this succinct approach will enhance daily clinical practice.

PALLIATIVE SEDATION THERAPY: GENERAL GUIDELINES

DEFINITIONS

"Palliative Sedation Therapy" (PST)

The Champlain Region defines "Palliative Sedation Therapy" as the intentional continuous induction of a reduced level of consciousness in order to relieve a refractory symptom or symptoms in a patient who is at the end of life (i.e. last days and weeks). The intent is to relieve suffering and not to hasten death. ***PST is therefore not euthanasia.***

The term "palliative sedation therapy" is preferred. PST constitutes an ethically acceptable therapeutic option when done according to appropriate guidelines in a very small select group of patients that meet the criteria for PST. PST is practiced within the holistic framework that constitutes palliative care.

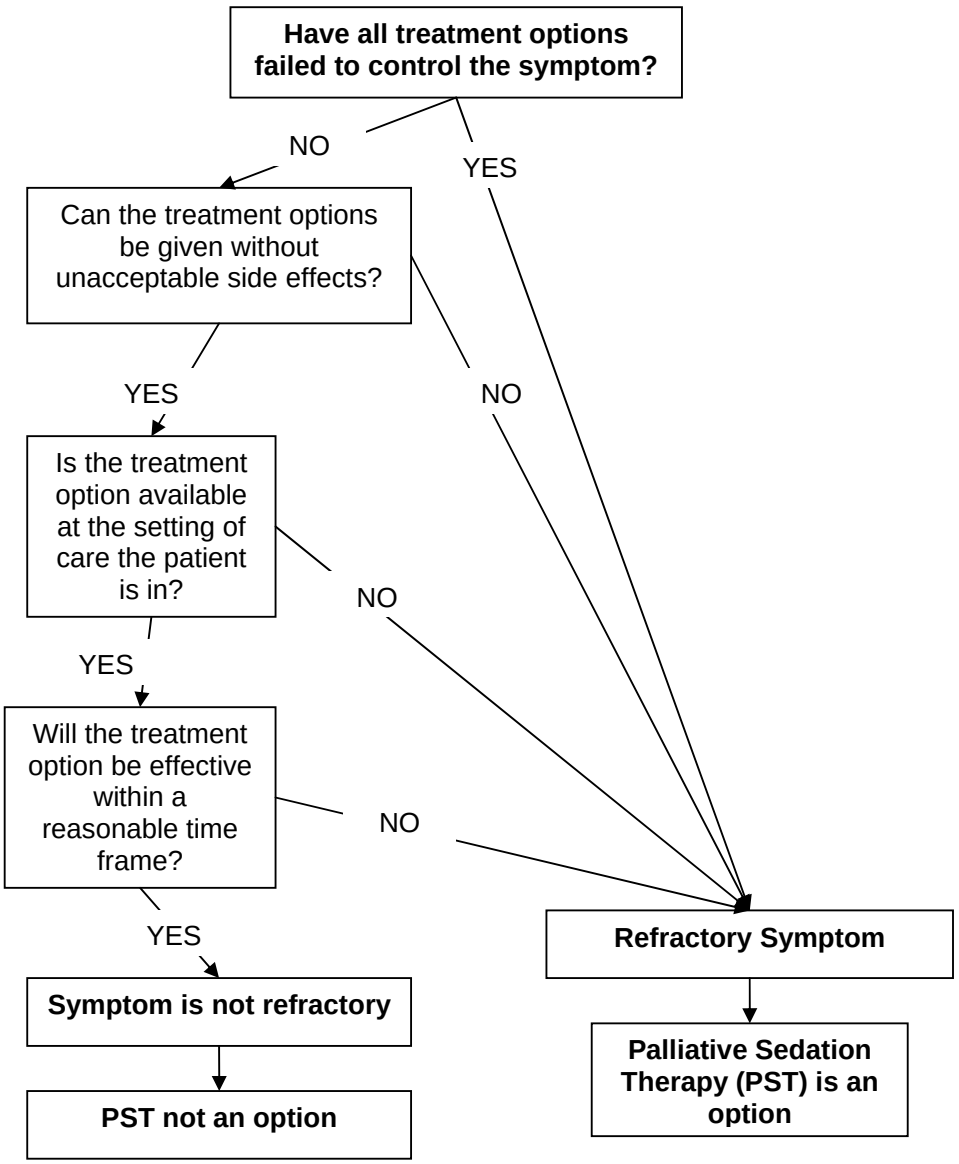
Although PST is usually associated with deep levels of sedation, some patients may find relief of their intractable symptom at light or moderate levels of sedation. Given the variations in the clinical presentation of the problem and the broad inter-individual variability in response to the medications used in PST, doses of the medication are usually titrated to achieve the required goal, namely comfort and alleviation of the refractory symptom. The aim is to use the lowest dose of medication that achieves this goal. In some patients, symptom relief may be achieved at light levels of sedation with small doses of medication. In others, comfort can only be achieved at deeper levels of sedation. In some this is achieved with small doses of medications, while others require higher doses. Titration of the dose to achieve the goal is therefore essential.

Pharmacological sedation is not to be confused with the natural process of dying and progression of disease processes.

Refractory/ intractable symptom

The presence of a refractory (intractable) symptom is a core requirement for initiating PST. A "refractory or intractable" symptom is defined as a symptom for which there is no appropriate treatment available within the given time frame that the patient can tolerate or for which the risk-benefit ratio is not acceptable to the patient. (de Graeff et al. J Pall Med 2007) A symptom is deemed intractable if all other measures usually used to control the symptom have failed.

Figure 1: Deciding whether or not a symptom is refractory



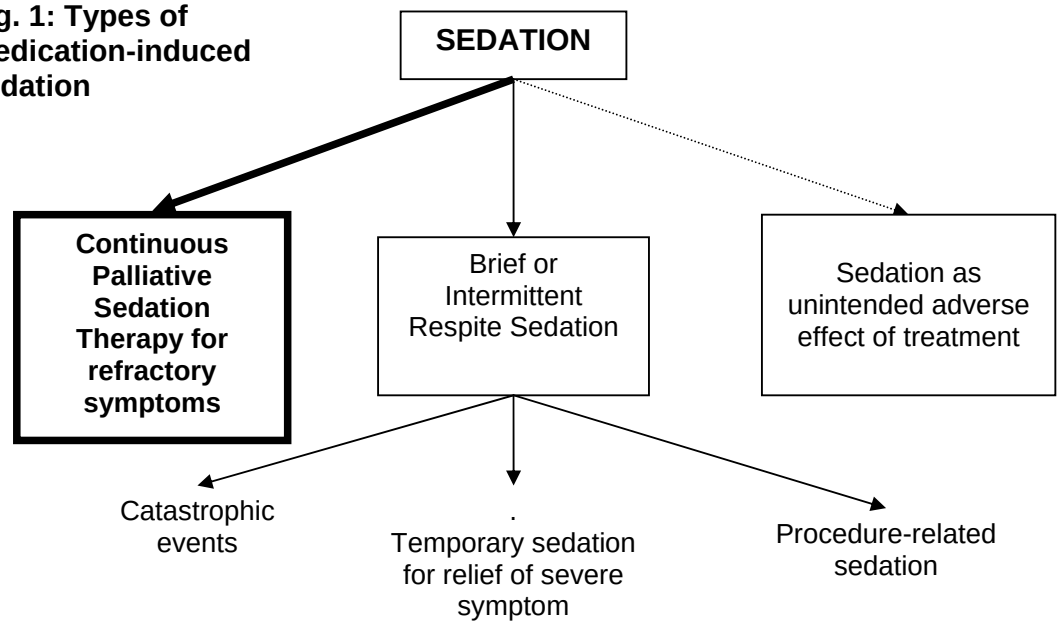
Sedation that is not considered "Palliative Sedation Therapy".

For the purposes of this set of guidelines, PST (often referred to simply as "palliative sedation") should be distinguished from other forms of sedation (see Figure 1):

- Temporary use of sedation where the underlying causes of the symptom are reversible and attempts are being made to treat these causes. Once it is felt that these underlying causes have been reversed, sedation is withdrawn. If the causes are not reversed and a decision is made to continue with sedation indefinitely, sedation then by definition becomes PST and should be documented as such.
- Respite temporary sedation (e.g. where a patient receives deep sedation overnight to sleep and the sedation is withdrawn in the morning)

- Sedation as an unintended adverse effect of treatment (e.g. opioid-related sedation, sedation from the use of adjuvant analgesics, anxiolytics or anticonvulsants)
- Sedation by the temporary use of neuroleptic medications when managing delirium with medications such as haloperidol, methotrimeprazine and the atypical neuroleptics while attempts are being made to address the causes of the delirium (Chater, 1976, Weissman, 2002)
- Procedure-related sedation (e.g. sedation for dressing changes)
- Sedation intended to hasten death (this is euthanasia)

Fig. 1: Types of medication-induced sedation



It is also important to recognize that increasing sedation and loss of consciousness are also natural end-of-life phenomena. This natural dying process may be responsible for somnolence and reduced levels of consciousness in patients who on medications such as opioids or neuroleptics.

INDICATIONS FOR PALLIATIVE SEDATION THERAPY

Non controversial indications:

- Intractable Dyspnea
- Intractable Delirium
- Intractable Seizures
- Intractable Pain
- Intractable other symptoms

Controversial indications: (to be decided on a case-by-case basis but should generally be avoided):

- Existential/spiritual suffering
- Psychological suffering (e.g. fear of the future wish for PST to avoid future suffering)

It would be inappropriate to initiate PST when, in the absence of a refractory symptom, a patient requests it to avoid potential future suffering or wants it so that he/she can sleep through the time left.

An interprofessional specialist palliative team that includes specialist palliative care physicians and nurses, and a psychologist, chaplain and social worker would need to assess whether or not a psychological, spiritual, existential or social source of suffering is deemed refractory. It is also recognized that the assessment and management of these sources of suffering take longer and are often more complex than that for physical symptoms.

CRITERIA AND PROCESS

Criteria
Each of the following criteria needs to be in place prior to considering PST:

1. A progressive, incurable illness is present with a limited life expectancy. In all but the most unusual cases death must be imminent within days
2. The presence of a refractory/intractable symptom or symptoms
3. All attempts have been made to control symptoms using other interventions.
4. Informed consent of the patient or his/her surrogate decision maker must be obtained and documented.
5. A "Do not resuscitate" (DNR) order is in effect; i.e. the patient agrees to the team "Allowing a natural death" (AND) to occur. This must be clearly documented.

Process
In addition to the above criteria, the team must undertake the following critical process steps before PST is initiated:

1. All criteria are met
2. The primary attending care team shall ensure that a palliative care specialist team is consulted to review the case and ensure that all other interventions have been considered.
3. The criteria and rationale for considering and/or initiating PST are documented in the patient chart.
4. In addition to discussing PST and explaining what it is, a discussion also occurs with the patient or his/her surrogate decision maker regarding hydration and nutrition (or medically assisted hydration and nutrition). Where death is imminent, artificial nutrition and hydration may be withdrawn or withheld. This should however be addressed on a case-by-case basis.

OTHER CONSIDERATIONS:

Medically Assisted (Artificial) Hydration and/or Nutrition
The gradual cessation of voluntary intake of fluids is often an indication of approaching death. The vast majority of patients have virtually ceased eating and drinking by the time PST is considered. Artificial hydration or nutrition is considered futile treatment, and therefore a burden rather than benefit, in patients who are imminently dying.

If the patient is competent and still able to take fluids and food himself/herself, the physician must discuss with the patient and his family the consequence of initiating moderate or deep, continuous sedation on the ability of the person to take oral fluids or flood himself or herself. . If the patient expresses a strong and persistent wish to continue taking fluids and/or food by mouth, then light, intermittent sedation may be considered to allow him/her to continue taking fluids. Alternatively, artificial hydration (by hypodermoclysis) may be continued in these situations. If a patient already has a PEG tube in place, hydration or feeding may be considered through the tube. However, it would not be considered appropriate to insert a feeding PEG tube to provide artificial feeding or hydration in a patient requiring PST.

Bladder Catheterization
Patients who are moderately to deeply sedated may require catheterization once they are sedated. If not, the team must regularly assess whether or not the patient has urinary retention.

Other medications
Continue a patient's analgesic regimen if he/she was requiring it prior to the initiation of PST. However, if a patient was on an oral analgesic (including opioid) regimen prior to the PST, then switch it to a parenteral route.

Review the patient's medications and discontinue any redundant medications (e.g. antidepressants) if the patient is receiving moderate to deep sedation.

Ethical considerations
Palliative sedation therapy, when applied appropriately according to accepted guidelines, is an ethically justified therapeutic option. The intent is to alleviate the suffering caused by a refractory symptom. It is also noted that PST is applied in the context of a patient who is imminently dying, so a death is expected.

Recent studies show that if used appropriately, PST does not invariably shorten life. However, it may be possible that in some cases PST may shorten life. In these cases, the intent should be to alleviate the symptoms, not shorten life. If the intent is to shorten life, then it would be considered euthanasia, not PST. In the event that it may shorten life where this result is not the intent, PST is considered acceptable and is not euthanasia.

PALLIATIVE SEDATION THERAPY: MEDICATION PROTOCOLS

Midazolam (Versed™) is the drug of choice for PST because of its potency, short half life and the ability to titrate the dose up or down fairly rapidly. It also has amnesic properties. The subcutaneous route (SUBQ) is usually preferred, although the intravenous route may be considered if a patient already has a central /PICC line. For PST, midazolam is usually administered by a continuous subcutaneous or intravenous infusion (CSCI or CIVI), particularly if sedation is expected to continue for more than one or two days. However, it is recognized that in some settings, such as a patient's home where access to a pump for CSCI is not readably available, midazolam may be administered on a PRN hourly basis.

Methotrimeprazine (Nozinan™) is another medication that is often used for PST. It may either be used as the first line agent (at high doses- see below) or as an adjuvant added to midazolam if midazolam alone is not optimally effective.

Phenobarbitone is usually not considered a first-line medication for initiating PST. However, in certain circumstances, it may be considered as first line, particularly if the patient has been experiencing seizures or the patient is in a setting where there is no access to a pump for continuous infusion of midazolam or there is no access to methotrimeprazine. It may also be considered first line if there is no access to a midazolam and the patient has a history of extrapyramidal side effects to methotrimeprazine. Otherwise, phenobarbitone may be considered as a second line, added to midazolam, if midazolam is not effective.

Opioids should not be used for PST therapy. They are ineffective in this role. There exists a high risk of neurotoxicity and/or respiratory depression if these medications are titrated too rapidly, which may be required in PST.

MEDICATION PROTOCOLS FOR PST

Goal:

1. To identify the lowest possible dose of medication and lightest level of sedation that achieves comfort. In some cases comfort may be achieved with light to moderate sedation while others will require deeper levels of sedation. The doses required to achieve these various levels of sedation may vary considerably between individuals. A patient may achieve a light level of sedation with a small dose of midazolam, while another may become deeply sedated with a small dose of the same drug.

1st LINE (Initiating PST)

Option 1:(Midazolam by continuous infusion). This is the preferred option.

1. Administer a loading dose of Midazolam: 2.5 mg or 5mg SUBQ or IV stat
2. Then start a continuous infusion of midazolam at 0.5 or 1 mg/hour SubQ or IV infusion via an infusion pump.
   - Titrate up (or down) by 1 mg/hr every 30 minutes if needed until the goal is achieved.* The usual dose required to achieve PST is between 1mg/hr and 6mg/qhr.

- The initial titration may need to be rapid (i.e. dose adjusted by 1mg/hr every 30 minutes until the patient is comfortable. (The short half life of a few minutes allows this. However, with long-term continuous administration, the half life may increase).
- Note: titration is influenced by the availability of clinical staff. In-patient palliative care unit, Midazolam infusions may be titrated every 30 minutes with the appropriate monitoring (see Patient Monitoring). This rapid titration may not possible in a home setting if there is no experienced nurse or physician available.

3. Once the goal is achieved, the dose is maintained.
4. Over time (usually many hours to days) the dose may need to be increased by titration (as above) to achieve an appropriate level of comfort as some patients may develop some tolerance to the midazolam.
   - A very small group of patients may experience a paradoxical effect to midazolam (i.e. agitation) to a maximum of 6mg per hour until goal is achieved.
5. If crises occur, may give a bolus dose of midazolam 2.5mg or 5mg q30 minutes PRN.
6. If doses of greater than 10mg /hr are required, then consider adding methotrimeprazine or phenobarbitone (preferred). See doses below.

Option 2 (Methotrimeprazine or Nozinan™)

1. Administer a Stat dose of Methotrimeprazine 25mg SubQ (12mg in a very small, frail individual)
2. Then follow up with methotrimeprazine 12.5-25mg SubQ q 8hrs and Methotrimeprazine 12.5-25mg SubQ q1hr PRN.
   - In most cases, the higher dose (25mg) is required if PST is the intent.
3. The dose may be increase to a maximum of 25mg SubQ q6 hrs to achieve the goal of PST.
   - If higher doses than this are required, consider switching to Midazolam (option 1; preferred) or adding phenobarbitone (see Option 3)

Option 3 (Phenobarbital)

1. Administer Phenobarbital 60 mg, 90mg or 120 mg SubQ or IV stat (the higher dose in a situation of extreme suffering where sedation is required more rapidly
2. Then start Phenobarbital 60 mg SubQ BID
   - May increase Phenobarbital to 120 mg SubQ TID until goal reached.
   - The maximum daily dose is 720mg in 24 hours.
   - Note that the half life of phenobarbitone is very long (53-118 hours). This makes it difficult to titrate rapidly and several days need to pass (to achieve steady state) before the full impact of a specific dosing regimen can be adequately assessed.

Option 4 (Midazolam SubQ PRN)

1. Consider this option as a short-term solution if midazolam is preferred but a pump is not available for continuous infusion.
   - Administer midazolam 2.5mg to 5mg SubQ q30 to 60min PRN.

- This is a temporary solution (12 to 24 hours)
- The problem with this approach is that the half life of midazolam is only a few minutes (9 to 13) and the duration of action is short.

2nd LINE (When 1st line approaches have failed or are suboptimal)

- In the case of failure or suboptimal PST with midazolam (Option 1), add phenobarbitone.
- In the case of failure or suboptimal PST with methotrimeprazine (Option 2), switch to midazolam.
- In the case of failure or suboptimal PST with phenobarbitone at optimal doses (Option 3), add midazolam.

3rd LINE

- If 1st and 2nd line options have failed, propofol may be considered.
- However, propofol is a powerful anesthetic agent and should only be considered as an absolutely last resort.
- It is extremely rare to require propofol.
- Special close monitoring of patients is required.
- Its use is limited to acute hospital settings. The hospital's guidelines on the use of propofol need to be adhered to.

TITRATION AND MAINTENANCE OF SEDATION

Titrate the medications to achieve the desired goal. This is the lowest dose possible that achieves the lightest level of sedation that has the patient comfortable. Over time, doses may need to be titrated up because of progression of the disease and its complications, or the development of tolerance to the sedative. Sometimes doses may need to be titrated down, particularly when it is apparent that the level of sedation is excessive for the goal desired (e.g light sedation is sufficient to control the symptom).

When the dose is found that achieves the desired goal (i.e. comfort), maintain the sedative at that dose for a day or two, unless further titration is required (see paragraph above). Then consider reducing the dose slightly to try and find the lowest dose that will achieve the goals. If the symptoms worsen, return to the previous effective dose of the sedative.

It is understood that some situations constitute a major crisis, requiring very rapid titration (e.g. intractable delirium in which the patient may harm himself or others, or stridor secondary to tracheal obstruction).

Note too that titration is also influenced by the availability of clinical staff. In an in-patient palliative care unit, midazolam infusions may be titrated every 30 minutes with the appropriate monitoring (see Patient Monitoring section). This may not possible in a home setting if there is no experienced nurse or physician available.

PATIENT MONITORING

The frequency of patient monitoring and the parameters to be monitored is influenced by the setting, circumstances and the availability of clinical staff.

Some parameters should be monitored routinely, while others are on a case-by-case basis. The parameters being assessed may also change over time.

Parameters that should be assessed routinely:

1. **Level of sedation**
   - Various clinical assessment instruments to assess the level of sedation are used in palliative care programs across the world. These include the Riker Scale, the Rudkin Scale and the Richmond Agitation Sedation Scale (RASS- attached as appendix). The use of such a clinical instrument standardizes the assessment method and provides physicians and nurses a standardized method of communicating about PST, assessing the effectiveness of treatments, and setting treatment goals.

   - ***This guideline recommends that the RASS be utilized to assess the level of sedation.***

2. **Level of comfort or discomfort**
   - Assess the degree to which the patient reports (if he/she is able to) comfort or discomfort. If the patient is unable to do so, the clinician or nurse must assess what they perceive the patient's level of comfort or discomfort to be.

3. **Airway patency and air entry** (if sedation is not being done for irreversible airway obstruction)
   - This is to avoid airway obstruction because of poor positioning of the patient or from vomiting. Reposition the patient and pull the jaw forward if there appears to be airway obstruction.

Parameters that may be assessed on a case-by-case basis:

4. Respiratory rate
5. Oxygen saturation
6. Bladder fullness
   - If not catheterized, do bladder ultrasound bid or tid if this is available. If not available, consider an in and out catheter daily to assess if urinary retention occurring.
   - If it is occurring, consider indwelling urinary catheter.
   - Note (Urinary retention can cause significant distress and sometimes prompt increases in sedation because of discomfort).

Respiratory rate and oxygen saturation should only be considered in exceptional cases. It is important to note that changes in respiratory rates and patterns, as well as reductions in oxygen saturation are normal end-of-life changes and will occur whether or not the patient is receiving PST. To titrate PST according to these parameters would therefore be inappropriate when death is imminent.

Any parameters that are assessed should be documented in the patient chart.

Frequency of monitoring

This may vary from setting to setting and the rapidity of titration of the medication.

	In-patient settings and Hospices	**Home, residential or long-term care facility setting**	
	Midazolam, Methotrimeprazine and/or Phenobarbitone	**Midazolam**	**Methotrimeprazine* and/or Phenobarbitone***
When initiating PST	Monitor every 15 minutes (and titrate the medication doses as required) until the goal of PST is achieved (comfort). Continue monitoring every 15 minutes until 1 hour has passed and the patient remains comfortable without requiring additional PRN doses or dose titrations up or down. Then monitor q 4hrs.	Monitor every 15 minutes (and titrate the medication doses as required) until the goal of PST is achieved (comfort). Continue monitoring every 15 minutes until 1 hour has passed and the patient remains comfortable without requiring additional PRN doses or dose titrations up or down. Then monitor q 8hrs. Patient must have sitter (eg, family member) present at all times and they need to be instructed to call team members if patient becomes uncomfortable and told about the signs of impending death.	Monitor every hour (and titrate the medication doses as required) until the goal of PST is achieved (comfort). Then monitor q 8hrs. Patient must have sitter (eg, family member) present at all times and they need to be instructed to call team members if patient becomes uncomfortable and told about the signs of impending death.
Maintaining PST	Then monitor q 4hrs.	Monitor q 8hrs. However, a team member must be available to respond immediately to any requests for reassessment by the patient sitter.	Monitor q 8hrs. However, a team member must be available to respond immediately to any requests for reassessment by the patient sitter.
Any dose adjustments made or additional bolus/PRN doses given	Restart monitoring q15min as above until the patient is comfortable and then q4hrs thereafter.	Restart monitoring q15min as above until the patient is comfortable and then q8hrs thereafter. Sitter must be present.	Restart monitoring q1 hr as above until the patient is comfortable and then q8hrs thereafter. Sitter must be present.
			* if these medications are used in conjunction with midazolam, then the monitoring suggested by the "midazolam" column applies.

DOCUMENTATION

Documentation of all the steps, medication changes, and assessments is imperative. This also includes the indications of initiating PST, consultations by a palliative care specialist service (a criteria for PST) and any discussions with the patient and/family or POA.

REGULAR REVIEWS OF PST ARE REQUIRED

PST should be reviewed regularly. If it appears that the patient is becoming more uncomfortable, reassess the patient for any causes for the discomfort that may have been missed or occurred since the last assessment (e.g. urinary retention). Regularly re-evaluate the need for PST- it may be possible to reduce or discontinue medications if the indications for PST have changed

IMPORTANT NOTES

1. Continue other symptom management measures, example opioid for pain and other comfort measures
2. Many family members and other team members experience significant distress when a loved one or patient is receiving PST. Provide them with emotional support and address any concerns they may have PST.

Modified Richmond Agitation Sedation Scale- Note: See attached PDF file for scale

NOTE: Contact the Champlain Regional Palliative Pain and Symptom Management Consultation Service at **1-800- 651-1139** to access palliative care experts who are available 24/7 for the entire Champlain Region

NOTE: Contact the Champlain Community Care Access Center at 613-745-5525 for supplies, equipment and assistance in obtaining the medication for your local pharmacies

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