Continuous palliative sedation therapy

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Although various definitions of *palliative sedation* exist, in general, it is accepted to be

> 1) the use of (a) pharmacological agent(s) to reduce consciousness; 2) reserved for treatment of intolerable and refractory symptoms; and 3) only considered in a patient who has been diagnosed with an advanced progressive illness.[1]

Although there are various types of sedation, including intermittent and respite sedation, and sedation as a side effect of medications such as opioids,[2] continuous palliative sedation therapy (CPST) at or near the end of life is the focus of this article. *Continuous palliative sedation therapy* is the use of ongoing sedation for symptom management, considered during the end of life when a patient is close to death (ie, within hours or days[3] or up to the last 2 weeks of life[1]) and continued until the patient's death. Palliative sedation should be a last resort for patients who have intolerable, refractory symptoms.[3] The term *refractory* describes a symptom that "cannot be adequately controlled despite aggressive efforts to identify a tolerable therapy that does not compromise consciousness."[4]

Health care providers, including family physicians, might be uncomfortable with CPST owing to unfamiliarity, differing terminology (eg, previous use of the term *terminal sedation*[5]), ethical and legal challenges,[6] and misconceptions about it being a form of euthanasia or physician-assisted suicide.[2,5,7,8] Consultation with a physician who has knowledge of and expertise in both symptom management and CPST is strongly advised when considering CPST.[1,6] Interprofessional team members, where available, can provide valuable input and important assistance with decision making regarding CPST.[3]

Two of the most common indications for CPST, nonreversible refractory agitated delirium and refractory and intolerable dyspnea,[2,3] are the focus of this article. The use of CPST when symptoms are nonphysical (eg, existential distress) remains controversial[2,9] and is not discussed. Similarly, initiation, continuation, or discontinuation of hydration and artificial feeding should be considered separate issues[3] and are also not discussed.

Owing to the lack of randomized controlled trials and the differences in clinical settings and types of medications used, there is no evidence for the recommendation of one particular medication over another for CPST.[2,3] However, sedating neuroleptic or antipsychotic medications and benzodiazepines are the most commonly used, while barbiturates and propofol are used only occasionally[1,3,7] In general, the lowest necessary level of sedation to provide adequate relief of suffering,[3] or *proportionate sedation*, should be implemented. It is important to note that opioids should not be used for palliative sedation, as the high doses required for sedation will inevitably lead to opioid-induced neurotoxicity and possible respiratory depression.[1,7] However, they should be continued if used to manage other symptoms such as pain and dyspnea.

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Case 1: nonreversible refractory agitated delirium

Mrs A.Z. is a 60-year-old woman with breast cancer and known metastases to bone and brain. She received whole-brain radiation therapy 2 months ago. Mrs A.Z. has a do-not-resuscitate order and an advanced directive with her husband, who is identified as the substitute decision maker (SDM). She is admitted to hospital with a 1-week history of headache and agitated confusion. She is started on haloperidol around the clock (ATC) and every hour as needed. At home, she was taking morphine ATC and as needed for pain (averaging 1 to 2 breakthrough episodes per day) and low-dose dexamethasone for her brain metastases. Although she has no signs or symptoms of opioid-induced neurotoxicity, in case her current opioid might be contributing to her confusion, it is rotated to hydromorphone. She appears to be well hydrated and is not hypoxic. There are no obvious sources of infection, such as pneumonia, urinary tract infection, or skin infections. Her medication list is reviewed for drug interactions; none is found. Bloodwork results, including complete blood count, blood glucose levels, liver enzyme levels, creatinine levels, and chemistry results, are within normal limits. She does not have hypercalcemia. Her delirium is likely related to her brain metastases. A trial of an increased dose of dexamethasone does not improve her agitation. Her delirium is ultimately considered nonreversible.

Over the next several days, her agitation increases such that she is yelling out and repeatedly crawling out of bed. Frequent as-needed doses of haloperidol are not effective in treating her refractory agitated delirium. A discussion is held with her husband about the option of CPST. Because Mrs A.Z. has a nonreversible refractory agitated delirium that is not responding to haloperidol,

methotrimeprazine is tried. Her husband provides informed consent after discussion of the intent and side effects of methotrimeprazine, which is then started ATC and every hour as needed for her agitated delirium. Details of the discussion with the patient's husband and the health care team are documented in her chart.

Unfortunately, Mrs A.Z. does not respond to increasing doses of methotrimeprazine. Discussions are held with her husband about changing the medication for sedation to a continuous subcutaneous infusion (CSCI) of midazolam. Dosing and proportionate titration are discussed with her husband. He is reassured, as before, that this will not shorten her life, but rather, Mrs A.Z. will ultimately die of her underlying disease. An infusion of midazolam is started and the dose is titrated proportionately to an amount that alleviates her agitation. Mrs A.Z.'s personal care, including mouth care and regular turning to preserve skin integrity, is maintained. She is regularly checked for level of consciousness and side effects of the sedation therapy. Mrs A.Z.'s hydromorphone is maintained, which is used for ongoing pain control (not for sedation). Her husband's questions are addressed, and he continues to receive support from the staff throughout the process. Mrs A.Z. dies 3 days after the CSCI of midazolam is started.

On palliative care units, 49% of delirium episodes are reversible.[10] More than 80% of patients with advanced cancer develop delirium or cognitive impairment in the last weeks before death.[10,11] Thus, consultation with a palliative care specialist can assist in screening for potentially reversible causes. It is important to look for and consider treatment of reversible factors, such as medication side effects, drug interactions, infections, metabolic disturbances (particularly hypercalcemia), and hypoxia. Informing the family or the SDM about the completion of the workup for reversible causes helps to emphasize that the delirium is nonreversible. It is essential to provide ongoing information and updates to the family or SDM about the intent and aim of sedation, how it will be administered, how the patient will be regularly observed, and what can be expected during the dying process.[3]

Case 2: refractory and intolerable dyspnea

Mr B.Y. is a 56-year-old man with non–small cell lung cancer with intrathoracic metastases. He was living in a rooming house, has no immediate family, and has a do-not-resuscitate order, but no advanced directive. He is admitted to hospice with increasing shortness of breath. Although he does not appear to be in respiratory distress, he rates his dyspnea as 8 out of 10 on a visual analogue scale. He is receiving 4 L/min of oxygen that was initiated 2 weeks ago at his residence. He reports a fear of increasing shortness of breath and subsequent "suffocation." Plans to further investigate for possible reversible causes of his dyspnea and subsequent treatment options are discussed with him, including the possibility of CPST as a last resort for symptom management if all other options are ineffective. Availability of a CSCI of midazolam is explained to him, including its intent and goal for symptom management. Because of his underlying disease and secondary intolerable dyspnea, the infusion would be expected to continue until his death. The discussion with input from the team is documented in his chart.

He is hypoxic according to a pulse oximetry assessment, and his oxygen is increased to 6 L/min. He is started on oxycodone ATC and every hour as needed for dyspnea, and a fan is directed toward his face. A chest x-ray scan reveals hilar lymphadenopathy, loss of right lung volume with no evidence of pneumonia, and a moderate-sized left pleural effusion. He undergoes a thoracentesis, but this fails to alleviate his dyspnea; 3 days after admission, he rates his dyspnea as 9 out of 10.

He is becoming tachypneic and is unable to recline in bed. His dyspnea rating is now 10 out of 10. His ATC oxycodone dose is increased, and upon his request, he receives increased doses of oxycodone for breakthrough episodes. During the next 2 days, his oxygen requirements increase to 15 L/min. His medication is rotated to hydromorphone without improvement in his dyspnea and he then starts receiving low-dose ATC methotrimeprazine. These measures fail to adequately alleviate his dyspnea. His tachypnea increases, and he is now tripoding with increased work of breathing and use of accessory muscles. He asks if anything else can be done to make him more comfortable and less short of breath, as he is no longer able to tolerate being so dyspneic. The option of CPST is discussed in detail with him again, including its intent and goal. He requests that a CSCI of midazolam be started, and it is titrated to effect to alleviate his dyspnea. His personal care is maintained, and he dies 1 day after starting the CSCI of midazolam.

As in case 1, health care providers should look for and treat potentially reversible causes of dyspnea that the patient agrees to have treated. Some of these might include pleural effusions, pneumonia, pulmonary embolism, or anemia. Irrespective of whether reversible causes are present or treated, oxygen might be started and adjusted accordingly. Similarly, opioids, if not already taken for pain, could be started and titrated to alleviate dyspnea. In addition, there is some evidence to support a trial of low-dose neuroleptic medications, such as phenothiazines, for dyspnea.[12] Unlike patients with nonreversible refractory agitated deliriums, patients with dyspnea considered for CPST are often alert and might be able to participate in decision making. They might be the ones to request CPST for dyspnea,

which they deem refractory and intolerable. Similar to patients receiving CPST for nonreversible refractory deliriums, patients with dyspnea require ongoing observation while under sedation, maintenance of personal care, and support for the family or SDM.

Dr Voeuk was a Year of Added Competency resident with the Edmonton Zone Palliative Care Program in Alberta at the time of writing. **Dr Oneschuk** is a physician consultant with the Edmonton Zone Palliative Care Program.

Competing interests
None declared

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BOTTOM LINE

- Continuous palliative sedation therapy (CPST) is indicated for intolerable refractory symptoms (distinguished from *difficult-to-manage symptoms*) in the setting of a terminal disease at the end of life (hours to days; up to 2 weeks). When considering CPST, consultation with a palliative care specialist is strongly recommended.

- A do-not-resuscitate order should be in place, and informed consent should be obtained from the patient or the substitute decision maker (SDM) after having a discussion about CPST. Family members or an SDM should be involved in decision making regarding CPST and should be advised of the intent and aim of CPST. Documentation of discussions about CPST with the patient, the family or SDM, and team members is essential.

- Neuroleptics and benzodiazepines, and less often barbiturates and propofol, are used for CPST. Proportionate titration should be used to reach the lowest dose of medication necessary to achieve sedation that provides relief of the symptoms for which the patient is receiving CPST. Opioids can be continued for symptom management, but should not be used specifically for CPST.

- A separate discussion regarding artificial hydration and feeding should occur before initiating CPST. During sedation, continued observation for patient comfort and provision of highly respectful and diligent personal care is essential.

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