

Pain Management and End-of-Life Care CME Program

Module 7

Registration: The registration page and test questions are at the end of this article. The questions must be answered and submitted to the CSA in order to receive the CME credit. The full text of each module of this CME program, along with references, also will be accessible through the CSA Web Site, www.csaahq.org, in the Bulletin/Online CME section and as part of the online *CSA Bulletin*.

Fees: This is a free service for CSA members. Non-members will be charged \$25 per CME credit hour. Your CME certificate will be mailed from the CSA office.

Availability: This module is available from September 30, 2005, until September 30, 2008.

Target Audience: California law now requires that every licensed physician complete 12 credit hours in pain management and end-of-life care by the end of 2006. This module fulfills one credit hour of CME toward that requirement. This program is intended for all licensed physicians, including anesthesiologists, residents, and physicians with an interest in pain management.

Faculty and Disclosures for Module 7:

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The California Society of Anesthesiologists Educational Programs Division designates this educational activity for a maximum of 1 credit hour toward the AMA Physician's Recognition Award.

Evaluation: An evaluation of Module 7 of this series is offered after the test questions. Please fill in your responses and return them to the CSA office.

Objectives: At the conclusion of this course, participants should be able to:

- Delineate the goals and methodology of palliative care;
- Discuss the ethical principles which define the practice of palliative care.

Resources: These materials, including questions, are offered online at the CSA Web Site at www.csahq.org. Instructions for the *Bulletin* version are on the registration page.

Palliative and End-of-Life Care

By Jack M. Berger, M.S., M.D., Ph.D., Associate Professor of Clinical Anesthesiology, Keck School of Medicine, University of Southern California

Dr. Berger earned his B.A. and M.S. degrees from the University of California Berkeley. After completing his Ph.D. degree in Environmental Medicine from New York University, he went on to Medical School at the University of Bologna in Italy. Returning to the United States, he completed an anesthesiology residency and became board certified in 1984. In addition, Dr. Berger received a certificate of extra qualification in pain management from the American Board of Anesthesiology. He has worked in private practice anesthesia as well as pain management since 1981. For the last 10 years he has been an Associate Professor of Clinical Anesthesia at the Keck School of Medicine of the University of Southern California in Los Angeles, serving as the director of all pain management services from 1995-2000 and, more recently, as the director of regional anesthesia residency training. From 1997-2000 he was the director of symptom management and palliative care at LAC+USC Medical Center working under a private grant to demonstrate that palliative care could be provided in an urban hospital that served primarily an indigent and uninsured population. Dr. Berger lectures throughout the country on pain management, is well published, and has been a visiting professor and scholar at the Cleveland Clinic, University of Oxford, and Memorial Sloan Kettering Medical Center.

Palliate: To lessen, ease, make less severe without curing. *It doesn't mean do nothing, nor does it mean that you can't operate. Some operations such as a bowel diversion, a tracheotomy or a PEG are palliative.* William Osler is quoted to have advised physicians in 1904, "**Do the kind thing, and do it first.**" What could be more kind than controlling pain?

William Osler, again in his presentation of The Ingersoll Lecture given in 1904 on Science and Immortality, presented the careful records of about 500 death-beds he studied, particularly with reference to the modes of death and the sensations of the

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dying.¹ He reported that about 20 percent suffered bodily pain or distress of one sort or another. Today this figure is 70 percent.²

We physicians are not doing as well today as Dr. Osler did 100 years ago with respect to controlling pain at the end of life. The old adage, to “cure rarely, relieve suffering often, and comfort always,” has been rewritten: the doctor’s job has become to “cure always, relieve suffering if one has the time, and leave the comforting to someone else.”³

At the time of Osler, a doctor could visit a patient and tell the patient’s family that death was imminent. The patient usually was at home. The doctor’s duty was then to provide comfort to the patient and the family, and to diminish suffering as the patient received ample opium and plenty of “*humane care*.” Today, with our modern interventions, we can prolong the dying process, (dialysis, ventilators, intravenous fluids, antibiotics), and often we are unable to recognize when the patient is dying or going to die. *Nor do we even know what causes one to actually die.*

In the article “Care of the Dying: An Ethical and Historical Perspective,” it was concluded that despite the miraculous advances in medical theory and medical practice, the ethics surrounding medical care for the dying are more troubling today than they were in ancient Athens.⁴ In classical antiquity, the primary concerns were for health and living well. The Middle Ages saw the emergence of the principle of sanctity of life. To these basic ideals, the Renaissance and the Enlightenment added the aspiration to prolong life. Finally, in the 20th century, modern science has rendered this aspiration a reality, but possibly of unclear merit.

As anesthesiologists, we are facing a future in which we will be called upon to anesthetize or sedate patients who are in the terminal stages of life. We must recognize that intubation and mechanical ventilation as part of a general anesthetic does not violate the patient’s request to not be resuscitated. However, should a patient suffer a cardiac arrest or other catastrophic event during surgery while under our care, the patient has a right to choose not to undergo chest compressions, et cetera, if this has been discussed and established prior to surgery. Just as we honor the right of a Jehovah’s Witness not to receive blood products, we must be prepared to honor a chemical code only request by our dying patients.

Where people die also has changed drastically in the last 50 years. One study reported that today for 67 percent of patients, the last place of care was an institution, with 38.4 percent dying in a hospital and 30.5 percent in a nursing home. Only 33 percent died at home. Of these, 49.3 percent were on home hospice care while 38.2 percent received no formal services, and 12.5 percent had home health care nursing services but without hospice participation.⁵ Reporting on the degree of satisfaction of bereaved family members with the care their loved ones received, hospice care at home received the highest level of overall satisfaction with 71 percent of respondents. Twenty-five percent of all patients with pain or dyspnea did not receive “any” or

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“enough” treatment. And inadequate pain management was 1.6 times more likely in a nursing home setting or with home health services and 1.2 times more likely in a hospital than with home hospice care.⁶

Fortunately palliative care as a specialty is growing, driven by new knowledge and an increase in medicine’s ability to relieve pain and suffering. In 2002 there were 800 hospital-based palliative care programs (none five years previously). Eight hundred eighty-five thousand dying Americans were served by 3,200 hospice providers in 2002, a 15 percent increase from 2001.⁶ There is a great need for physicians of all specialties to participate in and be more knowledgeable about end-of-life care and pain management.

“A pain crisis is any condition in which the experience of pain is out of control.” For the dying patient this is a cause of undue suffering. “Pain does not kill, so let’s find out what is wrong with you first. We don’t want to mask your symptoms.” This is the traditional philosophy by which most of us were trained. But we know now that poorly controlled pain will kill,⁷ and the patient who is dying is especially vulnerable to the detrimental effects of pain. The relief of pain will prolong life, but we must also control nausea, dyspnea, and anxiety, all of which will contribute to the suffering experience of the dying process.⁸

Unrelieved cancer pain causes unnecessary suffering, weakens already debilitated patients, increases poor compliance with cancer therapy, may delay treatment, impinges on work, leisure, role in family and society, and diminishes hope and increases depression. At the end of life, “**Pain is the emergency,**” and there is no need to delay administering analgesics during a diagnostic work-up.

As death approaches, treatment must take into account the four cardinal principles of medical ethics:

- Nonmaleficence (**minimize harm**), which comes from the philosophy of Hippocrates.
- Beneficence (“**do good**” if you can), which comes from the moral philosophy of St. Thomas Aquinas of the 13th century.
- Autonomy (**respect for the patient as a person**), which comes out of the United States Constitution and the Bill of Rights, as well as the Nuremberg trials of Nazi war criminals who performed experiments on human subjects without consent.
- Justice (**fair use of available resources**), which is affected by governmental and insurance companies’ regulation of health benefits.

Linked to these cardinal principles are the concepts of a “**respect for life,**” but at the same time an **acceptance of the “ultimate inevitability of death.”** Patients are not generally afraid of death itself, but they are often terrified at the thought of a **painful and prolonged dying process.** As physicians we are obligated to try and **balance the three dichotomies:**

- The potential benefits of treatment must be balanced against the potential burdens.
- Striving to preserve life but, when biologically futile, providing comfort in dying.
- Individual needs are balanced against those of society (there are limitations to health care resources).

It is helpful to define a goal-directed approach to treatment on three axes: The burden that the patient is willing to accept, the benefit that the patient wants to obtain, and the likelihood that the treatment being offered will be successful.⁹

Rule of Double Effect

This doctrine is taken from the moral philosophy of Saint Thomas Aquinas (13th century) which is the common law basis of all medical treatment but particularly for end-of-life pain management. It states that an action having two effects, one good and one bad, is permissible if five conditions are fulfilled:

1. The act itself is good or at least morally neutral, e.g., giving morphine to relieve pain.
2. Only the good effect is intended (relieving pain) and not the bad effect (killing the patient).
3. The good effect is not achieved through the bad effect (pain relief does not depend on hastening death).
4. There is no alternative way to attain the good effect (pain relief).
5. There is a proportionately grave reason for running the risk, e.g., relief of *intolerable* pain. (Notice, we avoid the term *intractable* pain because pain that is intractable by definition would preclude any treatment).

There are ethical and legal precedents for the use of whatever doses of opioids or sedatives are necessary **so long as death is not directly intended**. If the doses of opioids necessary to relieve pain are large enough to produce deep sedation, this too would be permissible, if suffering can be relieved in no other way. To justify use of this rule, the patient or surrogate decision maker would need to be informed of the risks (that is, hastening death) and give valid consent.

The use of an opioid is the strategy of choice for rapid titration in most clinical situations. Opioid side effects are usually manageable if frequent assessments are made. The management of an acute pain crisis involves *immediate* control of the pain, *maintenance* of analgesia, and *long-term* management. At the end of life the latter may mean only days to weeks. During the initial titration to pain relief, there is ample opportunity to evaluate the patient for the causes of the pain. The best way to gain control is to **titrate to effect**. The dose depends on the history of current use or whether the patient is naive to opioids, or tolerant, e.g., 1-4 mg of morphine, 0.2-1 mg hydromorphone (Dilaudid®), 10-50 mg meperidine (Demerol®), or the equianalgesic intravenous dose based on the patient's oral breakthrough medication history.

Opioids reach maximum plasma levels in 10 to 15 minutes after an intravenous bolus (except for fentanyl which is three to five minutes), so bolus doses every five to 10 minutes until the patient is comfortable or begins to have decreasing respiratory rate is the most effective method of opioid analgesic loading. An alternative method involves starting low, then doubling the dose every 30 minutes until comfort is achieved, with the effect usually being obtained in less than 90 minutes (range 4-215 minutes).¹⁰

After loading the patient and obtaining comfort, maintenance dosing must be ordered. IM or IV bolus dosing by the nursing staff on a PRN basis is a poor choice. The dose required to make the patient comfortable can be used as an estimate of the three-hour dose requirement for maintenance, as when converting to intravenous patient controlled analgesia (PCA).

So what is the correct dose of opioid analgesics? The correct dose is the dose that provides analgesia without producing intolerable and uncontrollable side effects. This was defined by Louis Lasagna and Henry Beecher in 1954, and the same principle holds today.¹¹ Opioids are not organ toxic. They do have side effects such as constipation, nausea and sedation, but these side effects do not represent organ toxicity, in contradistinction to acetaminophen liver toxicity or NSAID renal toxicity.

In the elderly or debilitated terminal patient there is increased CNS sensitivity to opioids leading to enhanced sedation, analgesia, and side effects, including delirium. This effect is enhanced by multi-organ system failure common in terminal patients. However, the experience of pain tends to counteract the sedative effects of opioids. Therefore patients who have not received adequate doses of opioid analgesics and who are still experiencing pain do not suffer respiratory depression. It has been suggested that opioid inhibition of J-receptor function in the lung leads to increased tidal volume; and also that the cortex of the brain is affected by opioids before the brainstem, and therefore sedation occurs before respiratory depression.¹²

Methadone in Chronic Cancer Pain

Methadone is an opioid with excellent oral and rectal absorption. It can be used intravenously but not subcutaneously. It has a higher potency, lower cost, and longer duration of action than other opioids, with no active metabolites that will accumulate in renal failure patients (when compared to morphine). It has a broad spectrum activity, i.e., Mu-opioid agonist, N-methyl-D-aspartate (NMDA) receptor antagonist, and a norepinephrine and serotonin reuptake inhibition effect similar to the tricyclic antidepressants.¹³ It is thought to produce apoptosis (cancer cell death) in certain cancers like lung cancer.¹⁴

However, it is not a straightforward drug with respect to initiation or conversion from another opioid, and care must be taken to start low and titrate slowly.¹⁵ There is some evidence of possible Torsade de pointes arrhythmias induced by rapid increase of

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methadone.¹⁶ Certain drugs administered together with methadone can lead to increased plasma levels through inhibition of various enzyme systems.¹⁵

Use of methadone is limited by limited knowledge of equianalgesic conversion ratios.¹⁷ There also is the stigmata associated with its use in drug addiction treatment. The ratio of conversion from morphine changes with the total daily dose of morphine and the prior duration of morphine use.¹⁸ For patients requiring 30-90 mg/day morphine, the ratio range is 1/2.5-8.8. For patients requiring 90-300 mg/day morphine, the ratio range is 1/4-10. For patients requiring >300 mg/day morphine, the ratio is 1/10-14.3.¹⁹ A six-day transition period is recommended.

Examples:

50 mg/day oral morphine = 20 mg/day methadone

300 mg/day oral morphine = 30 mg/day methadone

Hospitalized patients often can take advantage of IV pain medications. Temporary epidural or even intrathecal catheters can be used to administer opioids, local anesthetics and alpha-2 agonists such as clonidine. Intrathecal pumps can be implanted and are indicated for patients with life expectancies greater than four to six months, while epidural catheters such as “DuPens®” can be implanted for lesser time periods since they do tend to become infected in four to six months.

CT-guided alcohol celiac plexus neurolysis can be effective in controlling the pain of pancreatic cancer,²⁰ and intrathecal alcohol can be administered to control the pain of pelvic and lower extremity cancer pain.²¹ Intrathecal neurolysis will most likely result in paraplegia and incontinence, but these patients are usually already non-ambulatory and incontinent.

End-of-life pain management at home presents problems of assessment and administration of medication. Patients who are still able to swallow can be managed with oral medications. Rectal suppositories, transdermal medications and transmucosal medications also are available. Morphine and oxycodone are available in sustained release preparations, while fentanyl is available as a transdermal patch and as a buccal transmucosal preparation.

When patients are terminal and traditional analgesic regimens are unsuccessful at providing adequate analgesia and relief from suffering, the following solution can provide benefit.²²

**Ketamine (dissociative anesthetic, NMDA receptor antagonist),
2 mg/ml**

**Midazolam (benzodiazepine, reduces incidence of hallucinations,
provides sedative effects, antianxiety), 0.1 mg/ml**

Fentanyl (less nausea, pruritis, constipation), 5 mcg/ml

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Begin the intravenous infusion at **3-5 ml/hr** titrating to effect. If needed, the concentrations can be doubled to allow reduction of the volume infused. High concentrations can be used as subcutaneous infusions as long as the volume infused per hour remains below 2 ml. This would allow for home hospice care when intravenous access is not available.

Combinations of opioids with ketamine for PCA can provide synergistic relief in opioid tolerant patients with neuropathic pain conditions or severe pain at the end of life. Optimum pain control with minimal side effects can be obtained with a solution of 1 mg/ml morphine and 1 mg/ml ketamine, with a lockout period of eight minutes for PCA.²³ For home hospice, these agents could be given orally in concentrated solutions in the same ratio, e.g., 30 mg morphine with 30 mg ketamine q3-4h.

For patients who are going home on hospice care but have been dependent on intravenous opioid therapy because of inability to take oral medication, conversion to transdermal fentanyl patches can be considered appropriate if the pain is continuous. Equianalgesic principles must be used in converting. This author has found that 60 mg/day of intravenous morphine (or equivalent other opioid) or 180 mg/day of oral morphine or equivalent will require a 100 mcg/hr transdermal fentanyl patch. As with all sustained release opioids, this is for continuous pain that is opioid responsive. One still needs to consider breakthrough pain medications, fast onset, and short duration for activity-based pain. If the patient cannot take oral medication, transmucosal fentanyl is available for breakthrough pain management. Morphine, hydromorphone, and other opioids can also be given by suppository.

Adjuvant therapy is extremely important in end-of-life pain management. However, the side effects of medications such as the antidepressants with serotonin and norepinephrine reuptake inhibition may result in increased sedation, and orthostatic changes may place the patient at increased risk of falling. Because the addition of these medications may result in substantial reduction of pain, the risks versus the benefits must always be considered.

The anticonvulsants such as gabapentin have also found significant utility in end-of-life pain management of cancer and neuropathic pain, allowing for substantial reduction in the opioid requirements. NSAIDs and more specifically the cyclo-oxygenase II specific inhibitors are also useful in a polypharmacologic approach.

Patients in the terminal stages of life frequently suffer altered mental status, the most common causes in this scenario, however, being metabolic encephalopathy, infection or brain metastases, **not opioids**. However, the accumulation of the 3-glucuronide metabolite of morphine can lead to confusion or dysphoria. Patients receiving high doses of morphine who begin to experience more pain or dysphoria should be changed to a different opioid. Accumulation of normeperidine, the metabolite of meperidine, can lead to seizures.²⁴

Do Opioids Hasten Death?

No difference in survival was found between those patients requiring escalating doses of opioids versus those patients that were on stable doses of opioids, and it was concluded that “double effect” was not needed to justify use of opioids for the control of pain at the end of life.²⁵

Anesthesiologists are often presented with ethical dilemmas. Should we primarily facilitate surgeons operating on everyone? Are we obligated to operate because we can or because the surgeon wants to? Is age a factor in determining whether or not to operate? Must the surgeon operate because the patient or the family wants the operation? Must physicians always try to do something to cure the patient? As anesthesiologists, we cannot abdicate responsibility for a patient’s welfare to the surgeon. We should be active participants in the decision-making process. As anesthesiologists and pain management specialists, we are frequently presented with situations in which difficult choices must be made.

After nearly two decades caring for patients in the African jungle, Albert Schweitzer wrote, “We all must die. But that I can save him from days of torture. That is what I feel as my great and ever new privilege. Pain is a more terrible lord of mankind than even death itself.” This quote, selected for the introduction to John Bonica’s textbook, *The Management of Pain*, underscores the obligation and privilege of physicians caring for patients with pain.²⁶ As anesthesiologists we have expertise that places us in a unique position to provide assistance to patients at the end of life in controlling pain and other related symptoms. Failure to do so is a failure of conscience.

*...The relief of suffering and the cure of disease must be seen as twin obligations of a medical profession that is truly dedicated to care of the sick. Physicians’ failure to understand the nature of suffering can result in medical intervention that (though technically adequate) not only fails to relieve suffering but becomes a source of suffering itself.*²⁷

—Eric J. Cassel. *Nature of suffering and the goals of medicine*

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