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This educational activity is eligible for CME credit through April 30, 2005. The latest review of this material was March 31, 2003.

Educational Objectives
After studying the article by Greenberg, the participant will be able to:

- Monitor cognitive impairments in patients near the end of life in order to institute treatments for reversible causes and to keep patients with irreversible deficits comfortable.

This pretest is designed to facilitate your study of the material.

1. **What are clues to mild delirium?**
   a. Errors in handwriting
   b. Poor recall of 3 words
   c. Distractibility
   d. All of the above

Pretest answer and Posttest on page 68.

Disclosure of Off-Label Usage
The author of this article has determined that, to the best of her knowledge, haloperidol, olanzapine, perphenazine, quetiapine, and risperidone are not approved by the U.S. Food and Drug Administration for the treatment of delirium.

Preventing Delirium at the End of Life: Lessons From Recent Research

Donna B. Greenberg, M.D.

Preservation of the ability to think clearly, in comfort, is a goal of end-of-life care. Recent research on delirium at the end of life suggests clinical strategies for prevention of cognitive impairment. Clinicians should consider early warnings of mild delirium such as impairment in attention and short-term memory by following the patient's ability to remember 3 words or to attend to digit span before the patient is disoriented. If cognitive impairment is noted, clinicians should pay attention to reversible causes. This article reviews clinical concerns about opiates, benzodiazepines, steroids, hepatic encephalopathy, timely use of neuroleptic medications, and caretaking strategies at home.

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In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity was asked to complete a full disclosure statement. The information received is as follows: Dr. Greenberg has no significant commercial relationship to disclose relative to the presentation.

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The concept of the "appropriate death," the death that we would choose if we had a choice, includes the ability to think clearly as long as possible, in comfort, surrounded by those we love.[1] Being mentally aware in the setting of illness is a preference reiterated by seriously ill patients, bereaved families, physicians, and other health care providers.[2] Most seriously ill patients would not choose a treatment if the outcome is cognitive impairment; the greater the risk of cognitive impairment, the less inclined patients are to treatment.[3] This article reviews the data on delirium at the end of life in an effort to identify techniques that will, as much as possible, reduce the likelihood of a patient having a persistent confusional state at the end of life.

Delirium is a categorical psychiatric diagnosis characterized by a disturbance of consciousness and defects in attention, orientation, and memory. The patient is disoriented and cannot focus, sustain, or shift attention. He or she is unable to remember well or cannot use language without disorganization. This disability fluctuates over hours and days. The key finding of fluctuating consciousness sets delirium apart from dementia, and disorientation sets it apart from functional psychiatric disorders. In dementia, cognition is impaired despite the patient's alert state and ability to pay attention. In functional psychiatric disorders, patients may have delusions and hallucinations, but their orientation to time and place are not typically impaired.

EARLY IDENTIFICATION OF COGNITIVE IMPAIRMENT

Recall of 3 words, digit span, record of sleep pattern, and assessment of distractibility can provide early bedside warnings of mild delirium. A sample of handwriting collected each day can be helpful if the patient is willing to cooperate by providing a signature or sentence. In the setting of illness, patients may be lethargic due to fever, medications, or metabolic derangement. As the patient becomes less attentive and has more difficulty concentrating, cognitive deterioration is taken for granted as a common finding in illness. If the clinician pays attention to the milder signs of mental status change and considers what might reverse them, then the full syndrome of delirium may be prevented.

The Memorial Delirium Assessment Scale, developed by Breitbart et al.[4] to rate the severity of delirium, calls attention to simple bedside signs that can indicate mild delirium. The items in the scale include 10 dimensions rated 0 to 3: disturbances of consciousness, perception, thinking, memory, orientation, attention, wakefulness, psychomotor signs, delusion, and arousal. The scale was validated to psychiatrists' assessments on the Delirium Rating Scale,[5,6] the Mini-Mental State Examination, and a measure of global severity.

A few key bedside assessments that are not routinely considered by clinicians are used to advantage in the Memorial Delirium Assessment Scale (Table 1). Most clinicians think to ask about orientation, but not short-term memory impairment or digit span. The patient is asked to repeat 3 words and to recall 3 words 5 minutes after an intervening task to assess short-term memory. Difficulty with short-term memory is not easily recognized in a social conversation with a sick patient if it is not assessed directly. Digit span is a second measure of sever-

Table 1. Clinical Clues to Early Delirium From the Memorial Delirium Assessment Scale[a]

Can the patient recall 3 words?
How many numbers can the patient repeat forward and backward?
Daytime sleepiness and broken nighttime sleep
Is the patient easily distracted?
Handwriting samples

[a]Based on Breitbart et al.[4]

ity of cognitive impairment. The patient is asked to repeat first 3, then 4, then 5 digits forward and then 3, then 4 backward. Daytime sleepiness and broken sleep at night are recorded as signs of sleep-wake cycle abnormalities. The patient's distractibility is noted. These clues to mild degrees of confusion are added to the search for delusions, perceptual disturbances, disorganized speech, and hyperactivity.

On each dimension, the defects may move from less dramatic to more florid; for instance, if the patient does not see clearly, he or she may see a distorted image. This visual distortion may be accepted as ambiguous if the patient's thinking is clear. As the condition worsens, the visual distortion becomes an illusion; the patient interprets the image incorrectly, but with conviction. An intravenous bag and pole appear to be a person. Visual hallucinations may supervene as delirium becomes more florid. The patient sees a person with no stimulus in the room that relates to the image. The patient's ability to doubt the sensation decreases, and the conviction strengthens that what the patient sees is real. Thinking that was initially tangential and fragmented becomes completely disorganized. The ability to solve problems and to make decisions becomes more and more impaired as the patient becomes unable to focus. The patient cannot find a name easily, and writing words clearly in good-sized handwriting without errors becomes difficult until the response to the request, "Write a sentence" is mere scratches on the pad. Disorientation to date becomes disorientation to the kind of place the patient is in; he or she does not even know that it is a hospital.

Patients cannot remember if they cannot pay attention in the first place. As attention wanes, the ability of the patient to make new memories gets worse. Patients may be easily distracted, preoccupied, or frequently repeating themselves. What starts as broken nighttime sleep becomes persistent insomnia and nighttime confusion (sundowning) and global agitation. Consciousness fluctuates between hypervigilant and somnolent. Anxiety with no psychomotor component becomes combative, aggressive, and impulsive behavior.

EMOTIONAL PRESENTATIONS OF DELIRIUM

Since delirium often has an emotional component, early delirium may appear to be a problem in mood or anxiety. The patient at the end of life has many reasons to be fearful, anxious, or sad, so the mood may be attributed to the stress of illness. What appears at first to be anxiety about the situation may be panic, terror, and paranoia. Since the patient has a fluctuating consciousness and is in a dreamlike state, delusions may be unspoken and unrecognized, so the patient may be frightened that what he or she "dreamed" is happening. About half of patients remember the delirious episode.[7] More severe delirious episodes are more apt to be forgotten, but a remembered delusion can be one of the most distressing features of the experience.[7]

Suicidal thoughts and actions can occur in a delirium, and delirium can masquerade as depression. The patient may appear hypoactive and less cooperative. The staff may view the patient's lack of cooperation or initiative as lack of will. The patient is less attentive and appears less interested. Affect is labile. Key signs that distinguish depression from delirium are cognitive impairment and disorientation. Although delirium can be indicated by prominent slowing on the electroencephalogram, this laboratory test is often sought only when seizure is a consideration.

REVERSAL OF LIFE-THREATENING CAUSES

The first reason to recognize early decrements in thinking is to identify the reversible causes of delirium. Life-threatening causes of new-onset delirium that necessitate immediate treatment include hypoxia, hypoglycemia, thiamine deficiency, extremes of blood pressure, stroke, sepsis or meningitis, and overdoses of medications or intoxicants. The emergency room strategy of assessment of vital signs and treatment with thiamine, glucose, and naloxone comes from the need to consider this urgent differential diagnosis. These conditions can occur at the end of life and remain important conditions to treat if possible. However, intoxicants, such as narcotics, are often necessary for symptom relief.

Delirium is more common in those patients with a brain injured by age, stroke, or alcohol.[8] The risk of delirium is greater if the patient cannot see or hear, so eyeglasses and hearing aids are important defenses. Chronic kidney, liver, or lung failure increase risk by causing hypoxia, hypercapnia, azotemia, or hepatic encephalopathy or by affecting the metabolism of other drugs. The rate of delirium in more than 800 patients was diminished from 15% to 10% when risk factors were targeted. The risk factors for delirium were a Mini-Mental State Examination score less than 20, sleep deprivation, immobility, visual deficit less than 20/70, hearing deficit less than 6 out of 12 whispers, and dehydration (blood urea nitrogen/creatinine ratio greater than 18).[9]

Cerebral insufficiency is a common occurrence as the patient's organs fail or as the need for analgesia overrides the capacity for alert clarity of thought. The prevalence of

delirium in the palliative care setting is quite high, 26% in a palliative care unit.[10] Studying more than 300 consecutive patients admitted to a palliative care unit in Edmonton, Pereira et al.[11] found that 44% had impaired cognition on admission. The most common causes were opioid intoxication, infection, dehydration, brain metastases, renal impairment, hypercalcemia, sepsis, and hypoxia. It is noteworthy, however, that even in a palliative care unit, 29% of 87 surviving patients who had abnormal cognition on admission were normal at discharge. The responsible pursuit of clarity of thought can continue as long as the patient lives.

The medications that most frequently contribute to delirium are benzodiazepines, opioids, and steroids. In addition to hepatic failure, prerenal azotemia, hyperosmolality, hypoxia, brain injury, infection, and hypercalcemia also make significant contributions.[12–16] Strategies for prevention include simplification of medications that affect cognition, prevention of hepatic encephalopathy, hydration, and administration of oxygen.

PAIN AND DELIRIUM

For the patient with pain who is treated at the end of life, pain relief often requires opiates, and pain is difficult to assess when the patient is already confused. Moaning, grimacing, and agitation that may occur in the nightmare of agitated delirium can be misunderstood as a physically painful state. Patients who are in pain but frequently disoriented, with problems in memory and attention, cannot report accurately whether a remedy worked. They cannot press a button for patient-controlled analgesia in a timely fashion or call for as-needed medications in a practical way. The benzodiazepines and opioids administered in the hope of treating distress can worsen confusion. It has been noted that patients in pain ask for more breakthrough medications in the morning, while patients with delirium take more breakthrough medications later in the day.[17]

Opiates

At the end of life, narcotics become the mainstay of analgesic treatment. Lawlor[18] has recently reviewed the relationship between narcotics and cognitive decline. The degree of cognitive impairment is related to dose and route (the rapidity of distribution to the brain based on serum level and rate of change). Lawlor reminds us of the simple pharmacologic response. In normal subjects, steady-state morphine infusion, compared with saline infusion, prolongs reading time and impairs performance on the recall of a previously read test. Dose increases of 30% compared with the previous dose lead to sedation and cognitive decline.[19] Tolerance develops to cognitive side effects when the dose is stable. Cognitive impairment is worse immediately after a dose increase.

Among narcotic compounds, meperidine, which has a neurotoxic metabolite, is associated with more cognitive dysfunction,[20] but the research supporting distinctions among other compounds is limited.

It is most important to understand the rate at which the narcotic is taken in, the serum level achieved, and the pharmacokinetics of elimination. Intravenous morphine affects the serum drug level rapidly and can thereby impair cognition. It is eliminated rapidly.

With the fentanyl patch, for instance, the upper skin layers serve as a depot for the fentanyl. The serum opiate levels are achieved more slowly, between 12 and 24 hours, with peaks at 18 hours. The slow onset of action is an advantage for preservation of cognition, but the serum level rises further after several (3) 72-hour patches are used. With a stable dose of fentanyl, the higher serum dose on day 10 may be associated with greater cognitive impairment. After discontinuation of the patch, 50% of the fentanyl is removed at an average of 17 hours later. The longer elimination phase suggests that cognition may be affected by fentanyl for some time after the patch is removed.

It has been thought that the metabolites of narcotics, normeperidine, morphine-3-glucuronide, and hydromorphone-3-glucuronide, are culprits contributing to cognitive decline. The levels of metabolites are higher in terminal patients after they become delirious, but it is unclear if the metabolites contributed to the delirium more than the basic drug.[21] In some studies, the metabolite and renal impairment have correlated with cognitive decline.

The older patient is at greater risk of opiate-induced delirium; the risk of delirium from any cause is also greater if the patient is older. Delirium is more likely to be missed if the patient is lethargic and presents no management problem.

Reduction of opioid dose and/or rotation of the narcotic, i.e., a change to an alternate narcotic, initially at a lower dose equivalent, are reasonable treatment options. For instance, a patient who becomes delirious with morphine may be switched to hydromorphone or methadone. The benefit of opioid rotation is attributed to change in receptor activity, asymmetry in cross-tolerance among different opioids, differences in the efficacy of different opioids, and changes in toxic metabolites.[22]

Considerations for Prevention of Opiate Delirium

To prevent cognitive impairment from opiates, the dose is best titrated slowly from lower doses to higher doses with careful assessment of benefit. It is tempting to adjust the dose of a long-acting agent such as the fentanyl patch before a steady state is reached. Short-acting medications can be used as they are needed until the full efficacy of a lower-dose long-acting agent can be assessed.

Table 2. Prevention of Delirium With Opiates[a]

The clinician should:
Stop unnecessary medications
Keep the dose low in the elderly
Keep track of cognition
Maintain hydration
Consider why an opiate regimen is not working before increasing the dose

[a]Adapted from Lawlor.[18]

Table 3. Questions to Ask if Narcotics Do Not Seem to Work[a]

Is the pain incidental, like bone pain that is worse with movement? Can we compromise to control pain at rest and target analgesia for movement?
Does the pain have neuropathic qualities like burning, lancinating, or root distribution? Other drugs may be more effective
Are we underdosing a patient who has a long history of narcotic use and who is very tolerant to the dose we are giving?
Is there a history of addiction and narcotic craving?
Is there a history of focus on bodily complaints to express global distress (somatization)?

[a]Based on Lawlor[18] and Bruera et al.[23]

Lawlor[18] summarizes key strategies to prevent opioid-related delirium, including (1) minimizing unnecessary medications, (2) adjusting the dose in the elderly, (3) monitoring cognition, (4) maintaining hydration, and (5) rotating opioids if cognition is impaired (Table 2).

When a narcotic is ineffective, the tendency is to give more drug. Lawlor cautions physicians to consider 5 reasons that a narcotic may not be working (Table 3[18,23]). These 5 considerations are helpful items to review before giving more drug when the marginal benefit is unclear. Residual pain that is incidental and worse with movement may be much more difficult to control than continuous pain. Control of pain with movement may come only at the expense of the patient's mental status. Neuropathic pain is less responsive to opiates than somatic pain; alternative medications may be better. The patient's previous use of narcotics may have been associated with development of tolerance. In effect, underdosing of narcotics might then explain the reason for persistent pain.

Another 2 considerations come from the patient's history. If the patient has a history of addiction, he or she may request pain medication regardless of pain, moved by craving. A patient with a history of chronic pain complaints as a feature of somatization may continue to complain. The pain complaints seem to have a course of their own that is related to psychic distress, but not necessarily related to the efficacy of narcotics.

Benzodiazepines

Benzodiazepines must be considered carefully in the evaluation of delirium at the end of life. Most often, the risk of delirium from benzodiazepines is underestimated. Lorazepam, 1 mg, causes more cognitive impairment than morphine, 10 to 15 mg.[24] Like alcohol, benzodiazepines cause drunkenness in a dose-related and time-related fashion. Amnesia is a prominent feature.

Benzodiazepine withdrawal, like alcohol withdrawal, is a life-threatening cause of confusion. Delirium can follow sudden discontinuation of clonazepam or alprazolam.

Benzodiazepines can precipitate hepatic encephalopathy. Parenteral benzodiazepines may be the specific treatment of partial seizures or status epilepticus if the confusion is caused by ictal or postictal confusion.

HEPATIC ENCEPHALOPATHY

Serum ammonia is poorly correlated with the grade of encephalopathy.[25] Low potassium alkalosis, gastrointestinal hemorrhage, constipation, dietary protein, azotemia, and sedatives are all precipitants. Treatments include lactulose, neomycin, metronidazole, rifaximin, and restriction of dietary protein. The γ-aminobutyric acid antagonist flumazenil can give partial benefit, even in those who did not have benzodiazepine levels at the start.

STEROIDS

The agitated manic state, emotional lability, and delusion that come with steroid treatment may mimic delirium. The syndrome is dose related. Psychiatric side effects are common at prednisone doses of 60 mg/day or the equivalent of 9 mg/day of dexamethasone. Removal of steroids does not immediately alleviate the syndrome; psychotropic medications, usually antipsychotic medications, are necessary to stabilize mood and sleep.

DRUGS TO TREAT DELIRIUM

After consideration of the differential causes of delirium, such as low sodium and hypercalcemia, treatment with psychotropic medication should be considered. The benefit of neuroleptic medication is more limited in the setting of hypoxia or structural brain disease such as dementia or brain cancer. Hepatic encephalopathy or seizures require different strategies.

The standard neuroleptic for treatment of delirium is haloperidol. It can be given orally or intravenously to clarify thinking and to calm the patient. Intravenous regimens can be reevaluated after 30 minutes, and oral medication can be reevaluated in 1 to 2 hours. The dose is increased until the patient is calmer. Haloperidol is the least-sedating widely used neuroleptic. The first day's dose may be the most critical. Perphenazine is also available for parenteral use. The drawback to classic antipsychotic medications is that they can have extrapyramidal side effects of parkinsonian posture and tremor or akathisia, a feeling of restlessness. While anticholinergic agents

reverse the parkinsonian side effects, restlessness is more difficult to reverse.[26–29]

The newer atypical antipsychotics with serotonergic-2A blockade also treat delirium. They are all sedating, but less apt to cause restlessness. They are not available parenterally. Olanzapine and risperidone have some risk of postural hypotension. Risperidone is available as a liquid. With risperidone, restlessness still occurs, but less often than with haloperidol. Quetiapine is widely used in parkinsonian patients because it is least apt to cause extrapyramidal side effects. It has the shortest half-life. Starting doses of risperidone, 0.25 to 0.5 mg b.i.d.; olanzapine, 2.5 to 5 mg h.s.; or quetiapine, 25 to 50 mg, have been recommended. Additional doses are used as needed for agitation. In general, these medications can be continued over the course of a week.[30–36]

DELIRIUM AT HOME

The patient who becomes delirious at home requires constant care. It is a challenge for caretakers to gain the patient's cooperation for movement and eating. Disorientation, impulsivity, intermittent agitation, or somnolence puts the patient's safety at risk and makes everything difficult. Family and children are frightened by the change in their loved one. They may feel that they have lost their family member or that he or she has gone crazy. When the family sees the patient's mental anguish, they may be particularly disturbed. Family may overvalue what the patient says during a confusional state. The fluctuating state of consciousness adds to the confusion. When the patient is asked to respond to a cognitive examination, the family may try to help by giving correct answers. Family may coach the patient. The most recently administered medication may be wrongly seen as the culprit that has compromised thinking. Medications may be added, switched, or withdrawn, but assessment of these changes may be difficult.

Educating the family about confusional states and good nursing interventions can facilitate care and family comfort.[37] The nurse or family can report changes in mental status to the medical staff. Is the patient oriented? Can he or she use the night table, call light, bathroom? Can he or she recognize the people in the room? What are the reasonable limits of self-care? How can caretakers communicate to the patient? Since the patient will be easily distracted, directives must be short and face-to-face. There is no point in long explanations or arguments. If the patient is perseverating on a troublesome thought or action, the caretaker can try to divert the patient's attention. If the patient has delusions, then the caretaker can pay attention to the feeling behind the delusion. For instance, the man who believes that he was unfairly put outside the hospital with strangers for a prolonged time when he was having difficulty breathing has the terror that anyone might have in that situation. He is asking not to be abandoned when he needs help. Getting him to understand that he was never left outside the hospital is not the important point. Reassuring him that he will not be abandoned is key. As his thinking clears, the conviction about the truth of the delusion will diminish.

Several strategies make it easier for patients who are struggling to function and to orient themselves. They need a simple environment and the same caretakers from day to day as much as possible. They need to be watched. A structured routine for the essentials of daily care like eating, bathing, and exercising makes it easier to orient. A clock and calendar in the room are classic cues for orientation.

CONCLUSIONS

The best way to prevent or reverse delirium at the end of life is to regularly monitor cognitive deficits with focused attention to short-term memory loss by digit span or recall of words. Notes on sleep pattern and distractibility are helpful. At the same time, the caretaker should pay attention to alertness, clarity of thought, and speech. Following a simple writing sample, for instance, may be helpful. If cognition declines, clinicians should reevaluate the role of medications and discontinue those that can affect the brain. They should consider the differential diagnosis of delirium and change what can be changed. Analgesic and sedating medications should be given in lower doses at lower rates until the desired effect is achieved, and neuroleptic medications should be used in a timely manner. Changes in mental status at home should be communicated to medical staff by reports about the limits of a patient's ability to take care of himself or herself. The family benefits from understanding the patient's confusion and by following guidelines to simplify the room and regimen. They can be advised to speak with the patient with the recognition that he or she will not pay attention for long. Emotionally, the task is to support and to reassure the patient that he or she is not alone and to insure comfort and physical safety.

Drug names: alprazolam (Xanax and others), clonazepam (Klonopin and others), dexamethasone (Decadron and others), fentanyl (Duragesic), flumazenil (Romazicon), haloperidol (Haldol and others), hydromorphone (Dilaudid-HP and others), lactulose (Constulose, Constilac, and others), lorazepam (Ativan and others), meperidine (Demerol and others), methadone (Dolophine, Methadose, and others), metronidazole (Flagyl and others), morphine (Astramorph PF, Duramorph PF, and others), naloxone (Narcan and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), prednisone (Deltasone and others), quetiapine (Seroquel), risperidone (Risperdal).

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For the CME Posttest for this article, see pages 68–69.