

# EPEC

Education for Physicians on End-of-life Care

## **Participant's Handbook**

Module 6

**Depression,**

**Anxiety,**

**Delirium**

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Emanuel LL, von Gunten CF, Ferris FD. The Education for Physicians on End-of-life Care (EPEC) curriculum, 1999.

Special thanks to the EPEC Team, the EPEC Advisory Group, and all other contributors.

## Abstract

Anxiety, confusion (part of delirium), and depression are 3 common and serious symptoms that occur in patients nearing the end of their lives. All 3 are underrecognized and undertreated. As approaches to their assessment and management are widely known, all 3 symptoms can be pursued by any physician. When assessing any patient, consider risk factors that are related to illness or treatment, or are preexisting. Conduct evaluations and investigations as appropriate. A mix of counseling-related therapy and medication is likely to be most effective. Continue surveillance of the patient and adjust to ideal treatment regimens as the underlying illness progresses. Refer difficult cases for consultation with a specialist.

## Key words

anxiety, anxiolytics, atypical antidepressants, behavioral intervention, benzodiazepines, delirium, depression, diagnosis, etiology, hypnotics, neuroleptics, pharmacotherapy, psychostimulants, psychotherapy, risk factors, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants

## Objectives

The objectives of this module are to:

- identify depression, anxiety, and delirium in patients facing the end of their lives
- describe approaches to manage each symptom

## Clinical case on trigger tape

The patient is Jack Wiley, a 34-year-old gay man with HIV disease. Jack presents for a routine exam after a bout with pneumonia. His partner, who is also present, is extremely worried about a recent change in Jack's behavior.

## Introduction

Depression, anxiety, and delirium may cause intense mental, emotional, and physical suffering and disability in patients facing the end of their lives. Major depression is under-diagnosed and undertreated in 2 out of 3 patients. Recognition and management of both anxiety and delirium are also poor, so physicians must remain alert to the development of all of these conditions. Detection and appropriate treatment can make it possible for patients and families to experience personal growth and complete their life closure together.

This module is intended to help physicians detect, diagnose, and manage these 3 important clinical entities that are common at the end of life. As in other aspects of end-of-life care, incorporation of appropriate members of the interdisciplinary health care team such as nurses, social workers, chaplains, and others will be helpful.

## Depression

Most patients with a serious illness experience periods of intense sadness and anxiety accompanied by depressive symptoms. These feelings are usually present for a relatively short period (days to weeks), and then resolve. However, in a variable number of patients, these feelings persist (between 25% and 77%, depending on the study).

As depression is a source of intense suffering, physicians will want to be particularly diligent at assessing and detecting associated signs and symptoms. Persistent symptoms of depression are not “normal” for patients at the end of life. It is a myth that feeling helpless, hopeless, depressed, and/or miserable are inevitable consequences of advanced life-threatening illness.

The earlier depression is diagnosed, the more responsive to treatment it is likely to be. Treatment for depression may help patients feel better and have the energy and interest to achieve their final goals before they die. This applies to teenage and young adult patients as well.

Unfortunately, in our society, depression is often viewed as something to be ashamed of, or as a sign of weakness. Through patient and family education, the physician can help correct this misconception.

### Risk factors

In patients with advanced illness, there are many risk factors for major depression. Poorly controlled pain and other physical symptoms are particularly important because they are remediable (see Module 4: Pain Management, and Module 10: Common Physical Symptoms). Progressive physical impairment and an advanced stage of disease also correlate with a higher incidence of depression. With some medications (eg, steroids and benzodiazepines), depression is a potential adverse effect. A few diseases (eg, pancreatic cancer, left hemispheric stroke) are also linked with depression. Finally, spiritual pain and conflicts over issues of meaning, guilt, and fear may manifest as depression.

Preexisting risk factors for depression that occur within the general population (eg, prior episodes of depression or mania, a family history of major depression, manic-depression or suicide attempts, and concurrent substance abuse) also apply to patients with advanced illness. Patients are also at increased risk when they lack social supports or are experiencing other stressful life events that are unrelated to their illness.

## Diagnosing depression in advanced illness

In the general population, somatic symptoms (eg, changes in appetite, weight, energy level, libido, or sleeping) are important when making a diagnosis of depression (DSM-IV, American Psychiatric Association, 1994). However, somatic symptoms are almost invariably present in patients with advanced illness. Therefore, assessment of depression in patients with advanced illness must focus on psychological and cognitive symptoms that are indicative of the diagnosis. Where possible, include the observations of family, friends, and other members of the health care team, as they may provide considerable information to add to the history. You may need the assistance of a child psychologist, child life specialist, or social worker if the patient is a child or adolescent.

The most reliable symptoms of major depression are persistent dysphoria, anhedonia (loss of pleasure), feelings of helplessness, hopelessness, and worthlessness, and loss of self-esteem. Other diagnostic criteria include feelings of excessive guilt, pervasive despair, bothersome ruminations about death, and thoughts of suicide. Pain not responding as expected, sad mood with flat affect and anxiety, irritability, or unpleasant mood may be significant signs of depression.

The screening question, “Do you feel depressed most of the time?” is a sensitive and specific question in this population. Requests to hasten death may be a marker of undiagnosed depression (see Module 5: Physician-Assisted Suicide). More specific screening tools (such as the Beck Depression Inventory) for the identification of depression are available. Ask an experienced psychiatrist for assistance as appropriate.

## Suicide

All patients with depressive symptoms should be assessed for their risk of suicide. Similarly, suicidal thoughts are an important sign of depression, even in patients with advanced life-threatening illness.

It is a myth that asking about suicide will “put the idea into someone’s head.” To the contrary, allowing patients to discuss the thoughts they are having may reduce the likelihood they will actually commit suicide, particularly if the physician acknowledges their feelings and desires, and addresses the root causes of their distress (see Module 5: Physician-Assisted Suicide).

Patients with recurrent thoughts of suicide or serious plans should be considered at high risk. Immediate consultation with a mental health specialist experienced in this area is indicated.

## Management of depression

To treat depressed patients who are living with life-threatening illness, use a combination of supportive psychotherapy, cognitive approaches, behavioral techniques, and antidepressant medication.

**Psychotherapeutic interventions:** Individual and group counseling have both been shown to reduce depressive symptoms. In addition to formal sessions with psychiatrists, psychologists, or other mental health professionals, nurses, social workers, and chaplains may also be able to conduct both formal and informal sessions, depending on their training.

**Cognitive approaches:** Time spent talking with patients about their feelings and reframing their ideas may be very helpful. These approaches can be used by the primary physician, as well as other colleagues.

**Behavioral interventions:** Relaxation therapy, distraction therapy with pleasant imagery, etc, have been shown to reduce depressive symptoms in patients with mild to moderate levels of depression. Complementary and alternative medical approaches may be useful adjuncts.

**Antidepressant medications:** A variety of medications that will be discussed below work with all severities of depression. They work better than psychotherapy alone in severe depression.

## Counseling goals

Physicians can weave supportive counseling that uses aspects of brief supportive psychotherapy into routine interventions. Include family members whenever possible. Refer seriously depressed or anxious patients for formal psychotherapy.

Supportive counseling has many goals. The interaction itself may be therapeutic. During the discussions, the physician can provide the patient with an improved understanding of his or her prognosis, potential treatments, and outcomes. These may help the patient put perceptions, expectations, needs, fears, and fantasies about his or her illness and death into a different perspective. Discussing short-term goals, and identifying and reinforcing the patient's previously demonstrated strengths and successful coping techniques, will help to establish or reestablish the patient's sense of self-worth and meaning (see Module 7: Goals of Care).

New coping techniques such as relaxation, meditation, guided imagery, or self-hypnosis can be introduced. The physician can spend time to educate the patient and family members about modifiable factors that contribute to anxiety and depression.

## Pharmacologic management

The principal medications used for the treatment of depression include psychostimulants, selective serotonin reuptake inhibitors (SSRIs), and tricyclic and atypical antidepressants. Specific drugs and doses are listed in the Medication Table at the end of the EPEC materials.

The time available for treatment will strongly influence the choice of medication for initial therapy. When reversal of depression is an immediate short-term goal, a rapid-acting psychostimulant is the best choice. If a response in 2 to 4 weeks is acceptable, an atypical antidepressant or SSRI may be an appropriate choice.

With all antidepressant medications, dosing should “start low and go slow.” Titrate the dose to effect and tolerability. Warn patients about possible adverse effects, which will usually ameliorate within a few days. If patients are not responding as expected, seek consultation with an experienced colleague, such as a psychiatrist.

## **Psychostimulants**

The psychostimulants methylphenidate, dextroamphetamine, and pemoline are underappreciated for their antidepressant qualities. They act quickly (in days) and produce minimal adverse effects. Some patients report increased energy and an improved sense of well-being within 24 hours.

Methylphenidate is usually started at 5 mg in the morning and at noon, and then titrated to effect. An extended-release formulation taken once in the morning may improve tolerability.

Psychostimulants can be used alone or in combination with other antidepressants. They may be continued indefinitely as their antidepressant effect persists over time. Tolerance to the antidepressant effect does not appear to develop. They may also be used to diminish opioid-induced sedation. Their potential as adjuvant analgesics has been reported.

Psychostimulants may produce tremulousness, anxiety, anorexia, and insomnia. These adverse effects should be monitored. If discontinued, psychostimulants should be tapered off slowly.

## **Selective serotonin reuptake inhibitors**

Selective serotonin reuptake inhibitors (SSRIs, eg, fluoxetine, paroxetine, sertraline, and citalopram) usually begin to act within 2 to 4 weeks. They are highly effective (70% of patients report a significant response). Low doses may be sufficient in advanced illness. Once-daily dosing is possible. SSRIs cause less constipation, sedation, and dry mouth than the tricyclic antidepressants, though nausea may be worse with the SSRIs.

## **Tricyclic antidepressants**

Tricyclic antidepressants (eg, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine) are not recommended as first-line therapy to manage depression unless they are being used as adjuvants to control neuropathic pain. Titration to achieve an adequate dosage may take 3 to 6 weeks, delaying the onset of therapeutic action. Anticholinergic adverse effects (eg, dry mouth, constipation, orthostatic hypotension, blurred vision, urinary retention, delirium) and cardiac conduction delays (proarrhythmic) are all seen

with some frequency. If a tricyclic antidepressant is to be used, the secondary amines nortriptyline and desipramine are preferable as they tend to have fewer side effects.

### **Atypical antidepressants**

This diverse group of older and newer medications is growing quickly. Examples include mirtazapine, bupropion, nefazodone, trazodone, and venlafaxine. Their precise role in patients with advanced disease is being studied.

### **Nonpharmacologic management**

Although this module focuses on equipping physicians with the medical knowledge, attitudes, and skills to manage depression, this does not exclude the role of nonpharmacologic management of depression. Use appropriate colleagues and team members to help address the emotional and spiritual issues that overlap and influence clinical depression. Complementary and alternative methods may be useful adjuncts for some patients. It is beyond the scope of this module to discuss these in detail.

Issues of grief and bereavement may be important. Although these topics are discussed in Module 12: Last Hours of Living, the concepts are also applicable in the context of evaluating and managing depression.

## **Anxiety**

Patients facing a life-threatening illness commonly experience anxiety over their fears and uncertainties about their future. Their distress may be related to any of a number of physical, psychological, social, spiritual, or practical issues, or it may be a component of many other syndromes (eg, an underlying panic disorder that is unmasked by advanced illness). Anxiety usually presents with 1 or more symptoms or signs including agitation, restlessness, sweating, tachycardia, hyperventilation, insomnia, excessive worry, and/or tension.

As anxiety may have many different origins, assessment may be complex. Input from family, friends, and other members of the interdisciplinary team may be invaluable. Attempt to differentiate between primary anxiety and delirium, depression, bipolar disorder, and medication side effects. Look for insomnia (see Module 10: Common Physical Symptoms) and other reversible causes of anxiety such as alcohol, caffeine, or medications (eg, increased doses of beta-agonists and methylxanthines for the management of dyspnea).



# Management of anxiety

## Nonpharmacologic management

The majority of patients will be receptive to compassionate exploration of the specific issues that are causing or exacerbating their anxiety. Concerns about finances, family conflicts, future disability, and dependency, and existential concerns will not resolve with medication. Instead, they will benefit from counseling and supportive therapy. Involve other appropriate disciplines such as nursing, social work, and chaplaincy. Complementary and alternative medical approaches may help some patients.

Issues of grief and loss are important dimensions to understand, particularly in evaluating anxiety and psychological distress. Although they are discussed in more detail in Module 12: Last Hours of Living, they are applicable earlier in the course of the illness for both patients and family members.

## Pharmacologic management

When it appears that pharmacologic therapy will be beneficial as part of a total plan of care for anxiety, benzodiazepines are generally the medication class of choice. Choose an agent based on the desired half-life. Longer-half-life medications have a more sustained effect, but may accumulate. Shorter-half-life medications may have a greater risk of withdrawal and rebound anxiety.

Whichever medication is chosen, start with low doses and titrate to effect and tolerability. Remember that benzodiazepines may worsen memory, particularly in the elderly, or cause confusion in patients with preexisting cognitive impairment. When discontinuing benzodiazepines, taper them slowly:

- long-half-life benzodiazepines
  - diazepam, 2–10 mg po q hs to q 8 h
  - clonazepam, 0.25–1 mg po q d to bid
- moderate-half-life benzodiazepines
  - lorazepam, 0.25–2 mg po, sl q 6 h

- short-half-life benzodiazepines
  - alprazolam, 0.125–0.5 mg po q 6 h
  - oxazepam, 10–30 mg po q 4–6 h

Atypical antidepressants (eg, mirtazipine, nefazodone, and trazodone) may be useful for patients with mixed anxiety and depression, or for patients with chronic anxiety, or panic disorder. If only a hypnotic effect is needed, trazodone is a useful alternative (25–100 mg po q hs).

## Delirium

Delirium is a global, potentially reversible change in cognition and consciousness that is relatively acute in onset. If a patient exhibits disorientation, a fluctuating level of consciousness, or other signs of cognitive impairment, delirium is likely present. The diagnosis needs to be distinguished from anxiety, depression, and dementia. Dementia is slowly progressive, usually irreversible, and commonly associated with unaltered consciousness until very late in its course. A tool such as the Folstein Mini-Mental Status Exam can be used for more definitive assessments.

### Causes to consider

There are many different causes of delirium, including infections, medications and street drugs (including withdrawal), metabolic abnormalities, hypoxemia, fecal impaction, renal or hepatic failure, urinary retention, tumor burden and secretions, vitamin deficiencies, changes in environment, etc (DSM-IV, American Psychiatric Association, 1994). Each must be given careful consideration during the history, physical examination, and appropriate investigations, as the patient's situation warrants.

### Medical management

Management of delirium begins by first evaluating the benefits vs burdens of seeking and treating reversible causes. For some patients, it may be most efficacious to try to treat the delirium rather than search for the underlying cause. In all cases, it makes sense to review the medication list and try to relate changes in medication to the onset of the symptoms. If medications are felt to be responsible, consider removing those that are nonessential.

General treatment measures are frequently beneficial. If the patient must be in the hospital, try to ensure that family and caregivers are present as much as they can be. Reduce excessive stimulation, and regularly orient and assure the patient of his or her safety. Familiar surroundings are more likely to be calming. If possible, discharge the patient home with the necessary supports in place, eg, home hospice.

If medications are needed, neuroleptics may be helpful. Haloperidol is less sedating than chlorpromazine. Monitor for extrapyramidal adverse effects, eg, dystonia or akathisia:

- haloperidol, 0.5–1 mg po, IV, SC q 1 h prn, titrate until settled, then q 12 to q 6 h to maintain. Total daily doses of 1–20 mg or more may be needed
- chlorpromazine, 10–25 mg po/IV q 4–6 h for sedating neuroleptic. Low doses are ideal for nighttime sedation, especially with day-night reversal, and/or in the elderly. Delirium may worsen in some patients because of chlorpromazine's anticholinergic effect. It also lowers the seizure threshold

Atypical neuroleptics (eg, risperidone, olanzepine, quetiapine) cause less dystonia and akathisia than typical neuroleptics (eg, haloperidol, chlorpromazine). Risperidone may be better in demented or agitated delirium:

- risperidone, 0.5–1 mg q 12 h and titrate

Sedating atypical neuroleptics (eg, olanzepine, quetiapine) are alternatives to chlorpromazine, though they have been less extensively used or studied in this population:

- olanzepine, 2.5–7.5 mg po q 12 h
- quetiapine, 75–100 mg po q 12 h

## Terminal delirium

Delirium is common in patients with advanced illness who are nearing death. It often presents as day-night reversal and can be much more complex to assess and difficult to manage. When patients who are dying experience agitation, restlessness, moaning, and/or groaning caused by terminal delirium, it is usually irreversible. Management is focused on symptomatic control and relief of the distress of both patient and family. Benzodiazepines or sedating neuroleptics are usually effective at settling the patient (see Module 12: Last Hours of Living).

## Evaluating treatment

Patients on medication should be monitored carefully and regular meetings arranged to discuss their progress. If there is a negligible or only partial response, reevaluate the diagnosis, consider adjusting the dosage, try a different medication, or inquire of family members and caregivers about adherence to medication. If delirium persists, seek advice from, or refer to, a specialist.

## Summary

Delirium, anxiety, and depression are important symptoms to assess and manage in end-of-life care. All 3 are widely prevalent and both underrecognized and undertreated. Risk factors that are related to illness or treatment or are preexisting should be borne in mind. Diagnostic

evaluations should be performed and both counseling-related therapies and medical intervention initiated. Ongoing evaluation is necessary to permit adjustment of the treatment regimens as the underlying illness progresses. Difficult cases warrant consultation from a specialist.

## Key take-home points

1. Depression, anxiety, and delirium are all underrecognized and undertreated.

### Depression

2. Don't assume that feelings of helplessness, hopelessness, and being depressed and/or miserable are inevitable consequences of advanced life-threatening illness.
3. The earlier depression is diagnosed, the more responsive it is likely to be to treatment.
4. Risk factors include poorly controlled pain or other symptoms, progressive physical impairment, advanced stage of disease, medications, pancreatic cancer, left hemispheric stroke, spiritual pain, lack of social supports, stressful life events unrelated to illness, and other factors that apply within the general population.
5. Somatic symptoms are common in patients with advanced illness and are rarely useful in diagnosing depression.
6. Assessment of depression in patients with advanced illness rests on recognition of psychological and cognitive symptoms, of which the most reliable are persistent dysphoria, anhedonia, feelings of helplessness, hopelessness, and worthlessness, and loss of self-esteem.
7. To treat depression, use a combination of supportive psychotherapy, cognitive approaches, behavioral techniques, and medication.
8. When reversal of depression is an immediate short-term goal, a rapid-acting psychostimulant such as methylphenidate is the best choice.
9. If a response in 2 to 4 weeks is acceptable, an atypical antidepressant or SSRI may be an appropriate choice.
10. Tricyclic antidepressants are not recommended as first-line therapy to manage depression unless they are also being used as adjuvants to control neuropathic pain.

### Anxiety

11. Anxiety is commonly experienced over fears and uncertainties about the future
12. It usually presents with 1 or more symptoms or signs including agitation, restlessness, sweating, tachycardia, hyperventilation, insomnia, excessive worry, and/or tension.

13. As assessment is complex, gather input by using a team approach (including family)
14. Concerns about finances, family conflicts, future disability, dependency, and existential concerns will not resolve with medication.
15. The majority of patients will be responsive to compassionate counseling and supportive therapy to explore issues that are causing or exacerbating anxiety.
16. When it appears that medications would be helpful, benzodiazepines are generally the medication class of choice.
17. Atypical antidepressants may be useful for patients with mixed anxiety and depression, chronic anxiety, or panic disorder.

## **Delirium**

18. Delirium is a potentially reversible, global change in cognition and consciousness that is relatively acute in onset (in contrast to dementia, which is relatively chronic in onset).
19. Day-night reversal may be the first manifestation of delirium in patients who are nearing death.
20. Terminal delirium (eg, agitation, restlessness, moaning, groaning associated with other signs of the dying process) is irreversible.
21. It may be most efficacious to try to treat the delirium rather than search for the underlying cause.
22. Review and discontinue any medications that may be causing or adding to delirium.
23. If medications may be helpful, choose a neuroleptic based on the degree of sedation desired and the risk of side effects (anticholinergic and extrapyramidal).

## **Pearls**

1. The screening question, “Do you feel depressed most of the time?” is both sensitive and specific.
2. Suicidal thoughts are an important symptom of depression.
3. Include family members wherever possible.
4. Start medications at low doses, especially when illness is advanced, titrating to either effect or tolerability.
5. Psychostimulants may be used alone or in combination with other antidepressants.
6. Psychostimulants may also reverse the sedation associated with opioids.
7. Low doses may be appropriate in advanced disease.

8. The secondary amines desipramine and nortipityline tend to have less adverse effects.
9. Look for reversible causes including insomnia, alcohol, caffeine, or medications (eg, beta agonists, methylxanthines).
10. Choose a benzodiazepine based on desired duration of action.
11. Agitated delirium is frequently misinterpreted as pain.
12. General measures (eg, reduced stimulation, regular orientation, reassurance) are frequently beneficial.
13. Low doses of chlorpromazine, 10 to 25 mg, are ideal for nighttime sedation, particularly with day-night reversal.

## Potential pitfalls

1. Forgetting that depressed patients are at increased risk of suicide.
2. Forgetting that benzodiazepines are amnestics. They may worsen memory or cause confusion in the frail and elderly, especially those with preexisting cognitive impairment.

## Resources

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