EPEC for Veterans

Education in **P**alliative and **E**nd-of-life **C**are for Veterans

Trainer's Guide

Module 5

Psychological Symptoms

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Module 5 trainer's notes

Principal message

Facility with the management and treatment of common psychological symptoms encountered in end-of-life care is important if quality of life and relief of suffering are to be achieved.

Module overview

Module 5 presents an approach to the assessment and management of a number of common psychological symptoms. Treatment options such as counseling and therapy are discussed as well as pharmacological approaches for management of acute and chronic anxiety.

The module is arranged as a series of presentations on individual symptoms. Each presentation deals with the pathophysiology, assessment, and management of a common symptom. Each can be presented in a 30-45 minute session.

Preparing for a presentation

1. Assess the needs of your audience

Choose from the material provided in the syllabus according to the needs of your expected participants. It is better for participants to come away with a few new pieces of information, well learned, than to come away with a deluge of information, but remembering nothing.

2. Presentation timing

Allow sufficient time to collect participants' demographic data and complete the pre-test.

The suggested timing for each part of this module is:

Introduction	2-3 minutes
Presentation	35 minutes
Summary	2-3 minutes
Post-test & Evaluation	5 minutes
Total	44-46 minutes

3. Number of slides: 62

4. Preparing your presentation

The text in the syllabus was not designed to be used as a prepared speech. Instead, the slides have been designed to trigger your presentation. Although the slides closely follow the text of the syllabus, they do not contain all of the content. Their use presumes that you have mastered the content. You may want to make notes on the slide summary pages to help you prepare your talk in more detail and provide you with notes to follow during your presentation.

You will not want to use all of the slides for a single 45-minute session. You will only be able to cover 1 or possibly 2 of the symptoms well. By giving a handout, you can refer participants to it for the information you choose not to cover. Alternatively, you might choose to present this material in several sessions in order to cover all of the symptoms comprehensively.

Practice your presentation using the slides you have chosen, and speaking to yourself in the kind of language you expect to use, until it is smooth and interesting and takes the right amount of time.

5. Preparing a handout for participants

The syllabus text and slides in the **Trainer's Guide** were designed to be reproduced and provided to participants as a handout, either in its entirety, or module by module. If the entire curriculum is not being offered, please include the following in each handout:

- **EPEC for Veterans Front Cover Page**
- **EPEC for Veterans Acknowledgment Pages** (to acknowledge the source of the material)
- Syllabus and slides for **Module 5**

6. Equipment needs

- computer with DVD capability or separate DVD player
- flipchart and markers for recording discussion points

Making the presentation

1. Introduce yourself

If you have not already done so, introduce yourself. Include your name, title, and the organization(s) you work for. Briefly describe your clinical experience related to the information you will be presenting.

2. Introduce the topic

Show the title slide for the module. To establish the context for the session, make a few broad statements about the importance of managing symptoms as a clinical skill. Identify which symptoms you will be covering. Tell participants the format and time you will take to present the session. Identify any teaching styles other than lecture that you intend to use.

3. Review the session objectives

Show the slide with the session objectives listed. Read each objective and indicate those that you are planning to emphasize.

4. Show the trigger tape or present the clinical case

After reviewing the objectives for the session, show the trigger tape or present one of the clinical cases below. It has been designed to engage the audience and provide an appropriate clinical context for the session. It was not designed to demonstrate an ideal interaction, but to 'trigger' discussion.

Clinical case (Part 1: Anxiety)

B.C. is a 62-year-old married Vietnam Veteran with metastatic lung cancer who is noted to have difficulty controlling his temper and getting along with people, including the staff on the palliative care unit. He notes frequent nightmares and flashbacks about his combat experience. He has chronic insomnia and says his nerves are "shot." He mistrusts his medical team and has not been adherent at times with his medications and outpatient appointments. His medications include ranitidine, dexamethasone, gabapentin, and albuterol. He uses opioids as needed for pain. His vital signs show mild hypertension, tachycardia, and an elevated respiratory rate. A CT scan confirms cerebral metastases. An initial Folstein Mini-Mental State Examination is normal.

Clinical case (Part 2: Depression)

B.H. is a 72-year-old married Veteran with severe congestive heart failure. He has a three month history of fatigue, insomnia, nausea with decreased appetite, and poorly controlled pain. He also reports feelings of sadness and hopelessness. His wife reports that he often states he is helpless and no longer enjoys his hobbies or spending time with her. She states he has had these feelings for at least two months, and they have been getting progressively worse. His medications include ranitidine, prednisone, gabapentin, and lorazepam. He uses opioids as needed for pain and dyspnea. Examination reveals depressed mood and flat effect. His vital signs are normal. An initial Folstein Mini-Mental State Examination is normal.

Clinical case (Part 3: Delirium)

A 72-year-old married Veteran with cirrhosis of the liver and newly diagnosed cellular carcinoma is admitted to a palliative care unit with a two-day history of confusion and aggressive behavior. Over the next two days, he demonstrates intermittent agitation, confusion, and disorientation. These seem to be worst at night, while in mid-morning, he was observed to be deeply asleep. At times he shouts out about Veterans 'going missing,' and believes that his life is in danger. Staff on the unit are unable to determine any recognizable pattern in his outbursts. His wife reports that in between periods of agitation, he can be cooperative and 'back to his normal self.' His medications include ranitidine, dexamethasone, gabapentin, and lorazepam. He uses opiate analgesics as needed for pain. Examination reveals non-specific neurological abnormalities. His vital signs show mild hypertension, tachycardia, and an elevated respiratory rate. An initial Folstein Mini-Mental State Examination demonstrates problems in orientation, recall, and attention, with a total score of 18 of 30.

Discussion

If the discussion is slow to start, you may want to ask more direct questions, like:

- Have they had similar patients?
- How did the patient react to the clinician's questions?
- How did the clinician start? What was well done? What was missing?
- What did the clinician do to foster a comfortable atmosphere?
- How did the physician address the patient's concerns?

Use the discussion to set the stage for the material to follow. Don't let the discussion focus on a critique of the technical quality of the trigger tape or how 'real' the players seemed. If the participants don't like something that was said or done in the trigger tape, ask them how they would do it themselves.

Setting limits to discussion time

Limit discussion of each scene of the trigger tape to no more than 5 minutes, then move on to the presentation. To help move on if the discussion is very engaged, try saying something like:

- Let's hear two last points before we move on.
- Now that you have raised many of the tough questions, let's see how many practical answers we can find.

5. Present the material

Recommended style: Interactive lecture

An interactive lecture will permit you to engage your audience, yet cover 2 to 3 symptoms within 45 to 60 minutes. Identify the symptoms you plan to cover and select the slides to go with those symptoms. Use your own case vignettes to illustrate clinical applications for the information presented.

Alternative style: Case-based

If you have mastered the material and the method, a case-based approach to teaching this module can be very effective.

Turn off the projector and turn up the lights. Use a flipchart or overhead projector.

There is a case vignette at the beginning of each symptom in this module. Ask a participant to read the vignette. In a Socratic way, ask participants to help 'solve' the cases. Ask them questions about assessment and management. Ask them to explain the known pathophysiology that underlies the management of each symptom. Write points on the overhead or flipchart. Draw diagrams yourself. Don't be concerned about your artistry, the points will come across.

Use the discussion to interweave the key take-home points from the syllabus.

6. Key take-home points

Anxiety

1. Anxiety causes dysfunction in Veterans and those near them and undermines quality of life and quality of care.
2. Assess openness to counseling as a personal management approach for the Veteran.
3. Choose a benzodiazepine for short-term pharmacological treatment needs; choose a selective serotonin reuptake inhibitor for chronic anxiety.
4. Posttraumatic Stress Disorder (PTSD) related to military service is increasingly recognized among Veteran populations. PTSD often worsens symptoms of anxiety associated with new stressors such as advanced cancers and other life-limiting illnesses.

Depression

5. Depression is treatable, even in patients with advanced cancer.
6. The screening question, "Do you feel depressed most of the time" is sensitive and specific.

7. Psychostimulants (for rapid effect) can be started at the same time as antidepressants (such as the SSRIs) that take longer to work.
8. Counseling plus pharmacotherapy is more effective than either alone.

Delirium

9. Delirium is common among the seriously ill, particularly the elderly and demented.
10. Initial management should focus on environmental changes and neuroleptics.
11. Explain to the family that behaviors associated with delirium do not reflect his or her personality or relational meaning.
12. Lack of knowledge about terminal delirium is common. Memories of it among surviving family members can be traumatic. Learn to recognize and manage early.
13. It is not always clear if the current episode of delirium is a terminal event. A time trial of treatment of the symptoms and causes for the delirium that over a short time shifts to a terminal care approach when the course had declared itself.

7. Summarize the discussion

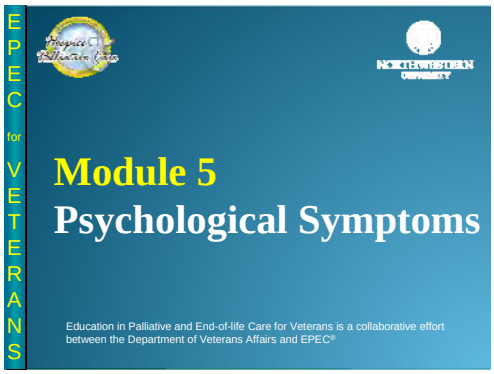
Briefly review each part of the presentation. Recap 2 or 3 of the most important points that were discussed.

8. Post-test/evaluation

Ask the participants to evaluate the session.

Abstract

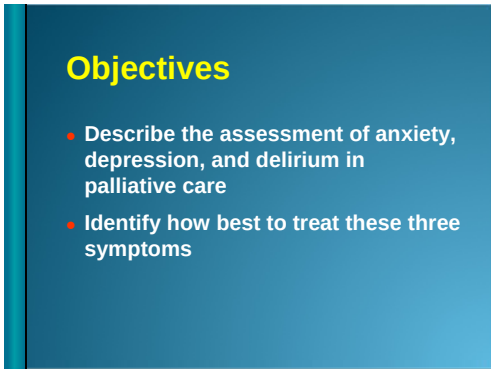
Slide 1



Depression, anxiety, and delirium may cause mental, emotional, and physical suffering and disability for Veterans in palliative care. These three conditions can all be difficult to diagnose and manage and yet they can have profound effects on Veterans' quality of life and the experiences of their families. They require both medical and psychosocial approaches to their treatment. This module is intended to help clinicians detect, diagnose, and treat these three important clinical entities that are common in palliative care. As in other aspects of palliative and end-of-life care, incorporation of appropriate members of the interdisciplinary team is crucial.

Objectives

Slide 2



After studying this module, clinicians will able to:

- describe the assessment of anxiety, depression, and delirium in palliative care; and
- identify how best to treat these three symptoms.

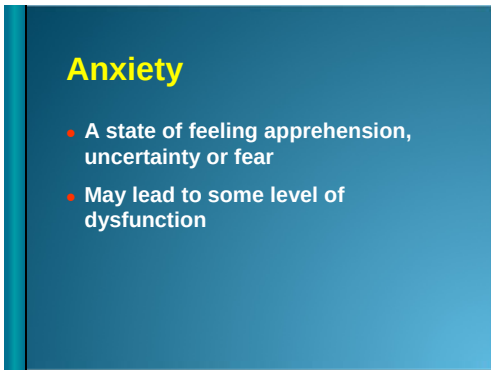
Part 1: Anxiety

Clinical case

B.C. is a 62-year-old married Vietnam Veteran with metastatic lung cancer who is noted to have difficulty controlling his temper and getting along with people, including the staff on the palliative care unit. He notes frequent nightmares and flashbacks about his combat experience. He has chronic insomnia and says his nerves are "shot." He mistrusts his medical team and has not been adherent at times with his medications and outpatient appointments. His medications include ranitidine, dexamethasone, gabapentin, and albuterol. He uses opioids as needed for pain. His vital signs show mild hypertension, tachycardia, and an elevated respiratory rate. A CT scan confirms cerebral metastases. An initial Folstein Mini-Mental State Examination is normal.

Introduction

Slide 3



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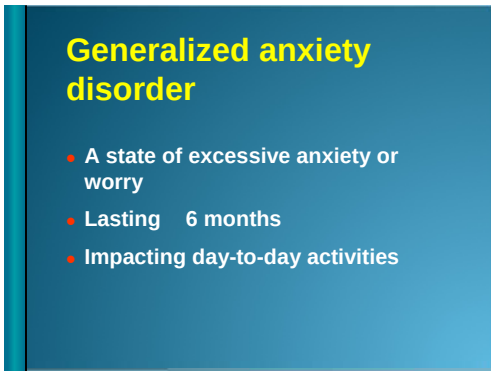

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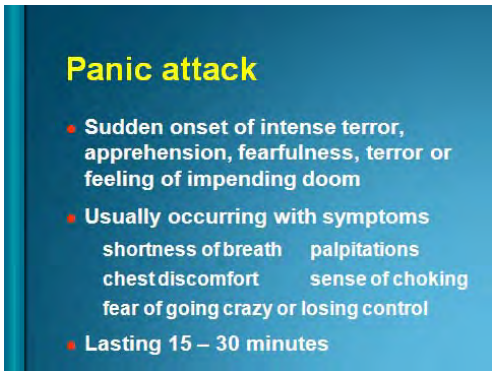


There are a number of definitions of anxiety and related states.

Anxiety is *a state of feeling apprehension, uncertainty and fear*.

A **generalized anxiety disorder** is *a state of excessive anxiety or worry lasting at least six months and impacting day-to-day activities.*[1]

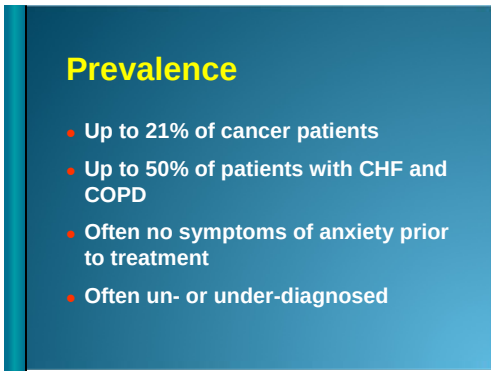
A **panic attack** is *the sudden onset of intense terror, apprehension, fearfulness, or a feeling of impending doom, usually occurring with symptoms such as shortness of breath, palpitations, chest discomfort, a sense of choking, and fear of "going crazy" or losing control.*[1] Panic attacks are discrete in nature and time course, usually lasting 15 – 20 minutes.

Veterans with advanced illness and their families commonly experience anxiety over fears, therapies, their ability to live life as they have known it, and uncertainty about their future. Their distress may also be related to other physical, psychological, social, spiritual, practical, end-of-life, and loss issues that derive from the illness, or it may be a component of other syndromes, e.g., a primary anxiety disorder or an underlying panic disorder that is unmasked by serious life-threatening illness. Such anxiety symptoms may be significant but not reach the threshold for an anxiety disorder.

Anxiety often co-occurs with adjustment disorders and/or depression. An adjustment disorder is *a psychological response to an identifiable stressor which results in the development of clinically significant emotional or behavioral symptoms.*[1] Depression is defined and reviewed in the section that follows. Common symptoms in depression, such as loss of appetite, decreased libido, and insomnia may also be part of anxiety states.[2]

Prevalence

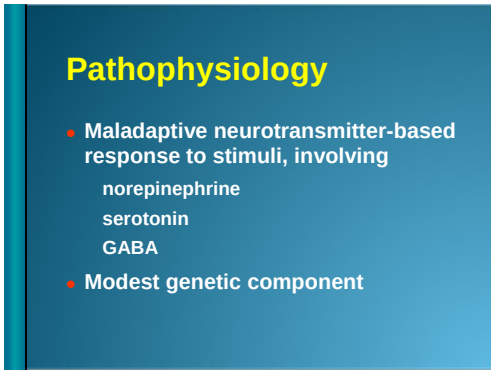
Slide 6



Up to 21% of cancer patients may have persistent anxiety symptoms, although it appears that only a small percentage had any symptoms of anxiety prior to the diagnosis of cancer.[3] Up to 50% of patients with CHF and COPD experience anxiety.[4] Anxiety can be manifested in patients with any life-limiting illness. Some diseases such as COPD may have anxiety as a symptom of dyspnea while treatments such as beta-agonists and methylxanthines (e.g., theophylline) also can contribute to anxiety even when used as directed.

Pathophysiology

Slide 7

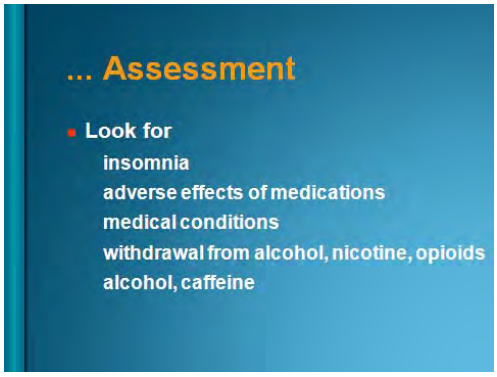


A biological understanding of anxiety is only just emerging. It can be characterized by an excessive response to stress primarily involving the neurotransmitters norepinephrine, serotonin, and gamma-aminobutyric acid (GABA). In contrast with depression, genetic factors appear to play a modest role. Environment, particularly early in life, is thought to be more important. However, associated physical conditions such as hypoxia, sepsis, poorly controlled pain, and adverse medication reactions (or medication withdrawal) may be associated with anxiety.[5]

Assessment

Slide 8

Slide 9



Anxiety usually presents with one or more symptoms or signs, including: excessive worry, apprehension, dread, foreboding, tension, agitation, restlessness, hyperarousal, irritability, insomnia, sweating, tachycardia, hyperventilation, shortness of breath, gastrointestinal distress, and/or nausea.

Anxiety should be evaluated in every clinical encounter. Ask questions like:

- "Do you find yourself worrying a lot?"
- "Are you often fearful?"
- "Do you feel anxious or nervous?"

Input from family, friends, and other members of the interdisciplinary team may be invaluable. Tools such as the Hospital Anxiety and Depression Scale, the Profile of Mood States or the Geriatric Anxiety Inventory may be helpful.[6,7,8] Posttraumatic Stress Disorder (PTSD) may be a previously-known diagnosis. For other Veterans, the stress of illness may precipitate symptoms and lead to a new diagnosis of anxiety. PTSD is now recognized as an anxiety disorder and many of the symptoms overlap with more straightforward anxiety.[9] Additionally, the anxiety that can accompany PTSD may worsen with life-limiting illness. PTSD is described in EPEC for Veterans module 8.

In addition to the above basic signs and screening symptoms of anxiety, look for the following:

- insomnia (see the EPEC for Veterans Module 6b: Constitutional Symptoms);
- adverse effects of medications;
- medical states such as pulmonary emboli, uncontrolled pain, abnormal metabolic states (including hyperthyroidism), and cardiac arrhythmias;
- withdrawal from alcohol, nicotine or opioids; and
- excessive alcohol, nicotine or caffeine.

Management

Slide 10

Treat Veterans experiencing anxiety with a combination of supportive care, complementary or alternative therapies and pharmacotherapy. Treat any reversible causes. Lack of improvement within days to short weeks may indicate a need for more aggressive therapy and consultation with a psychiatrist or psychologist trained in psychotherapy and psychopharmacology.

Supportive counseling

Slide 11

Slide 12

The majority of Veterans and their families will be receptive to compassionate exploration of the specific issues that are causing or exacerbating their anxiety. Concerns about treatment options, finances, family conflicts, future disability, dependency, existential questions, and dying will not resolve with medication. Instead, they will benefit from counseling and supportive therapy.

Weave in supportive counseling that uses aspects of brief supportive psychotherapy into routine interventions. Spend time educating the Veteran and family members about modifiable factors that contribute to anxiety and depression.

Supportive counseling has many goals. The interaction itself may be therapeutic. During the discussions, provide the Veteran with an improved understanding of his or her prognosis, potential treatments, and outcomes. These may help the Veteran put perceptions, expectations, needs, fears, and fantasies about his or her illness and death into a different perspective. Discuss short-term goals. Identify and reinforce the Veteran's previously demonstrated strengths and successful coping techniques. This will help the Veteran and family to establish or reestablish their sense of self-worth and meaning (see EPEC for Veterans Module 1: Goals of Care).

It is important to understand issues of loss and grief when evaluating anxiety and psychological distress. They can occur at anytime during the course of the illness and bereavement for both Veterans and family members. They are discussed in more detail in EPEC for Veterans Module 12: Loss, Grief and Bereavement.

Time spent by clinicians talking with Veterans about their feelings and reframing their ideas may be very helpful. This can be done by any clinician involved in a Veteran's care even if not a mental health specialist. In addition, formal and informal sessions with psychiatrists, psychologists, social workers, and chaplains may also be beneficial.

Complementary therapies

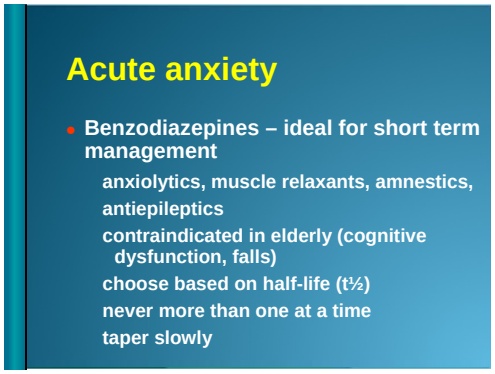
Slide 13

Complementary or alternative medical approaches may help some Veterans. Massage therapy, guided imagery, hypnosis, meditation or aromatherapy can be useful tools to decrease anxiety.[2,10] As interventions for anxiety, each of these therapies requires expertise that many clinicians may not have. The first step for any clinician, however, is to recognize the possibility of an alternative or complementary approach and refer to local experts in these techniques. The NIH's National Center for Complementary and Alternative Medicine has an extensive website that reviews the basics of many alternative approaches. It is available at: http://nccam.nih.gov/.

Pharmacological management

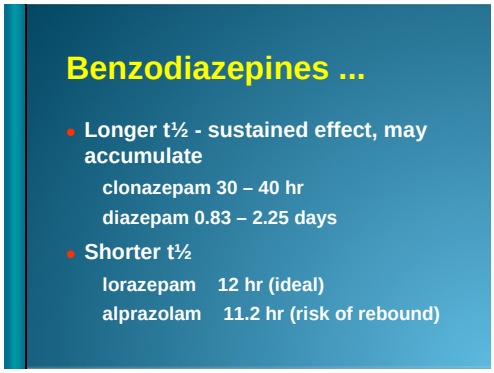
Acute anxiety

Slide 14



Benzodiazepines are usually the medications of choice for the short-term management of acute anxiety reactions when immediate relief is desired. They have four major actions as anxiolytics/hypnotics, amnestics, skeletal muscle relaxants and antiepileptics. Choose a benzodiazepine based on the desired half-life.

Slide 15



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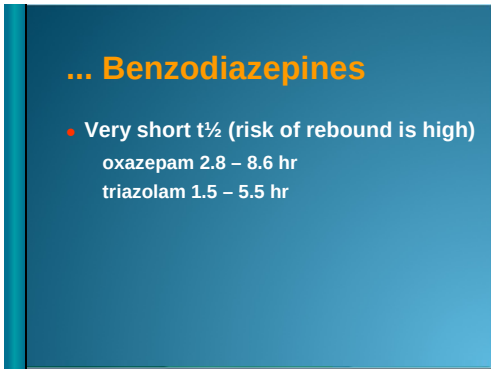


Longer half-life benzodiazepines, e.g., clonazepam, have a more sustained effect, although some, e.g., diazepam, may accumulate, and may cause prolonged sedation.

Common starting doses are:

- Clonazepam 0.5–2 mg PO qd to bid PRN, or
- Diazepam 2 mg PO qd or bid.

Shorter half-life benzodiazepines, e.g., lorazepam, can be dosed more frequently. Lorazepam may also reduce anticipatory nausea and vomiting associated with chemotherapy.[11,12]

Common starting doses are:

- Lorazepam 0.25–2 mg PO, SL q 6 hrs PRN.

Very short half-life benzodiazepines, e.g., alprazolam, are not indicated for long-term use, but may be useful in the acute setting. Clinicians should be aware of potential for withdrawal or rebound anxiety.

Common starting doses are:

- Alprazolam 0.25-0.5 mg PO q 6 hrs PRN.

Whichever medication is chosen, start with low doses and titrate to effect and tolerability.

Benzodiazepines and anticholinergic medications may worsen confusion or induce delirium, particularly in the elderly.[13,14] They can also cause confusion in patients with preexisting cognitive impairment, or increase gait instability.

Do not use more than one benzodiazepine at a time. When discontinuing benzodiazepines, taper them slowly by reducing the dose by 25-50% each day or two.

Slide 17

When benzodiazepines are contraindicated, e.g., among elderly patients who are susceptible to falls or confusion, or there has been a significant adverse event, then gabapentin or trazodone may be better choices.[15] Although they do not have as much of an anxiolytic effect as the benzodiazepines, they can be useful medications. Common starting doses are:

- Gabapentin 300 mg PO at bedtime. If ineffective, increase the dose every 3-5 days: first to 300 mg PO q 12 hrs, then to 300 mg PO q 8 h, then by 300 mg q 8 h. The maximum dose is 3,600 mg daily.
- Trazodone 12.5 mg PO q 2 h PRN for anxiety or agitation; or
- Trazodone 25–50 mg PO at bedtime for insomnia.

Chronic anxiety

Slide 18

Slide 19

Selective serotonin reuptake inhibitors (SSRIs) are effective in managing chronic anxiety.[16] Some SSRIs, such as fluoxetine are more 'activating' than sedating and should be avoided for the treatment of anxiety. Four SSRIS which are sedating and used for anxiety are: paroxetine, citalopram, escitalopram and sertraline. Paroxetine is often chosen because it tends to be more sedating and can provide a calming effect. Common starting doses are:

- Paroxetine 10-20 mg PO daily. Target is 20-40 mg PO daily. Maximum dose is 60 mg/day.
- Citalopram 10-20 mg PO daily. Increase weekly by 10-20 mg PO daily. Usual target is 40 mg PO daily. Maximum dose is 60 mg/day.
- Escitalopram 5-10 mg PO daily. Maintenance and maximum dose is 10-20 mg PO daily.
- Sertraline 25-50 mg PO daily; target dose is 50-150 mg daily with 200 mg/d maximum.

Antidepressants can also help to ameliorate mixed states of anxiety and depression. For severe anxiety or panic disorder, consider starting both a benzodiazepine and an SSRI together. Once the SSRI becomes effective in 4 to 6 weeks, the benzodiazepine can be tapered.

If there is a question about the appropriate treatment or if initial treatments are not working in a timely manner, i.e., days to 1-2 weeks, consult a psychiatrist or psychologist. For complicated benzodiazepine discontinuation or when alcohol withdrawal is involved, also consider consulting a psychiatrist.

Summary

Slide 20

Anxiety is common among Veterans and their families. It is often overlooked and/or not treated aggressively. Careful, proactive attention to anxiety will improve adherence to treatment, psychosocial and family stress, quality of life, and ultimately quality of dying. Counseling, complementary or alternative therapies, and medication all play a role in the management of anxiety. Therapies can be tailored to an individual Veterans' and family's needs and preferences. Do not hesitate to consult with mental health professionals, including psychiatrists, psychologists, nurses, social workers, and chaplains as appropriate if there is a question about anxiety or if simple interventions do not yield improvement in a timely manner.

Key take-home points

1. Anxiety causes dysfunction in Veterans and those near them and undermines quality of life and quality of care.
2. Assess openness to counseling as a personal management approach for the Veteran.
3. Choose a benzodiazepine for short-term pharmacological treatment needs; choose a selective serotonin reuptake inhibitor for chronic anxiety.
4. Posttraumatic Stress Disorder (PTSD) related to military service is increasingly recognized among Veteran populations. PTSD often worsens symptoms of anxiety associated with new stressors such as advanced cancers and other life-limiting illnesses.

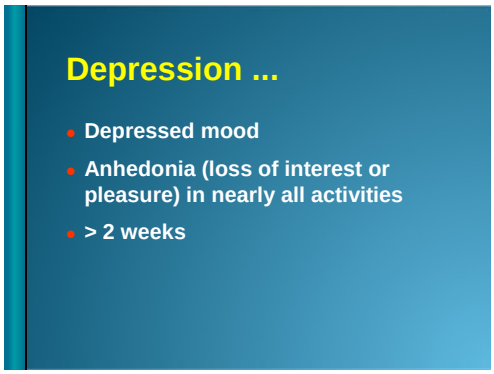
Part 2: Depression

Clinical case

B.H. is a 72-year-old married Veteran with severe congestive heart failure. He has a three month history of fatigue, insomnia, nausea with decreased appetite, and poorly controlled pain. He also reports feelings of sadness and hopelessness. His wife reports that he often states he is helpless and no longer enjoys his hobbies or spending time with her. She states he has had these feelings for at least two months, and they have been getting progressively worse. His medications include ranitidine, prednisone, gabapentin, and lorazepam. He uses opioids as needed for pain and dyspnea. Examination reveals depressed mood and flat effect. His vital signs are normal. An initial SLUMS (St. Louis Mental Status) Exam is normal.

Introduction

Slide 21



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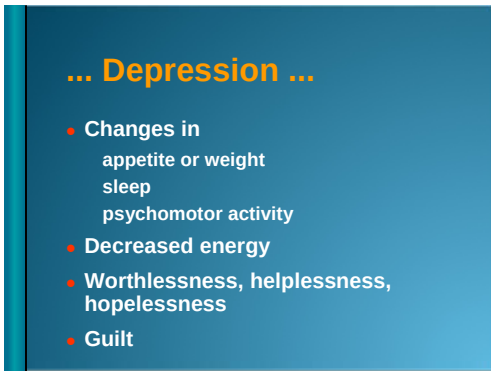

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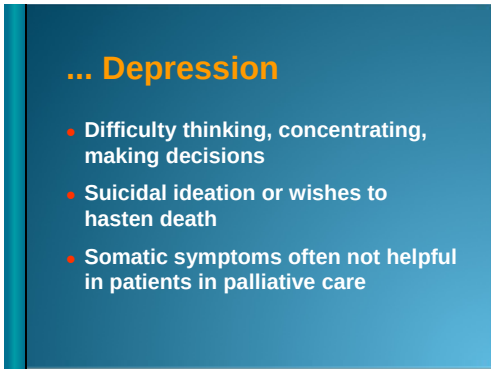


Major depression is *an episode during which the patient complains or is noted to have depressed mood or the loss of interest or pleasure in nearly all activities for a period of at least two weeks.*[1]

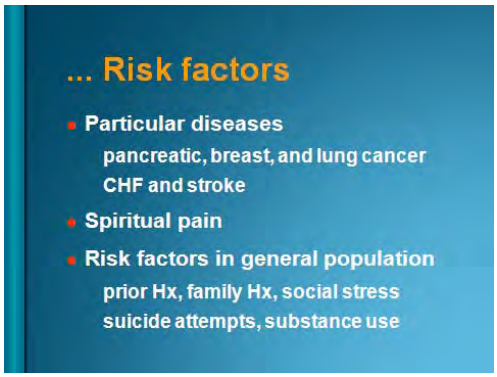
Veterans with depression also experience other symptoms including: changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts.[1] Depression may be viewed by Veterans or family members as something to be ashamed of, or as a sign of weakness. Through education, clinicians can help correct this misconception.

Persistent depression is not 'normal' for Veterans with a serious illness or at the end of life. It is a myth that feeling helpless, hopeless, depressed, and/or miserable are inevitable consequences of advanced life-threatening illnesses.[17]

Risk factors

Slide 24

Slide 25



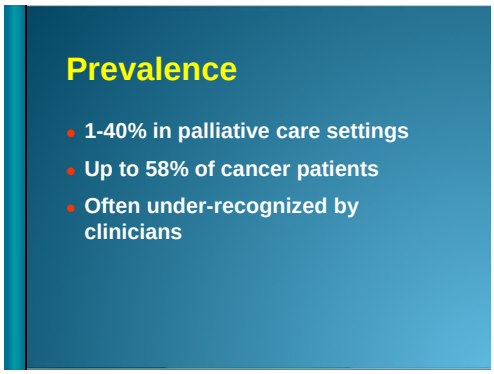
For Veterans in palliative care, there are many risk factors for major depression. Poorly controlled pain and other physical symptoms contribute to depression and are particularly important because they are frequently remediable (see EPEC for Veterans Module 4: Pain Management).[17] Progressive physical impairment and an advanced stage of disease also correlate with a higher incidence of depression.[18] With some medications, e.g., steroids, benzodiazepines, and various chemotherapeutics, depression is a potential adverse effect.[19] A few cancers, e.g., pancreas, breast, and lung, are associated with a higher incidence of depression.[17] Depression often coexists with major medical illnesses such as diabetes, stroke, heart disease, Parkinson's disease and HIV/AIDS. Patients with such comorbidities often experience more severe symptoms of both the depression and the medical illness and treatment of the depression can improve the outcome of treating the comorbid medical illness.[20] Finally, spiritual pain and conflicts over issues of meaning, guilt, and fear may manifest as depression. [17]

Risk factors for depression that occur within the general population, e.g., prior episodes of depression or mania or a family history of psychiatric illness, also apply to patients in palliative care.[21] Veterans are also at increased risk when they lack social supports or are experiencing other stressful life events that are unrelated to or consequences of their illness.[17]

Issues of grief and bereavement may also be important risk factors for depression.[17] (See EPEC for Veterans Module 12: Loss, Grief and Bereavement).

Prevalence

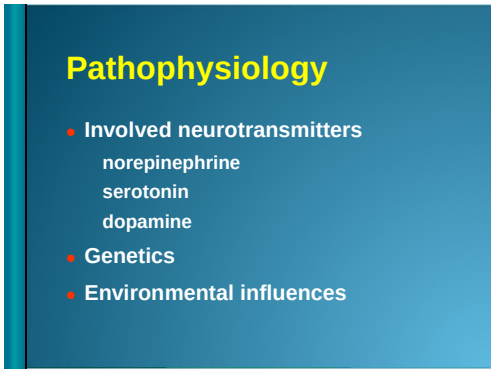
Slide 26



Many Veterans with a serious illness experience periods of intense sadness or hopelessness. These feelings are usually present for a relatively short period, and then resolve. For some patients, however, they may herald a major depressive illness. The prevalence of depression ranges from 1-40% in palliative care settings.[17] This very wide range is likely due to the variety of techniques clinicians use to assess depression. It occurs in up to 58% of cancer patients.[22,23] Unfortunately, it has been found that many clinicians who work with these populations underestimate the level of psychological distress of their patients.[24,25,26]

Pathophysiology

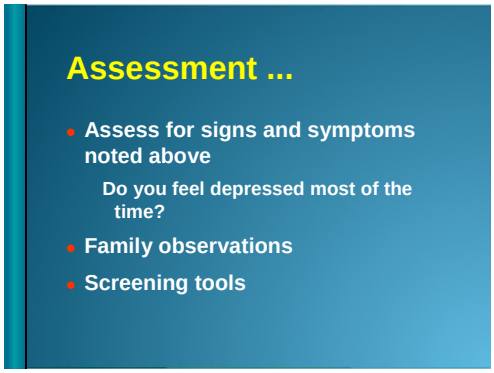
Slide 27



A biological understanding of depression is still in development. Recent pharmacological advances in the treatment of depression point to altered levels of norepinephrine, serotonin and dopamine.[27] Electroconvulsive therapy (ECT), effective for the treatment of major neuro-vegetative depression, induces small seizures which in turn release increased amounts of these neurotransmitters in the brain.[28] However, the precise mechanism of these neurotransmitters is not yet clear. Genetic and environmental influences play a role in the pathogenesis of depression.[29, 30]

Assessment

Slide 28



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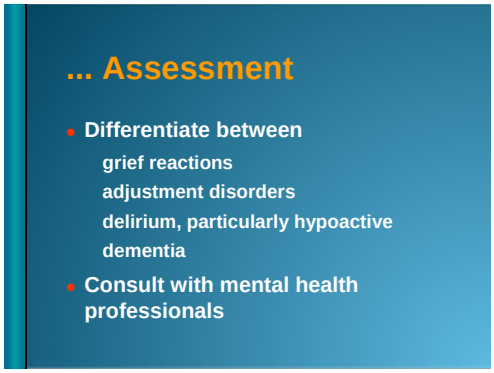


The earlier depression is diagnosed, the more responsive to treatment it is likely to be. Treatment for depression may help Veterans feel better and have increased energy and engagement in the world and achieve final goals before they die.

Focus assessment on psychological and cognitive symptoms that are indicative of the diagnosis. Reliable symptoms of major depression include persistent dysphoria, anhedonia (loss of pleasure), feelings of helplessness, hopelessness, worthlessness, and loss of self-esteem. Other symptoms 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 also be signs of depression.[17,31,32]

Somatic symptoms, e.g., changes in appetite, weight, energy level, libido, or sleeping, are important when making a diagnosis of depression in a non-medically ill population.[17] However, somatic symptoms are almost invariably present in patients with advanced illness, making it difficult to discern their etiology.[17]

The following question appears to be a sensitive and specific question in palliative care patients:[33]

- "Do you feel depressed most of the time?"

Requests to hasten death may be a marker of undiagnosed depression (see EPEC for Veterans Module 13: Responding to Requests for Hastened Death). Asking about the severity and time course of psychological and cognitive symptoms may help make the diagnosis.

When possible, inquire about the observations of family, friends, and other members of the health care team, as they may provide considerable information about baseline behaviors and add to the history.

There are specific screening tools for identifying depression, such as, the Beck Depression Inventory, or the Hospital Anxiety and Depression Scale or the PHQ-2 or PHQ-9. [34,35,31]

It is important and sometimes difficult to distinguish depression from grief reactions, adjustment disorders, or hypoactive delirium. Be aware that depression can present with

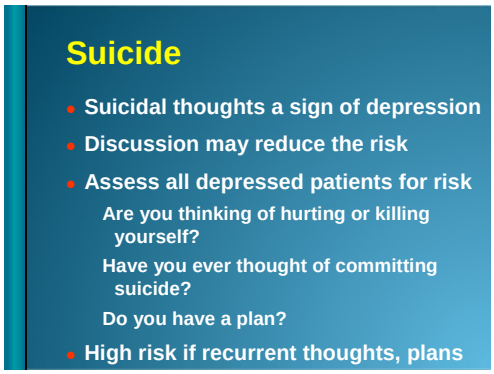
either psychomotor retardation or agitation. Depression that occurs in response to a psychosocial stressor is distinguished from an adjustment disorder with depressed mood in that the full criteria for a major depressive episode are not met in adjustment disorder. After the loss of a loved one, or even after receiving a diagnosis with a poor prognosis, depressive symptoms may be attributable to grief rather than to a major depressive episode, unless they persist for more than two months or include significant functional impairment, severe preoccupation with worthlessness, psychotic symptoms, psychomotor retardation, or suicidal ideation.[19] Hypoactive delirium can be mistaken for and be difficult to distinguish from depression (see Part 3 of this module). A detailed history of onset and time course of both mood and cognitive symptoms is essential. In delirium, the cognitive impairment is more profound and pervasive, and the onset is more abrupt.[36]

It is also important to recognize the depressive phase of Bipolar Disorder when present as it has significant implications for treatment. Patients with bipolar disorder meet DSM-IV criteria for a major depressive episode; typical symptoms can include anergia and hypersomnolence, which may be difficult to distinguish from the symptoms of their advanced disease. Treating the depressed bipolar patient with an antidepressant in the absence of a mood stabilizer (such as lithium, divalproex sodium, or atypical antipsychotics) may cause the patient to "flip" from the depressive phase to the manic phase of their illness. Psychiatric consultation is recommended for assistance with treating depression in a patient with known or suspected Bipolar Disorder.

Whenever you are uncertain how to complete a detailed assessment of depression, or the situation appears to be complex, ask a psychiatrist or a psychologist for assistance.

Suicide among patients with depression

Slide 30



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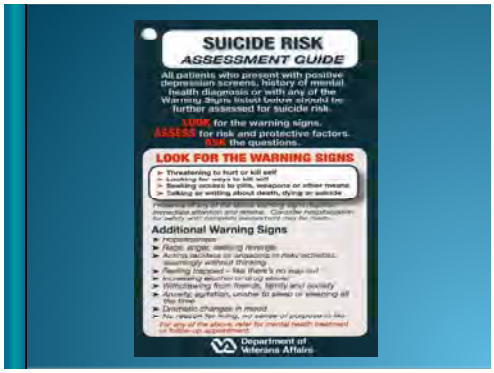


Suicidal thoughts are an important sign of depression. It is a myth that asking about suicide will 'put the idea into someone's head.' To the contrary, allowing patients to discuss the thoughts they are having may reduce the likelihood they will actually commit suicide, particularly if the health care professional acknowledges their feelings and desires, and addresses the root causes of their distress (see EPEC for Veterans Module 13: Requests for Hastened Death).

Approximately 1,000 suicides occur each year among Veterans utilizing VA care, with about 5,000 suicides occur per year among all living Veterans.[37] Veterans are twice as likely to die of suicide over time than the general population.[38]

As part of the Uniform Mental Health Service Package, each VA medical center employs a Suicide Prevention Coordinator, serving as a valuable resource for both patients and health care providers. A National Suicide Prevention Hotline exists for all patients: 1-800-273-TALK which is staffed by VA Mental Health professionals. In addition, the Department of Veterans Affairs has published a Suicide Risk Assessment Guide depicted in the slide above and is available at all VA facilities.

Assess all Veterans with depressive symptoms about thoughts and plans to commit suicide. Key questions include:

- "Are you thinking about hurting yourself?"
- "Are you thinking of ending your life?"
- "Do you have a plan?"

Consider Veterans with recurrent thoughts of suicide or plans to be at high risk. Consult a mental health professional experienced in this area immediately.[17]

All Veterans who present with a history of a mental health diagnosis or with any warning signs listed below should be further assessed for suicidality.

Warning signs include:

- threatening to hurt or kill self,
- looking for ways to kill self,

- seeking access to pills, weapons of other means, and
- talking or writing about death, dying or suicide.

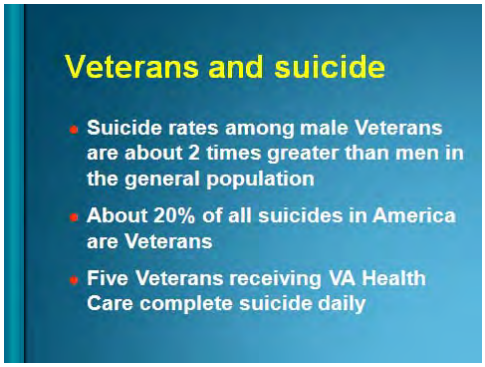
Any of these above requires immediate attention and referral to emergency services.

Additional warning signs that should prompt more in-depth evaluation include:

- hopelessness;
- rage, anger, seeking revenge;
- acting recklessly or engaging in risky activities;
- feeling trapped like there is no way out;
- increasing alcohol or drug abuse;
- withdrawing from family or friends;
- drastic mood changes; and
- no reason for living or sense of purpose.[39]

Veterans and suicide

Slide 32



In recent years, suicide prevention has become an area of increased emphasis within VA. Suicide is a serious health care issue both in active duty military personnel and in the Veteran population after discharge. Often this has been looked on with a nihilistic treatment attitude. In fact suicide is often preventable. Most suicidal Veterans want to live; they are just unable to see alternatives to their problems.

Suicidal ideation is often a "process," not a static occurrence and therefore a sustained prevention program is needed. Most suicidal Veterans (~ 80%) give definite warnings of their suicidal intentions, but others are either unaware of the significance of these warnings or do not know how to respond to them. 75% of elderly people who complete suicide have seen a physician in the preceding month. Contrary to popular myth, talking about suicide does not cause someone to be suicidal. In fact, an open and honest conversation can help reduce stigma and relieve feelings of isolation.[40]

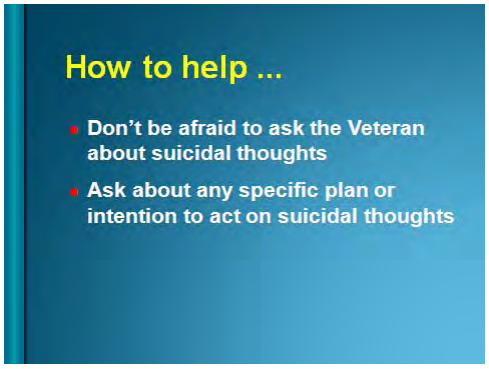
Suicidality and end-of-life care

Slide 33

It has been demonstrated that individuals who have serious and life-limiting illness often have suicidal thoughts. It is important to assess for these thoughts and feelings routinely. It is also important that the Veteran understand that it is not abnormal for these thoughts to occur but that it is important to provide excellent physical symptom control, emotional, practical, social and spiritual support in a nonjudgmental way and ensure that Veterans never feel abandoned. For the Veteran, issues of autonomy are often central to suicidal thoughts. Open discussion of goals of care with plans to maximize autonomy and maintain dignity is essential to effective end-of-life care.

Management of suicidality

Slide 34



Slide 35

Develop a safety plan with the Veteran; involve family and caregivers to ensure a safe environment. Suicide is often an impulsive act. It is important to take this into account

when developing a safety plan and openly discuss securing firearms and other potential dangerous things such as medication. Each step must be taken with sensitivity as the Veteran can feel that they are not trusted, and this may reduce the Veteran's sense of autonomy. It is important to work closely with mental health providers and offer hospitalization if there is imminent risk for suicide. The Department of Veterans Affairs has recognized the importance of assessment and prevention of suicide and has made prevention brochures and counseling recovery available at www.mentalhealth.va.gov/suicide_prevention/index.asp.

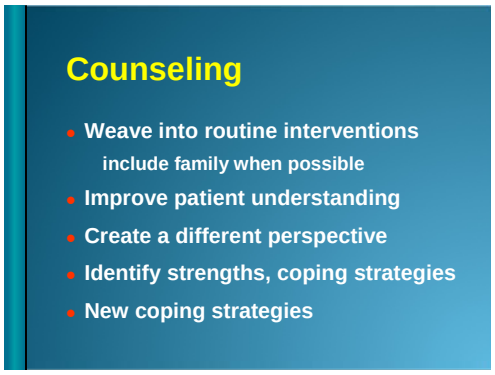
Management

Slide 36

Treat depressed Veterans with a combination of supportive and other psychotherapy modalities, and pharmacotherapy. In some Veterans, complementary therapies may also be helpful. Lack of improvement within a few weeks suggests a need for more aggressive therapy or a psychiatric consult. For overall approaches to management, there are a number of reviews on the management of depression[17,41] as well as consensus guidelines from the American Psychiatric Association[42] and Clinical Practice Guidelines from the American Medical Directors Association.[43]

Counseling

Slide 37



Individual and group counseling have both been shown to reduce depressive symptoms.[44,45] Weave supportive counseling that uses aspects of brief supportive psychotherapy into routine interventions. Spend time educating the patient and family

members about modifiable factors that contribute to anxiety and depression. Supportive counseling has many goals. The interaction itself may be therapeutic. During the discussions, provide the Veteran with an improved understanding of his or her prognosis, potential treatments, and outcomes. These may help the Veteran to put perceptions, expectations, needs, fears, and fantasies about his or her illness and death into a different perspective. Discuss short-term goals. Identify and reinforce the Veteran's previously demonstrated strengths and successful coping techniques. This will help the Veteran and family to establish or reestablish the Veteran's sense of self-worth and meaning (see EPEC for Veterans Module 1: Goals of Care).

Complementary therapies

Slide 38

Relaxation therapy, distraction therapy with pleasant imagery, etc. have been shown to reduce depressive symptoms in patients with mild to moderate levels of depression.[45,46] Other helpful techniques may include meditation training, guided imagery, massage therapy, aromatherapy, or self-hypnosis. If possible for the Veteran, exercise and exposure to sunlight can help to lift depressed moods.

Pharmacological management

Slide 39

Slide 40

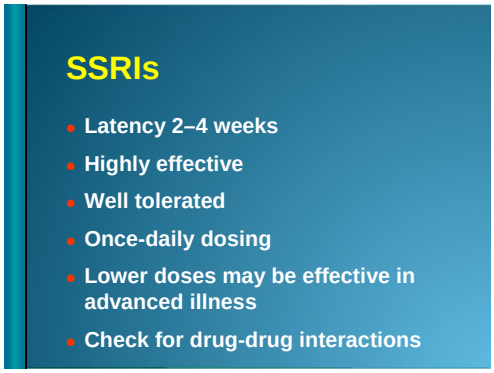
The principal medications used for the treatment of depression include selective serotonin reuptake inhibitors (SSRIs), psychostimulants, and other classes of antidepressants.

The time available for treatment will strongly influence the choice of medication for initial therapy. When reversal of depression and improvement of energy is an immediate short-term goal, a rapid-acting psychostimulant is the best choice. If a response in 2 to 4 weeks is acceptable, a selective serotonin reuptake inhibitor (SSRI), or other antidepressant (such as a serotonin/norepinephrine reuptake inhibitor or SNRI) is an appropriate choice.[17] In general, SSRIs/SNRIs are preferred over tricyclic antidepressants because the risk of adverse effects is significantly less and they can be dosed once daily.

With all antidepressant medications, 'start dosing low and go slow.' Titrate the dose to symptom relief and tolerability. Warn Veterans about possible adverse effects, which will usually ameliorate within a few days. Side effects that are persistent and significant enough to prevent dosage escalation should prompt a change in antidepressant. If Veterans are not responding as expected, consult a psychiatrist.

Selective serotonin reuptake inhibitors (SSRIs)

Slide 41



Selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, paroxetine, sertraline, citalopram, and escitalopram are recommended over tricyclic antidepressants as they are (1) as effective, (2) their onset of action is usually faster, and (3) there is much less risk of adverse effects.[47] All of the SSRIs, with the exception of escitalopram and controlled-release paroxetine, are now available in generic form making them affordable for the

majority of Veterans. Most SSRIs are available in oral solutions, except controlled release paroxetine and escitalopram.

Low doses may be sufficient in advanced illness, and once-daily dosing is possible. Use caution, as most of these medications (except for citalopram and escitalopram) have significant effects on hepatic metabolism and possible drug interactions, particularly with psychotropic medications. Evaluate all possible drug interactions before starting a SSRI. SSRIs cause significantly less constipation, sedation, and dry mouth than the tricyclic antidepressants, though nausea may be worse with the SSRIs.[15]

Choosing between SSRIs should be on the basis of desired side effect. For example some, such as fluoxetine are more activating, while others such as paroxetine are more sedating.

Expect to see results within two to four weeks. At that time, increase the dose if there is partial effect. If there is no effect, try an alternate medication or consult a psychiatrist. Do not increase doses faster than once weekly. Citalopram and escitalopram are good choices in this population as they have few drug-drug interactions and often a better adverse effect profile. Note that all SSRIs can either be activating or sedating, but some tend to be more of one than the other. If an SSRI is activating to the Veteran, give the dose in the morning, if it is sedating, give the dose nightly.

Common starting doses are:

- Citalopram 10-20 mg PO daily, increasing by 10-20 mg daily every 2 weeks; target is 20-40 mg PO daily. Maximum dose is 60 mg/day;
- Escitalopram 5-10 mg PO daily; maintenance and maximum dose is 10-20 mg PO daily typically, but some patients require 30-40 mg daily. 10 mg of escitalopram can be equivalent to 20-40 mg of citalopram;
- Sertraline 25-50 mg PO daily; increasing by 25-50 mg daily every 2 weeks to target dose of 50-150 mg daily; maximum dose is 200 mg/d;
- Paroxetine 10-20 mg PO daily, increasing by 10 mg daily every 2 weeks; target is 20-40 mg PO daily; maximum dose is 50 mg/day; to reduce the risk of adverse effects, consider an extended-release formulation, e.g., paroxetine CR 25 mg PO qd, increasing by 12.5 mg every 2 weeks. Target dose 25-62.5 mg, maximum 62.5 mg daily; or fluoxetine, 20-80 mg PO daily; or
- Fluoxetine 20 mg PO q am.

Psychostimulants

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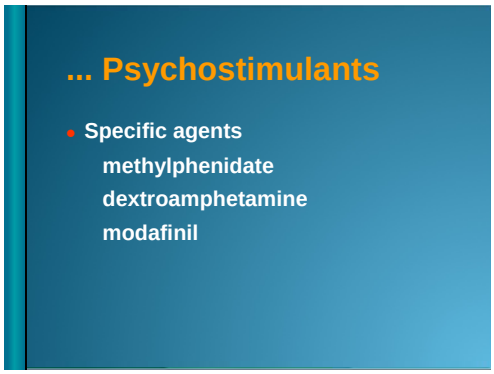
Slide 43

Slide 44



In Veterans whose derived response is in days, starting treatment with a psychostimulant is recommended. These can be given simultaneously with SSRIs or SNRIs. The psychostimulants are underappreciated for their antidepressant qualities.[17,48] They act quickly, in hours to days, and produce minimal adverse effects. Some patients report increased energy and an improved sense of wellbeing within 24 hours.

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, and they may potentiate opioid analgesia.[49,50]

Psychostimulants may produce psychosis, dependence, tremulousness, anxiety, anorexia, increased blood pressure, tachycardia, and insomnia. Monitor for these adverse effects.

Methylphenidate or **dextroamphetamine** are the medications of first choice as they are inexpensive and have a low risk of adverse effects. Common starting doses are:

- Methylphenidate 2.5-5 mg PO q AM and q Noon; increase every 1-2 days by 2.5-5 mg PO q AM and q Noon; maximum dose is 30 mg total a day. To improve tolerability, consider an extended-release formulation; or
- Dextroamphetamine 5 mg PO q AM and q Noon; increase every 1-2 days by 5 mg PO q AM and q Noon; maximum dose is 30 mg twice a day.

Modafinil is a newer psychostimulant agent that improves lethargy in patients with narcolepsy. This agent may help with lethargy in depression and improve response to antidepressants.[51,52]

Common starting doses are:

- Modafinil, start with 100 mg PO daily. Titrate to desired effect. The maximum dose is 400 mg/day.

Other antidepressants

Slide 45

A diverse group of medications that affect depression include mirtazapine (a tetra-cyclic antidepressant), venlafaxine, duloxetine, bupropion, Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), and tricyclic antidepressants. Like SSRIs, they have similar efficacy to tricyclic antidepressants, but most have less risk of adverse effects. Each of these can be effective in Veterans who have failed to respond to SSRIs.

Mirtazapine is a tetracyclic antidepressant which also has anxiolytic benefits that often take effect within days of initiation of treatment. The onset of antidepressant effects can be somewhat quicker than with the SSRIs. Mirtazapine can stimulate appetite and cause sedation at lower doses; making it a good choice for depressed, anxious Veterans who have diminished appetite and difficulty sleeping. If the sedative effects linger into the day, the dose can be increased to ameliorate this adverse effect. Mirtazapine has a lower risk of inducing sexual dysfunction than most antidepressants and has no effect on the cytochrome p450 system. It is also available in a Soltab, or orally disintegrating tablet.

Common dosing is as follows:

- Mirtazapine start with 15 mg PO at bedtime; increase every 1-2 weeks by 15 mg PO daily; maximum dose is 45 mg/day.

Venlafaxine, in addition to being used to treat depression, is also commonly prescribed for Generalized Anxiety Disorder, Social Anxiety Disorder, Panic Disorder, and Posttraumatic Stress Disorder. Dosage reduction must be made for renal and hepatic impairment and caution should be used for Veterans with cardiac impairment due to the potential for increasing blood pressure. Venlafaxine may have a positive impact on pain syndromes, and can be energizing in patients with fatigue or psychomotor retardation. Withdrawal reactions are not uncommon with venlafaxine and care must be taken to taper when discontinuing. Using the extended release preparation can improve tolerability, may reduce blood pressure elevations, and decrease the potential for withdrawal upon discontinuation.

Common dosing is as follows:

- Venlafaxine extended release 37.5 mg PO daily for the first week; increasing by 37.5-75 mg every week; target dose 75-225 mg /day with maximum of 375 mg daily; or
- Venlafaxine immediate release 25-50 mg PO daily in divided doses, i.e., 25 mg bid for the first week, increasing by no more than 75 mg weekly (keeping bid-tid divided doses) to maximum of 375 mg daily.

Duloxetine is FDA-approved not only for use in depression but also for peripheral neuropathy. It is commonly used off-label for fibromyalgia and other types of chronic pain and anxiety disorders. Like venlafaxine, caution should be used in Veterans with renal impairment. No dosage reductions are needed in mild to moderate renal impairment but duloxetine is not recommended for use in severe renal impairment or end-stage renal disease requiring dialysis. It should not be used in Veterans with hepatic insufficiency; there is risk of increased serum transaminase levels. Duloxetine can raise blood pressure. It should be used with caution in patients with cardiac impairment and in patients with a history of seizures.

Common dosing is as follows:

- Duloxetine 20 mg PO qd, increasing by 20 mg daily every 2-4 weeks to a target dose of 40-60 mg; maximum dose is 120 mg/day.

Bupropion is more stimulating than most other antidepressants and can be helpful in Veterans who have significant psychomotor retardation, hypersomnia, or fatigue. Some Veterans experience anxiety, agitation, or insomnia as adverse effects. If such symptoms are already present, bupropion may not be the antidepressant of first choice. If used in such Veterans, dosing should begin as low as possible and titration should be slow. Potential benefits of bupropion include a lower incidence of sexual dysfunction than other antidepressants and a lower risk of inducing mania in bipolar patients. The

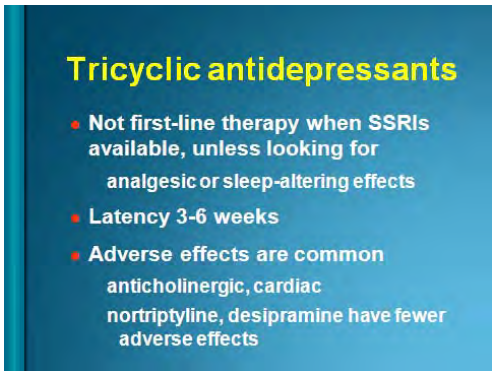
sustained release preparation can be used for smoking cessation and in conjunction with nicotine replacement therapy.

Bupropion is often added to SSRIs as an augmentation strategy for treating depression. Bupropion should not be used in Veterans with a history of seizures, anorexia or bulimia; in patients who are abruptly stopping alcohol or sedative use; or in patients with recent head injuries or CNS tumors. It is available in immediate release form, dosed tid, sustained release dosed bid, and an XL preparation dosed once daily.

Common dosing is as follows:

- Bupropion immediate release 75 mg PO bid for a week, increasing to 100 mg PO bid after 1-2 weeks, then 100 mg PO tid for 1-2 weeks then 150 mg PO tid if needed; target dose is 150-450 mg with a maximum dose of 450 mg daily in divided doses with the maximum single dose no more than 150 mg; avoid dosing in the evening to minimize insomnia;
- Bupropion SR 100 mg PO bid, increasing to 150 mg PO bid after 4-7 days; wait several weeks before increasing further to 200 mg PO bid; target dose is 100-300 mg daily; maximum dose is 400 mg daily; maximum single dose 200 mg; avoid dosing in the evening to minimize insomnia; or
- Bupropion XL 150 mg PO q am, increasing to 300 mg PO q am after 4-7 days; target dose is 150-300 mg/day and maximum dose is 450 mg daily.

Slide 46



Amitriptyline is the tricyclic antidepressant (TCA) listed by the World Health Organization (WHO) as an Essential Medicine.[53] It is also used as an analgesic to manage neuropathic pain. Doxepin and imipramine were also considered to have similar clinical effects by the WHO. Other secondary amine tricyclic antidepressants to consider are desipramine and nortriptyline. Of all of the tricyclic antidepressants, amitriptyline has the highest prevalence of adverse events (due to its anticholinergic activity), especially in the elderly.

When other antidepressants are available, tricyclic antidepressants are not recommended as first-line therapy to manage depression due to their adverse effect profile, unless they are being used as adjuvants to control neuropathic pain or if the Veteran has had good results with these medications before.

Titration to achieve an adequate dose should be guided by serum levels and may take 3 to 6 weeks, delaying the onset of therapeutic action.

Anticholinergic adverse effects, e.g., dry mouth, constipation, orthostatic hypotension, blurred vision, urinary retention, delirium, and cardiac conduction delays are all seen with some frequency. If a tricyclic antidepressant is to be used, the secondary amines desipramine and nortriptyline are often preferable as they tend to have fewer adverse effects, but these may be activating instead of sedating. Dose all TCAs similarly.

Common starting doses are:

- Amitriptyline (or any other tricyclic antidepressant) 10-25 mg PO nightly; every 3-7 days, increase by 10-25 mg PO nightly; maintenance dose is typically 150 mg PO nightly; maximum dose is 300 mg/day.

Summary

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Depression is common among those with advanced, life-threatening illnesses. It is often overlooked and/or not aggressively treated. Attention to depression will improve outcomes of anticancer therapies, quality of life, psychosocial and family stress, and ultimately quality of death. Psychotherapy, psychopharmacology, and alternative medicine approaches all have a role to play in the treatment of depression, and treatments can be tailored to an appropriate time frame to best help the Veteran. Do not hesitate to consult with mental health professionals if simple interventions do not yield improvement. Suicidal ideation or a wish to hasten one's own death is cause for serious concern, and a psychiatric consult is warranted.

Key take-home points

1. Depression is treatable, even in patients with advanced cancer.
2. The screening question, "Do you feel depressed most of the time" is sensitive and specific.
3. Psychostimulants (for rapid effect) can be started at the same time as antidepressants (such as the SSRIs) that take longer to work.

4. Counseling plus pharmacotherapy is more effective than either alone.
5. SSRI/SNRIs can be effective in 2-4 week time frames. In choosing an SSRI/SNRI, consider desirable side effects such as sedation, reduction in anxiety, or stimulation to augment treatment of the distressing symptoms.
6. Suicidality is a major health threat and must be assessed in all Veterans with mental health problems.

Part 3: Delirium

Clinical case

A 72-year-old married Veteran with cirrhosis of the liver and newly diagnosed cellular carcinoma is admitted to a palliative care unit with a two-day history of confusion and aggressive behavior. Over the next two days, he demonstrates intermittent agitation, confusion, and disorientation. These seem to be worst at night, while in midmorning, he was observed to be deeply asleep. At times he shouts out about Veterans 'going missing,' and believes that his life is in danger. Staff on the unit are unable to determine any recognizable pattern in his outbursts. His wife reports that in between periods of agitation, he can be cooperative and 'back to his normal self.' His medications include ranitidine, dexamethasone, gabapentin, and lorazepam. He uses opiate analgesics as needed for pain. Examination reveals nonspecific neurological abnormalities. His vital signs show mild hypertension, tachycardia, and an elevated respiratory rate. An initial Folstein Mini-Mental State Examination demonstrates problems in orientation, recall, and attention, with a total score of 18 of 30.

Introduction

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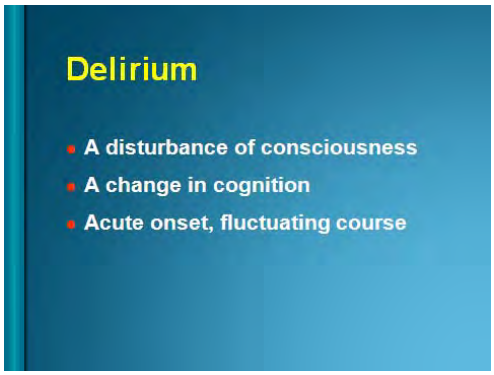

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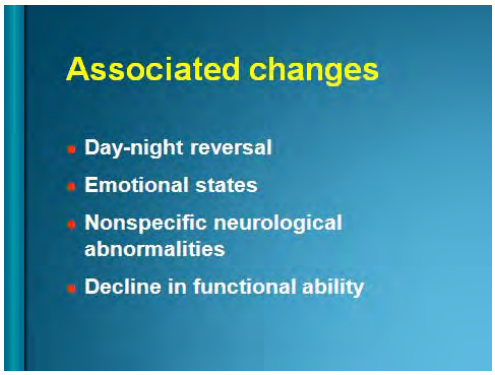

Delirium is defined as *both*:

- *A disturbance of consciousness* with reduced awareness of the environment and reduced ability to focus, sustain, or shift attention, and
- *A change in cognition* with memory deficits, disorientation, language disturbance, or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.[1]

In contrast to dementia which develops slowly, delirium develops over a short period of time, usually hours to days, and fluctuates during the course of the day. Delirium, however, is frequent in patients with pre-existing dementia.[54]

There may be associated alterations in sleep patterns, e.g., day-night reversal, emotional states, non-specific neurological abnormalities and a sudden and significant decline in functional ability.[55] While delirium presents with psychiatric symptoms, it is important to remember that these symptoms are manifestations of medical abnormalities and not primary psychiatric illness.

It is particularly important to be vigilant about delirium postoperatively, after chemotherapy treatment, when infections are present, and in advanced chronic diseases. Older patients are particularly susceptible and recover slowly. 25% of delirious patients die within six months.[56] Elderly patients are at particular risk for complications such as pneumonia, skin ulceration and falls.[57] Symptoms can be very distressing for Veterans and extraordinarily difficult on their families and caregivers.

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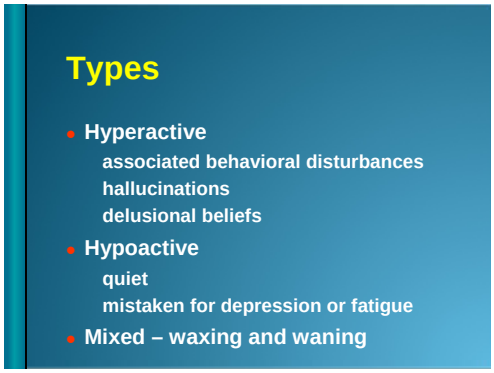

Delirium has two major clinical presentations or subtypes.

The *hyperactive* subtype is most often recognized due to its associated behavioral disturbances and the frequent occurrence of psychotic symptoms such as hallucinations or delusional beliefs.

The *hypoactive* subtype, or quietly delirious patient, is often mistaken for depression or fatigue.

Not infrequently, patients will present with a 'mixed' subtype with symptoms of both 'hyper' and 'hypo' active subtypes over the course of a day. Often, it is the waxing and waning nature and time course of onset that points to the diagnosis of delirium. Once the

diagnosis of delirium is suspected, the underlying cause of the disturbance can be investigated.[55,58]

Prevalence and prognosis

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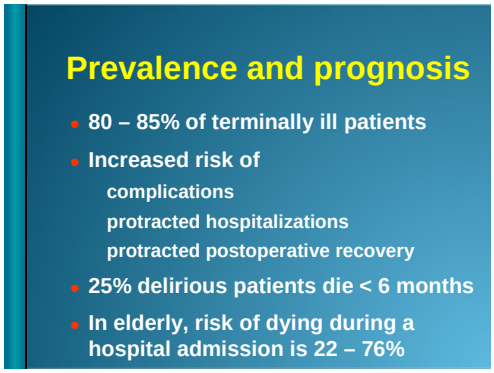

Delirium is a common, yet under-recognized and under-treated medical condition. It has been reported to be present at some point in the course of up to 80-85% of terminally ill patients. [55,59] Although data vary, it is generally associated with a poor prognosis when it is found in patients with advanced disease. In the elderly, delirium increases the risk of dying during a hospital admission by between 22 and 76%.[60,61]

Pathophysiology

Pathophysiology

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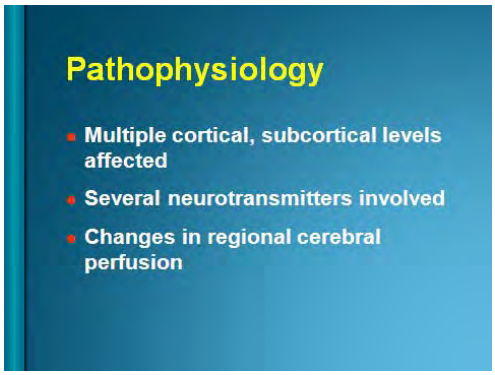

Several cortical and subcortical areas appear to be affected by delirium. Three areas of the prefrontal cortex appear to be involved in certain presentations of delirium. The dorsolateral prefrontal cortex has been associated with executive cognition. Damage to the orbitomedial prefrontal cortex can result in a disinhibition. Abnormalities in the function of the anterior cingulate gyrus may account for the lack of language or perseveration sometimes seen in delirious patients. The parietal cortex has also been shown to be affected by delirium. The third major area of the brain affected by delirium is the thalamus and caudate. Its connections with the reticular activating system accounts cerebral perfusion during periods of delirium in comparison to studies after recovery.[62]

Neurotransmitter changes in these areas noted have been implicated in the development of delirium. There are several neurotransmitters involved, including acetylcholine, dopamine, serotonin, GABA, norepinephrine, glutamine, and histamine. Reduced acetylcholine, either through pathologic processes or anticholinergic medications, is a common cause of delirium.

Higher cognitive and executive functions associated with this area of the brain must remain intact for normal behavior, cognition, and planning

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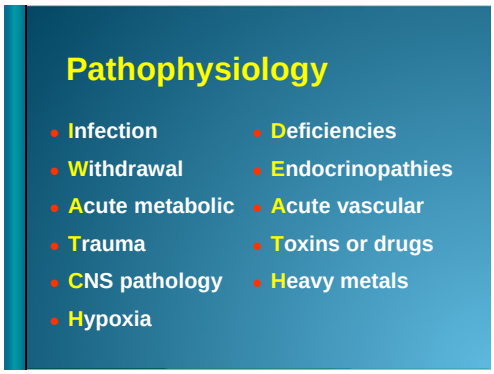

There are many possible causes of delirium.[63] **Table 1** presents the most important and potentially life threatening causes and with a mnemonic 'I WATCH DEATH'.[55]

Table 1: Causes of delirium

Infection	Encephalitis, meningitis, syphilis, HIV, sepsis
Withdrawal	Alcohol, barbiturates, sedative-hypnotics
Acute metabolic	Acidosis, alkalosis, electrolyte disturbance, hypercalcemia, hepatic failure, renal failure
Trauma	Closed head injury, heatstroke, postoperative, severe burns
CNS pathology	Abscess, hemorrhage, hydrocephalus, subdural hematoma, infection, seizures, stroke, tumors, metastases, vasculitis
Hypoxia	Anemia, CO poisoning, hypotension, pulmonary or cardiac failure
Deficiencies	Vitamin B12, folate, niacin, thiamine
Endocrinopathies	Hyper/hypoadrenocorticism, hyper/hypoglycemia, myxedema, hyperparathyroidism, hypercalcemia
Acute vascular	Hypertensive encephalopathy, stroke, arrhythmia, shock, dehydration
Toxins or drugs	Medications, chemotherapeutics, illicit drugs, solvents
Heavy metals	Lead, mercury

Medications, both prescription and over the counter, are the most common cause of delirium. Anticholinergic medications are often associated with delirium. **Table 2** outlines various medication classes associated with delirium.[21]

Table 2: Medications potentially causing delirium

Analgesics	H2 blockers
Anesthetics	Corticosteroids
Antiasthmatics	Immunosuppressives
Anticholinergics	Insulin
Anticonvulsants	Muscle relaxants
Antihistamines	Salicylates
Antihypertensives	Psychotropics, especially those with anticholinergic properties
Antimicrobials	Sedatives
Antiparkinson medications	

Assessment

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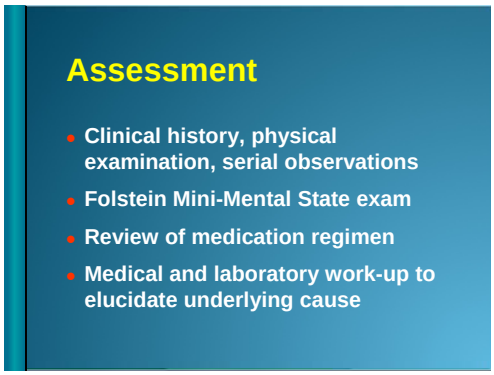

To assess for delirium take a careful history, perform a physical examination, carefully observe the Veteran's ability to maintain attention over time, and order appropriate investigations (see **Table 3**).[1,55]

The Folstein Mini-Mental State Examination (MMSE) is a screening tool to assess cognitive impairment. Serial administration of the tool can aide in the assessment of delirium and the response to treatment.[64] Several other tools have been developed to assess delirium, including the Confusion Assessment Method (CAM),[65] Delirium Rating Scale (DRS),[66] and the Memorial Delirium Assessment Scale (MDAS, validated as both a screening tool and a severity rating scale).[67] These are shorter and are generally partnered with the MMSE for severity of inpatients.

The CAM consists of 5 criteria to diagnose delirium. Three of these must be present: acute change in mental status, symptoms that fluctuate over minutes or hours, and inattention. In addition, either an altered level of consciousness or disorganized thinking must be present. The DRS and MDAS are more likely to be used by psychiatrists or palliative medicine physicians who are experts in delirium assessment and management.

While laboratory investigations are not specific or sensitive enough to make a definitive diagnosis of delirium, they can help to determine the underlying cause. As always, consider the relative burden and likelihood of specific investigations changing management.

Table 3: Assessment of delirium

Physical status	Mental status	Basic laboratory	Additional investigations
History Physical and neurological exam Review of medical records Review of medications	Interview Cognitive tests Clock face drawing CAM Folstein mini-mental state examination	Electrolytes Glucose Calcium BUN / Creatinine LFTs CBC Serum drug levels Urinalysis and culture Urine drug screen	Lumbar puncture CT or MRI brain Chest X-ray

Delirium vs. dementia

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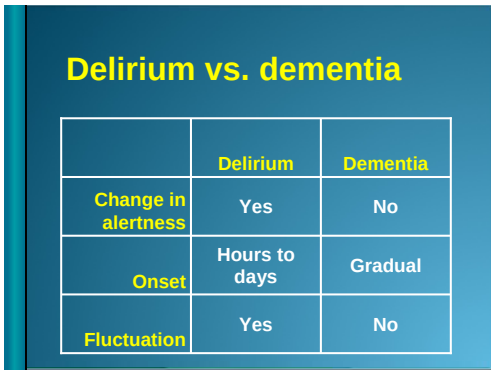

It is often necessary to differentiate delirium from dementia. While memory impairment is common to both, dementia is not associated with a change in alertness or any disturbance in consciousness. The temporal profile is also different. In delirium, symptoms usually develop over hours to days and often fluctuate over a 24-hour period. In dementia, symptoms typically develop much more gradual and there is little or no variation of symptoms over time. This is summarized in **Table 4.**

Table 4: Differences between delirium and dementia

	Delirium	Dementia
Change in alertness/ Disturbance of consciousness	Yes	No
Onset	Usually develop quickly,	Gradual onset

	over hours to days	
Fluctuation over a 24-hour period	Yes	No

Management

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The management of delirium is multifaceted and multidisciplinary. Interventions to treat the underlying causes, and ameliorate the troublesome symptoms are of utmost importance.

As medications are frequently implicated, decrease or discontinue any unnecessary medications, particularly those with anticholinergic properties. Some analgesics, e.g., meperidine, are strongly anticholinergic, and have a high risk of adverse effects such as CNS excitation.[68] Medications may accumulate secondary to half-life, dehydration, changes in renal clearance, or liver function abnormalities. As opioid clearance is dependent on renal function, reduce the routine opioid dose by at least 50% when urine output is < 500 ml/24 hr, and consider stopping routine dosing when urine output is < 200 ml/24 hr. However, discontinuing opioids when they are needed for the relief of pain or dyspnea may worsen delirium due to the uncontrolled symptoms and withdrawal if the Veteran has been taking the opioid for more than a few weeks. If opioids are suspected of contributing to delirium, consider opioid rotation and also pharmacological treatment of the delirium so that the needed opioid can be continued

Other reversible causes of delirium that can be quickly determined and sometimes treated are hypoglycemia, hypoxia or anoxia, hyperthermia, substance or medication withdrawal.

Non-pharmacological management

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A hyperactive delirium can be quite distressing to the observer. Help family understand that what the Veteran is experiencing might be quite different from what the family is observing.

A number of the following factors are important when treating Veterans with delirium:[69]

- communicate clearly and concisely with the Veteran;
- include frequent reminders of the date and time;
- always identity important individuals;
- minimize the number of different staff working with the Veteran;
- provide materials to help reorient the Veteran, e.g., a clock, calendar, and schedule of daily activities;
- encourage the family and caregivers to bring in familiar objects from home;
- to minimize excess noise and ensure optimal stimulation by nursing staff, move delirious Veterans to single rooms, close to the nursing station;
- minimum excess noise; control other environmental factors, e.g., temperature and lighting;
- avoid understimulation. As sensory impairments can make delirium worse, provide needed glasses and hearing aids; and
- if Veterans are restless, provide sitters to calm and reorient them. Only use physical restraints if there is a high risk of harm to the Veteran or staff. One-to-one sitters are almost always a better option then physical restraints.

Pharmacological management

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Veterans with delirium may require antipsychotics and occasionally, benzodiazepines. While there is some question about how to treat delirium depending on the goals of care, the type of delirium (hyperactive, hypoactive, or mixed), or whether the etiology is thought to be reversible or irreversible, there are advantages to treating delirium consistently, regardless of type or etiology.[36]

Antipsychotic medications

Antipsychotic medications are the medications of choice to treat delirium. Depending on the goals of care, those that are non-sedating may be preferred over those that tend to be sedating.

Haloperidol has been shown to be superior to the benzodiazepine lorazepam for the treatment of delirium.[70] Since its development, haloperidol has been the gold-standard pharmacotherapy for delirium.[63] It is available in oral, intravenous/subcutaneous and intramuscular formulations.

It is important to consider age and reduce dosing IV/SC in the elderly (haloperidol 0.25-0.5 mg IV/SQq 4 h in the elderly). While a wide range of doses have been reported if the Veteran is not responding to haloperidol 10 mg/day; oral equivalent dose, reconsider diagnosis and consultation with psychiatry or palliative care specialist is warranted. IM dosing is discouraged since SC dosing is available and IM injections are painful.

In the mid to late 1990s, a new class of antipsychotic medication came into use. These “atypical antipsychotics” have a different mechanism of action. Instead of primarily blocking dopamine receptors, as with the older antipsychotics, these new medications act through different mechanisms in addition to dopamine receptors. More data are accumulating about the use of these atypical antipsychotics, including risperidone, olanzapine, and quetiapine.[71,72] These agents may offer an advantage over haloperidol by means of a lower incidence of extrapyramidal side effects. This reduction in extrapyramidal side effects may be helpful in Veterans that have a Parkinson’s syndrome or Lewy Body disease. However, the atypical antipsychotics are often much more expensive, do not come in convenient parenteral forms and there are no trials demonstrating their equivalence to haloperidol in treatment of delirium. They have been

used in the treatment of delirium and previously published case series as well as a recent Cochrane Review have shown equivalent efficacy to haloperidol.[71,73,74,75] Olanzapine or quetiapine may be preferred for nighttime dosing to encourage sleep in Veterans with day-night reversal.

Common starting doses are:

- Risperidone (non-sedating) 0.5-1 mg PO q 12-24 h 0.25 mg qd-bid in elderly,
- Olanzapine (sedating) 2.5-5 mg PO q 12-24 h, or
- Quetiapine (sedating) 25-50 mg qhs, increase slowly due to risk of orthostasis; titrate to effect; typical dose is 25-200 mg PO nightly.

Managing adverse effects

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Adverse effects of antipsychotics include extrapyramidal effects, neuroleptic malignant syndrome, akathisia, lowering of the seizure threshold, and QTc prolongation (i.e., > 450 msec). All of these side effects may lessen with a decreased dose. Akathisia can be managed with a beta-blocker or benzodiazepine.

Extrapyramidal effects can be managed with anticholinergic medications such as benztropine or diphenhydramine. Tardive dyskinesia is a permanent movement disorder that results from long-term (years) exposure to antipsychotics. Although it is often listed as a side effect, it is generally not a concern with the short term use of these medications in palliative care settings.

For dystonic reactions, e.g., oculogyric crisis (rotating eyeballs), dysphagia, torticollis (cervical muscle spasm producing unnatural twisting of the head), consider:

- Diphenhydramine 25-50 mg PO, IM, IV q 4 h PRN, discontinue the antipsychotic and consult a psychiatrist urgently.

For akathisia (a sense of constant motor restlessness), consider:

- Benztropine 1-2 mg PO daily-bid.

For Parkinsonian reactions (tremor, bradykinesia, rigidity, abnormalities of gait and posture), consider:

- Benztropine 1-2 mg IV, IM acutely; then 1-2 mg PO daily-bid. in elderly, 0.5 mg acutely then 0.5-1 mg bid.

Benzodiazepines

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If the delirium is secondary to specific states, e.g., alcohol withdrawal, or benzodiazepine withdrawal, a benzodiazepine taper is the appropriate treatment. Alcoholism is a common disorder. While abstinence from alcohol is often an appropriate goal when alcohol use is leading to medical problems and interpersonal stress, acute alcohol withdrawal can lead to morbidity and mortality. Judicious use of alcoholic beverages to prevent withdrawal, even in an inpatient VAMC, may be the safest and most effective way to manage this problem.

For all other causes of reversible delirium, avoid benzodiazepines as first line therapy. They are more likely to cause further disinhibition rather than sedation in this state and in geriatric populations.[69]

Side effects of benzodiazepines include sedation, behavioral disinhibition, amnesia, ataxia, respiratory depression, dependence, and delirium. Special attention must be given to the accumulation of benzodiazepines with longer half-lives (such as diazepam and clonazepam).

Terminal delirium

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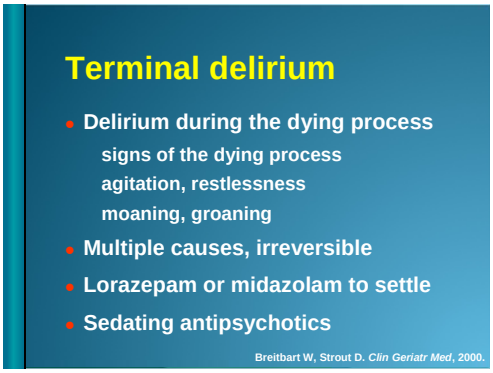

Terminal delirium is *delirium that occurs during the active dying process*. It is always associated with other signs of the dying process, e.g., decreased level of consciousness, changes in breathing patterns, loss of ability to swallow, peripheral cooling, venous pooling/mottling, oliguria or anuria (see EPEC for Veterans Module 11: Last Hours of Living).

Unlike the delirium that occurs earlier in an illness, once a Veteran is actively dying, end-organ failure, hypoxia, infections, medication toxicity (e.g., opioids), metabolic disturbances can all contribute to neuronal compromise and/or death and a picture of delirium that is irreversible.[76,77]

In addition to decreased alertness and level of consciousness, terminal delirium typically manifests as restlessness, confusion, tremulousness, hallucinations, mumbling and moaning/groaning associated with day-night reversal. If unmanaged, it can evolve to include myoclonic jerks and seizures. It can also be very distressing for everyone who watches.

As the delirium and the dying process are irreversible, the focus of treatment changes from reversing the underlying cause to settling the Veteran and educating and calming the family. Benzodiazepines are ideal for this as they are anxiolytic/hypnotics, muscle relaxants, amnestics and antiepileptics. Antipsychotic medications, such as IV haloperidol may be used adjuvantly as well.

Common starting doses are:

- Lorazepam 1.0-2.0 mg predissoved in 3-5 ml water q 1 h PRN. Place against oral or buccal mucosa; once the pain has settled, calculate the total amount of medication that was used in the last 24 hours, then dose routinely and offer a breakthrough dose; or
- Lorazepam 0.5 mg-1.0 mg SC/IV q 15 min PRN may be used instead of oral dosing. While IV lines are difficult to maintain SC lines are simple to place and maintain; in addition, lorazepam is and effective antiseizure treatment SC/IV but not by oral routes.[59,78] For Veterans with refractory delirium, a continuous infusion of lorazepam may be required.

Summary

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Delirium is an important clinical entity to recognize, diagnose, and treat in patients receiving end-of-life care. Effective treatment of delirium will decrease the suffering of Veterans and their families. Restoring a Veteran's ability to attend to his or her surroundings and environment decreases suffering, and facilitates communication with the treatment team and family. This ultimately allows for a better quality of life and death.

Key take-home points

1. Delirium is common among the seriously ill, particularly the elderly and demented.
2. Initial management should focus on environmental changes and neuroleptics.
3. Explain to the family that behaviors associated with delirium do not reflect his or her personality or relational meaning.
4. Lack of knowledge about terminal delirium is common. Memories of it among surviving family members can be traumatic. Learn to recognize and manage early.
5. It is not always clear if the current episode of delirium is a terminal event. A time trial of treatment of the symptoms and causes for the delirium that over a short time shifts to a terminal care approach when the course had declared itself.

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