EPEC™-O

Education In Palliative And End-Of-Life Care For Oncology

Self-Study Module 3h:

Depression

Module 3h: Depression

Abstract 3
Introduction 3
Case 4
Pathophysiology 5
Assessment 5
Management 7
Summary 12
Key Take-Home Points 12
Appendix: Depression Medication Table 13
References 2
Self-Assessment 3

Abstract

Many symptoms and syndromes are commonly encountered in patients with cancer. This module first presents general approaches to symptom management, followed by management of the specific symptoms and syndromes, including: anorexia/cachexia, anxiety, constipation, depression, diarrhea, fatigue, insomnia, menopausal symptoms and sexual health, mucositis, nausea and vomiting, and skin problems.

Any symptom can be debilitating and prevent the patient and family from achieving goals that are important to them. As with other aspects of medicine, tailored management is based on the underlying etiology and pathophysiology. When several symptoms occur together, they can be interrelated and management can be complex.

Introduction

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 2 weeks. In children and adolescents, their mood may be irritable rather than sad. Patients also experience a host of 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. (Ref. 1) Depression is often viewed by patients as something to be ashamed of, or as a sign of weakness. The physician can help correct this misconception through patient and family education.

As depression is a source of intense suffering, oncologists will want to be particularly diligent at assessing and detecting associated signs and symptoms. Persistent depression is not normal for patients 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. (Ref. 2)

Risk factors

There are many risk factors for major depression among patients with cancer. Poorly controlled pain and other physical symptoms contribute to depression and are particularly important because they are remediable (see EPEC™-O Module 2: Cancer Pain Management and EPEC™-O Module 3: Symptoms). (Ref. 2) Progressive physical impairment and an advanced stage of disease also correlate with a higher incidence of depression. (Ref. 3) With some medications (e.g., steroids, benzodiazepines, and various chemotherapeutics), depression is a potential adverse effect. (Ref. 4) Several cancers (e.g., pancreatic, breast, and lung) are associated with a higher incidence of

depression. (Ref. 2) Age may also play a role, with younger cancer patients being more prone to depression. (Ref. 5) (Ref. 6) Finally, spiritual pain and conflicts over issues of meaning, guilt, and fear may manifest as depression. (Ref. 2)

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 with cancer. (Ref. 7) Patients 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. (Ref. 2)

Issues of grief and bereavement may also be important risk factors. (Ref. 2) (See EPEC™-O Module 4: Loss, Grief, and Bereavement.)

Prevalence

Most patients 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, a major depressive illness occurs. The prevalence of depression ranges from 1 to 40% in palliative care settings. (Ref. 2) It occurs in up to 58% of cancer patients. (Ref. 8) (Ref. 9)

Unfortunately, it has been found that most professionals who work with these populations are unable to accurately estimate the level of psychological distress of their patients. (Ref. 10) (Ref. 11) (Ref. 12)

Prognosis

Depression has been demonstrated to be associated with poor prognosis. This has mainly been studied related to increased risk of suicide. However, length of life and quality of life are both influenced by depression. When depression is treated, overall prognosis improves.

Professionals and families are concerned about what to tell the patient. Will knowing the true extent of disease and an accurate prognosis lead to depression and adverse outcomes? In a survey of 106 patients with advanced cancer at home, no such correlation was found. (Ref. 13)

Case

Review the case below, and keep it in mind as you progress through the module. How would you approach the assessment of this patient? What interventions might be appropriate?

B.H. is a 72-year-old married man with metastatic lung cancer; he has a 3-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 2 months, and they have been getting progressively worse. His medications include ranitidine, dexamethasone, gabapentin, and lorazepam. He uses opiate analgesics as needed for pain. Examination reveals nonspecific neurological abnormalities. His vital signs are normal. CT scan shows cerebral metastases. An initial Folstein Mini-Mental State Examination is normal.

Pathophysiology

A biological understanding of depression is still in development. Recent pharmacologic advances in the treatment of depression point to the involvement of norepinephrine, serotonin, and dopamine. Electroconvulsive therapy, which is effective for the treatment of major depression, induces seizure which in turn releases increased amounts of these neurotransmitters in the brain. However, just how and why these neurotransmitters are involved is not yet clear.

Genetic and environmental influences play a role in the pathogenesis of depression. (Ref. 14) A number of conditions have been associated with depression, including cancer. Some medications, including corticosteroids, procarbazine, vincristine, and vinblastine, are also associated with depression. (Ref. 15) A causal link has not been established, but the association is clear.

Assessment

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 pursue further anticancer therapy, live life to the fullest, and achieve final goals before they die. This applies to teenagers and young adults as well as to older patients. (Ref. 2) (Ref. 16)

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), and 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 that does not respond as expected, sad mood with flat affect, and anxiety, irritability, or unpleasant mood may also be significant signs of depression. (Ref. 2) (Ref. 17) (Ref. 18)

Somatic symptoms (e.g., changes in appetite, weight, energy level, libido, or sleep) are important when making a diagnosis of depression in a non-medically ill population. (Ref. 2) However, somatic symptoms are almost invariably present in patients with advanced cancer, making it difficult to discern their etiology. (Ref. 2) These symptoms of depression are often indistinguishable from these same symptoms of fatigue, cachexia, or weakness.

An affirmative response to the following simple screening question appears to be sensitive and specific for the presence of depression in this population: (Ref. 19)

“Do you feel depressed most of the time?”

Requests to hasten death may be a marker of undiagnosed depression (see EPEC™-O Module 14: Physician-Assisted Suicide). Asking about the severity and time course of the aforementioned psychological and cognitive symptoms may help make the diagnosis.

Mental health professionals may use more specific screening tools (e.g., the Beck Depression Inventory or the Hospital Anxiety and Depression Scale) for the identification of depression. (Ref. 17)

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.

It is important to distinguish between depression from grief reaction, adjustment disorders, delirium, or dementia, and this is often difficult. Be aware that depression can present with either psychomotor retardation or agitation. Depression that occurs in response to a psychosocial stressor can be distinguished from an adjustment disorder with depressed mood because the full criteria for a major depressive episode are not met in adjustment disorder. (Ref. 1) If the patient has a diagnosis with a poor prognosis and/or suffers the loss of a loved one or other significant loss, attribute depressive symptoms to grief or bereavement rather than to a major depressive episode, unless the symptoms persist for more than 2 months or include:

- Significant functional impairment.
- Severe preoccupation with worthlessness.
- Psychotic symptoms.
- Psychomotor retardation.
- Suicidal ideation. (Ref. 1)

Hypoactive delirium is often mistaken for and difficult to distinguish from depression (see EPEC™-O Module 3g: Symptoms - Delirium). A detailed history of onset and time course of both mood and cognitive symptoms is essential. Often in delirium the

cognitive impairment is much more profound and pervasive, and the onset is more abrupt. (Ref. 20) Similarly, an individual with a major depressive episode is much more likely to have a relatively normal premorbid state and abrupt cognitive decline associated with the depression, compared with a dementia, where there is often a protracted history of declining cognitive function. (Ref. 1)

When you are uncertain how to complete a detailed assessment of depression or the situation appears to be complex, seek help from a psychiatrist or psychologist.

Suicide

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 that they will actually commit suicide, particularly if the physician acknowledges their feelings and desires, and addresses the root causes of their distress (see EPEC™-O Module 14: Physician-Assisted Suicide).

Assess all patients with depressive symptoms for thoughts and plans to commit suicide. Ask questions like:

- “Have you ever thought of committing suicide?”
- “Do you have a plan?”

Consider patients with recurrent thoughts of suicide or serious plans to be at high risk. Consult a mental health specialist experienced in this area immediately. (Ref. 2)

Management

Treat depressed cancer patients with a combination of supportive and other psychotherapy modalities, alternative medicine approaches, and pharmacotherapy. Lack of improvement within a few weeks suggests a need for more aggressive therapy or a psychiatric consult. There are a number of reviews on the management of depression, (Ref. 2) (Ref. 21) including Consensus Guidelines from the American Psychiatric Association (Ref. 22) and Clinical Practice Guidelines from the American Medical Directors Association. (Ref. 23)

Counseling

Individual and group counseling have both been shown to reduce depressive symptoms. (Ref. 24) (Ref. 25) 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, and the interaction itself may be therapeutic. During the discussions, 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. Discuss short-term goals. Identify and reinforce the patient's previously demonstrated strengths and successful coping techniques. This will help the patient and family establish or reestablish the patient's sense of self-worth and meaning (see EPEC™-O Module 9: Negotiating Goals of Care).

Oncologists, psychiatrists, psychologists, or other mental health professionals can conduct formal counseling sessions. Others, including nurses, social workers, and chaplains, may also be able to conduct both formal and informal sessions, depending on their training. These approaches can also be used by the primary physician, as well as other colleagues.

Time spent talking with patients about their feelings and reframing their ideas may be helpful.

Complementary therapies

Relaxation therapy and distraction therapy with pleasant imagery, etc., have been shown to reduce depressive symptoms in patients with mild to moderate levels of depression. (Ref. 26) Other helpful techniques may include meditation training, guided imagery, massage therapy, aromatherapy, music therapy, or self-hypnosis. If possible for the patient, exercise and exposure to sunlight can help to lift a depressed mood.

Pharmacologic management

The principal medications used for the treatment of depression include tricyclic antidepressants, 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 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 SSRI, a tricyclic, or another antidepressant may be an appropriate choice. (Ref. 2) When they are available, SSRIs are preferred over tricyclic antidepressants, as the risk of adverse effects is significantly less, even though they may not be as effective as tricyclic antidepressants.

Patients will often respond to specific antidepressants if they have a family member who has had a positive response to that same antidepressant.

With all antidepressant medications, “start dosing 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, consult a psychiatrist.

Tricyclic antidepressants

Amitriptyline is the tricyclic antidepressant listed by the World Health Organization (WHO) as an Essential Medicine. (Ref. 27) It is also used as an analgesic to manage neuropathic pain. Doxepin and imipramine are considered to have similar clinical effects by the WHO. Other second-generation tricyclic antidepressants to consider are desipramine and nortriptyline.

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.

Titration of tricylcics to achieve an adequate dosage 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 [proarrhythmic]) 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 3-5 days, increase by 10-25 mg PO nightly. Maintenance dose is typically 50-100 mg PO nightly. Maximum dose is 150 mg/day. When using doses of 100 mg or more, follow blood levels to anticipate and minimize the risk of adverse effects.

Selective serotonin reuptake inhibitors

When SSRIs (e.g., fluoxetine, paroxetine, sertraline, citalopram, and escitalopram) are available and affordable, they are recommended over TCAs as: 1) they are almost as effective antidepressants, 2) their onset of action is usually faster, and 3) they have much less risk of adverse effects.

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 an SSRI for any patient, especially a patient on many medications, but certainly when psychotropic medication is involved. SSRIs cause significantly less constipation, sedation, and dry mouth than the tricyclics, though nausea may be worse. (Ref. 28) Expect to see results within 2 to 4 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 have a better adverse effect profile. Paroxetine can be used if nighttime sedation is a welcome side effect. Note that all SSRIs can be either activating or sedating, but some tend to have more of one effect than the other. If an SSRI is activating to the patient, give the dose in the morning; if it is sedating, give the dose nightly. Fluoxetine is generally not recommended due to its long half-life, but it does come in liquid form, which may be useful in this population. Common starting doses are:

- **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 at night.
- **Paroxetine**, 10-20 mg PO daily. Target dose is 20-40 mg PO daily. Maximum dose is 50 mg/day. To reduce the risk of adverse effects, consider an extended-release formulation.

Psychostimulants

The psychostimulants methylphenidate, dextroamphetamine, and pemoline are under-appreciated for their antidepressant qualities. (Ref. 2) (Ref. 29) They act quickly, within hours to days, and produce minimal adverse effects. Some patients report increased energy and an improved sense of well-being 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 may potentiate opioid analgesia. (Ref. 30) (Ref. 31)

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

If discontinued, taper psychostimulants slowly. Monitor liver function tests if the use of pemoline is prolonged.

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**, 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. To improve tolerability, consider an extended-release formulation.
- **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.

Pemoline is a stimulant unrelated to amphetamine, and is somewhat less potent. It offers the advantage of decreased sympathomimetic effects, little abuse potential, and absorption through the buccal mucosa.

- **Pemoline**, start with 18.75 mg PO q am and q noon. Increase by 18.75 mg PO q am and q noon. Maximum dose is 150 mg/day.

Modafinil is a novel non-stimulant agent that improves lethargy. This agent may help with lethargy in depression and improve response to antidepressants. (Ref. 32) (Ref. 33)

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

Other antidepressants

A diverse group of older and newer medications that affect depression is growing quickly, including mirtazapine, bupropion, trazodone, and venlafaxine. Like SSRIs, they are thought to be about as effective as tricyclics, but most have less risk of adverse effects.

Trazodone, though not considered a potent antidepressant, may have a role in cancer patients as an adjunctive analgesic due to its serotonergic properties. It can also be highly sedating in low doses, making it an effective sedative hypnotic. (Ref. 2) (Ref. 28) A common starting dose is:

- **Trazodone**, 50 mg PO nightly. Increase every 7 or more days by 50 mg PO nightly. Maximum dose is 400 mg/day.

Bupropion and venlafaxine may have a positive impact on pain syndromes, and can be energizing in patients with fatigue or psychomotor retardation. (Ref. 28) Common starting doses are:

- **Bupropion**, start with 100 mg PO bid for a few days. Increase to 100 mg PO tid for a few weeks. Maximum single dose is 150 mg. Maximum daily dose is 450 mg. To simplify dosing and reduce the risk of adverse effects, consider an extended-release formulation (e.g., Bupropion XL).
- **Venlafaxine**: The usual staring dose is 37.5 mg PO bid or 75 mg of the sustained-release preparation daily. Some patients may need to be started at 37.5 mg PO qd for several days to acclimate to the effects of the medication. Titrate by adding 37.5 mg to the daily dose each week until reaching a dose of 150 mg SR qd. Continue on this dose for 4 weeks. If the desired effect is not achieved, continued titration up to a dose of 225 mg per day can be attempted. Although daily doses up to 350 mg per day have been used, there is little data on the safety and efficacy of Venlafaxine above a daily dose of 225 mg per day.

Mirtazapine may help with pain syndromes, is an effective antidepressant, tends to be sedating at lower doses, and has been associated with increased appetite. It may be particularly helpful in patients who are depressed, have trouble sleeping, and also have a suppressed appetite. If sedation is too great, try increasing the dose to ameliorate this adverse effect.

- **Mirtazapine**, start with 15 mg PO daily. Increase every 1-2 weeks by 15 mg PO daily. Maximum dose is 45 mg/day.

Summary

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 timeframe to best help the patient. If simple interventions do not yield improvement, do not hesitate to consult with mental health professionals, including psychiatrists or psychologists. Nurses, social workers, and chaplains may also be instrumental in helping the patient suffering from depression during the course of his or her illness. 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. The earlier depression is treated, the better the prognosis.
4. If the therapeutic goal is rapid reversal of depression, a psychostimulant is indicated.
5. Psychostimulants (for rapid effect) can be started at the same time as antidepressants (such as the SSRIs) that take longer to work.
6. Counseling plus pharmacotherapy is more effective than either alone.

Pearls

1. If you feel sad and depressed when in the presence of a patient, it may indicate that the patient is depressed (countertransference).

2. Aggressively titrate psychostimulants to lift depression in days.
3. Make a partnership with your patient and the family caregiver; draw them into the interdisciplinary team and foster their active participation in the care plan.
4. Additional information can be found in Module 3: Patient Resources.

Pitfalls

1. Adopting standard outpatient psychiatry models for treatment where the time course may be months for effects.
2. Failing to escalate doses to effective levels.
3. Thinking a psychiatrist or other trained therapist is the only one who can offer brief supportive psychotherapy.

Appendix: Depression Medication Table

Below is the list of medicines that are addressed in the Depression Medication Table. The complete table with detailed information can be viewed by clicking the link below or to the right.

- Amitriptyline
- Bupropion
- Clomipramine
- Desipramine
- Dextroamphetamine
- Doxepin
- Fluoxetine
- Imipramine
- Methylphenidate
- Mirtazapine
- Nefazodone
- Nortriptyline
- Paroxetine
- Pemoline
- Protriptyline

- Sertraline
- Trazodone
- Trimipramine
- Venlafaxine

Depression Medication Table

Depression (antidepressants and stimulants)								
Generic Name	**Trade Name(s)**	**Dosage Forms/ Time C_{max}**	**Elimination $t_{1/2}$**	**Route of Elimination**	**Adult Doses**	**Pediatric Doses**	**Adverse Effects**	**Common Interactions**
Amitriptyline Tricyclic antidepressant for neuropathic pain	Various; Elavil® is an example: tabs: 10, 25, 50, 75, 100, 150 mg	PO: 4 hr	15 hr (range: 9-25 hr)	Liver metabolism: ≈50% of dose metabolized to nortriptyline Renal excretion:	start with 10-25 mg PO nightly, tid and if no adverse effect, increase q 3-4 days in 25-mg increments	☺	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • sympathomimetics
Bupropion Antidepressant	Various; Wellbutrin®, Zyban® are examples: caps: 75, 100 mg ER: 100, 150, 200 mg	PO IR: 2 hr PO ER: 3 hr	14 hr Metabolites: 20-37 hr	Liver metabolism: Considerable first-pass effect Renal excretion: 87% Feces: 10%	100 mg PO bid or 150 mg ER starting dose (max 300 mg/24h)	☺	• agitation • constipation • dizziness • dry mouth • headache • insomnia	• alcohol • anticoagulants, PO: • antidiabetic agents • antihistamines • benzodiazepines • β-blockers • carbamazepine
Clomipramine Tricyclic antidepressant for neuropathic pain	Anafranil® caps: 25, 50, 75 mg	PO: 2-6 hr	19 hr-37 hr Metabolite: 54-77 hr	Liver metabolism: extensive first-pass effect Renal excretion: 51%-60% Feces: 24%-32%	25 mg PO daily and titrate	25 mg PO daily up to 3 mg/kg or 100 mg daily, whichever is smaller	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • sympathomimetics

Depression (antidepressants and stimulants)								
Generic Name	**Trade Name(s)**	**Dosage Forms/ Time C_{max}**	**Elimination $t_{1/2}$**	**Route of Elimination**	**Adult Doses**	**Pediatric Doses**	**Adverse Effects**	**Common Interactions**
Desipramine Tricyclic antidepressant for neuropathic pain	Various; Norpramin® is an example: tabs: 10, 25, 50, 75, 100, 150 mg	PO: 3-6 hr	14.3-24.7 hr	Liver metabolism: extensive first-pass effect Renal excretion: ≈ 70%	10-25 mg PO daily and titrate	☺	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • sympathomimetics
Dextroamphetamine Stimulant	Various; Dexedrine® is an example: tabs: 5, 10 mg ER: 5, 10, 15 mg	PO IR: tablets: 60-180 minutes PO ER: capsules: ≈ 7-8 hr	7-34 hr, mean 12 hr	Liver metabolism: extensive Renal excretion: 17%-73%	5 mg PO q 9 am and noon to start and titrate (avoid late afternoon and evening doses as these can interfere with sleep)	☺ ☺	• nervousness • insomnia • dizziness • nausea/vomiting • cardiac effects • delirium • hypersensitivity	• MAOIs • pressor agents • guanethidine • bretylium • warfarin anticoagulants • TCAs • phenylbutazone
Doxepin Tricyclic antidepressant for neuropathic pain Prominent histamine H_1 receptor antagonist	Various; Sinequan® is an example: caps: 10, 25, 50, 75, 100, 150 mg	PO: 30-60 minutes	8-25 hr mean: 16.8 hr Metabolites: 33.2-80.7 hr mean 51.3 hr	Liver metabolism: to active metabolite Renal excretion: 0.5%	10-25 mg PO nightly and titrate	☺	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • sympathomimetics

Depression (antidepressants and stimulants)								
Generic Name	**Trade Name(s)**	**Dosage Forms/ Time C_{max}**	**Elimination $t_{1/2}$**	**Route of Elimination**	**Adult Doses**	**Pediatric Doses**	**Adverse Effects**	**Common Interactions**
Fluoxetine Selective serotonin reuptake inhibitor (SSRI) antidepressant	Prozac®: caps: 10, 20, 40 mg liquid: 20 mg/5 ml 90 mg timed-release capsule	PO: 6-8 hr	4-6 days, chronic administration Metabolites: 4-16 days	Liver metabolism: extensive to active metabolite, norfluoxetine Renal excretion: 60% Feces: 12%	start with 2.5-5 mg PO nightly; if no side effects, increase gradually q 1wk (max 80 mg/ 24 h, may take 4-5 wk to realize effect; reduce dose for elderly, hepatic and renal failure)	☺	• asthenia • constipation, diarrhea • dizziness • dry mouth • headache • insomnia, somnolence	• alcohol • anticoagulants, PO • antidiabetic agents • antihistamines • benzodiazepines • β-blockers • carbamazepine
Imipramine Tricyclic antidepressant for neuropathic pain	Various; Tofranil® is an example: tabs: 10, 25, 50, 75, 100, 150 mg	PO: 1 hr	6-18 hr Metabolite: desipramine 12-36 hr	Liver metabolism: extensive first-pass effect–desipramine Renal excretion: 0.05–0.1% (desipramine only) Imipramine metabolites excreted in urine	10-25 mg PO daily and titrate	☺ ☺	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • sympathomimetics

Depression (antidepressants and stimulants)								
Generic Name	**Trade Name(s)**	**Dosage Forms/ Time C_{max}**	**Elimination $t_{1/2}$**	**Route of Elimination**	**Adult Doses**	**Pediatric Doses**	**Adverse Effects**	**Common Interactions**
Methylphenidate Stimulant Antidepressant	Various; Ritalin® is an example: IR tabs: 5, 10, 20 mg ER tabs: 20 mg ER caps: 10, 20, 30, 40 mg Concerta ER tab: 18, 27, 36, 54 mg	PO IR: 1-3 hr PO ER: 6-8 hr	PO: 2-7 hr; mean 3 hr	Liver metabolism: rapid and extensive Renal excretion: less than 1% unchanged	5 mg PO q 9 am and noon to start and titrate 20-40 mg/24h reported (avoid late afternoon and evening doses as these can interfere with sleep)	☺ ☺	• nervousness • insomnia • dizziness • nausea/vomiting • cardiac effects • delirium • hypersensitivity	• MAOIs • pressor agents • guanethidine • bretylium • warfarin anticoagulants • TCAs • phenylbutazone
Mirtazapine Atypical antidepressant	Remeron®: tabs: 7.5, 15, 30, 45 mg ODT: 15, 30, 45 mg	PO: 1.5-2 hr	20-40 hr	Liver metabolism: extensive Renal excretion: 75% Feces: 15%	15 mg PO nightly	☺	• somnolence • dizziness • weight gain	• alcohol • diazepam
Nefazodone Antidepressant	Serzone® : tabs: 50, 100, 150, 200, 250 mg	PO: 0.5-2 hr	1.9-5.3 hr Metabolites: 2-33 hr	Liver metabolism: extensive first-pass metabolism Renal excretion: 55% Feces: 20%–30%	100 mg PO bid and titrate	☺	• dizziness • drowsiness • dry mouth • headache • nausea • constipation • blurred vision • hypersensitivity	• anticholinergics • antihypertensives • CNS depressants • digoxin • cisapride • triazolo-benzodiazepines • MAOIs • phenothiazines • phenytoin • SSRIs

Depression (antidepressants and stimulants)								
Generic Name	**Trade Name(s)**	**Dosage Forms/ Time C_{max}**	**Elimination $t_{1/2}$**	**Route of Elimination**	**Adult Doses**	**Pediatric Doses**	**Adverse Effects**	**Common Interactions**
Nortriptyline Tricyclic antidepressant for neuropathic pain	Various; Pamelor® is an example: caps: 10, 25, 50, 75 mg solution: 10 mg/5 ml	PO: 1 hr	15-39 hr	Liver metabolism: extensive Renal excretion: 2%	10-25 mg PO daily and titrate	☺ ☺	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • sympathomimetics
Paroxetine SSRI antidepressant	Paxil®: IR tabs: 10, 20, 30, 40 mg ER tabs: 12.5, 25, 37.5 mg suspension: 10 mg/5 ml	PO IR: 3-8 hr PO ER: 6-10 hr	15-22 hr	Liver metabolism: extensive Renal excretion: 65%-67% Feces 36%-37%	start 20 mg PO nightly; if no side effects, increase 10 mg PO q 1-2 wk (max 50 mg PO daily, may take 3-4 wk to realize effect; reduce dose for elderly, hepatic and renal failure)	☺	• asthenia • constipation, diarrhea • dizziness • dry mouth • headache • insomnia • somnolence	• MAOIs (avoid) • neuroleptics • nifedipine • pentazocine • phenothiazines • phenytoin • theophylline
Pemoline Stimulant	Various; Cylert® is an example: tabs: 18.75, 37.5, 75 mg	PO: 2-4 hr	7-13 hr	Liver metabolism: N/A Renal excretion: 50% (unchanged)	37.5 mg PO q am and titrate (112 mg/24h reported) (follow liver function tests)	☺ ☺	• liver failure • nervousness • insomnia • dizziness • nausea/vomiting • delirium • hypersensitivity	• MAOIs • pressor agents • guanethidine • bretylium • warfarin anticoagulants • TCAs • phenylbutazone

Depression (antidepressants and stimulants)								
Generic Name	**Trade Name(s)**	**Dosage Forms/ Time C_{max}**	**Elimination $t_{1/2}$**	**Route of Elimination**	**Adult Doses**	**Pediatric Doses**	**Adverse Effects**	**Common Interactions**
Protriptyline Tricyclic antidepressant for neuropathic pain	Vivactil® tabs: 5, 10 mg	PO: 8-12 hr	54-198 hr	Liver metabolism: extensive Renal excretion: slow rate of excretion (50% over 2 weeks)	5 mg PO tid and titrate	☺ ☺	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • sympathomimetics
Sertraline SSRI antidepressant	Zoloft®: tabs: 25, 50, 100 mg conc. solution: 20 mg/ml	PO: 4-8 hr	24 hr Metabolites: 62-104 hr	Liver metabolism: extensive Renal excretion: 40%-45% Feces: 40%-45%	start with 50 mg PO nightly; if no side effects, increase gradually q 1 wk (max 200 mg/24h)	☺	• asthenia • constipation, diarrhea • dizziness • dry mouth • headache • insomnia, somnolence	• alcohol • anticoagulants, PO • antidiabetic agents • antihistamines • benzodiazepines • β-blockers • Carbamazepine
Trazodone Antidepressant Sedative	Various; Desyrel® is an example: tabs: 50, 100, 150, 300 mg	PO: 0.5-2 hr	7.1 hr	Liver metabolism: extensive Renal excretion: 70%-75% Feces: 21%	start with 50 mg PO nightly; if no adverse effects, increase q 7 or more days up to 400 mg/24h	☺	• dizziness • drowsiness • dry mouth • headache • nausea • priapism • no risk of withdrawal • hypersensitivity	• anticholinergics • antihypertensives • CNS depressants • digoxin • general anesthetics • MAOIs • phenothiazines • phenytoin • SSRIs

Depression (antidepressants and stimulants)								
Generic Name	**Trade Name(s)**	**Dosage Forms/ Time C_{max}**	**Elimination $t_{1/2}$**	**Route of Elimination**	**Adult Doses**	**Pediatric Doses**	**Adverse Effects**	**Common Interactions**
Trimipramine Tricyclic antidepressant for neuropathic pain	Surmontil®: caps: 25, 50, mg	PO: 2 hr	23 hr	Liver metabolism: extensive	25 mg PO daily and titrate	☺ ☺	• anticholinergic AE • arrhythmias, QRS prolongation • drowsiness • nausea/vomiting • orthostatic hypotension • seizures	• alcohol • anticoagulants • barbiturates • cimetidine • clonidine • CNS depressants • histamine H_2 receptor antagonists • MAOIs • Sympathomimetic s
Venlafaxine Atypical antidepressant	Effexor®: caps: 25, 37.5, 50, 75, 100 mg ER: 37.5, 75, 150 mg	PO IR: 1-2 hr PO ER: 5.5 hr	5 hr Metabolite: 11 hr	Liver metabolism: extensive first-pass effect to active metabolite Renal excretion: 36%-60%	37.5 mg PO bid or 75 mg/24h ER; start lower in some patients	☺	• asthenia • constipation, diarrhea • dizziness • dry mouth • headache • insomnia, somnolence	• alcohol • anticoagulants, PO • antidiabetic agents • antihistamines • benzodiazepines • β-blockers • Carbamazepine

References

Module 3h: Depression

1 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th text revised ed. Washington, DC: APA; 2000.

2 Wilson KG, Chochinov HM, de Faye BJ, Breitbart W. Diagnosis and management of depression in palliative care. In: Chochinov HM, Breitbart W, eds. Handbook of Psychiatry in Palliative Medicine. New York: Oxford University Press; 2000:435.

The article provides a review of the impact, risk factors, assessment, and treatment of depression.

3 Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients. JAMA. 1983;249(6):751-757. PMID: 6823028.

Two hundred fifteen randomly accessed cancer patients (who were new admissions to three collaborating cancer centers) were examined for the presence of formal psychiatric disorder. Each patient was assessed in a common protocol via a psychiatric interview and standardized psychological tests. Results indicated that 47% of the patients received a DSM-III diagnosis, with 44% being diagnosed as manifesting a clinical syndrome and 3% with personality disorders. Approximately 68% of the psychiatric diagnoses consisted of adjustment disorders, with 13% representing major affective disorders (depression). The remaining diagnoses were split among organic mental disorders (8%), personality disorders (7%), and anxiety disorders (4%). Approximately 85% of those patients with a positive psychiatric condition experienced a disorder with depression or anxiety as the central symptom.

4 Stiefel FC, Breitbart WS, Holland JC. Corticosteroids in cancer: Neuropsychiatric complications. Cancer Invest. 1989;7(5):479-491. PMID: 2695230.

Corticosteroids have become an integral part of many cancer treatment regimens. Early reports of severe affective disorders appear less frequently today in patients receiving steroids, though controlled studies are rare. Minor mood changes are common, ranging from the euphoria of initial treatment to depressive symptoms on withdrawal. The most common severe disturbances seen clinically in cancer patients are the organic mood disorders and delirium. A more careful clinical delineation of the mental changes with steroids is desirable not only for clinical relevance, but for the potential understanding of the etiology of mood disorders and mental changes seen in delirium.

5 Kathol RG, Noyes R Jr, Williams J, Mutgi A, Carroll B, Perry P. Diagnosing depression in patients with medical illness. Psychosomatics. 1990;31(4):434-440. PMID: 2247573.

6 Levine PM, Silberfarb PM, Lipowski ZJ. Mental disorders in cancer patients: A study of 100 psychiatric referrals. Cancer. 1978;42(3):1385-1391. PMID: 698920.

Records of 100 consecutive hospitalized cancer patients referred for psychiatric consultation were reviewed. Fifty-six percent of the referred patients were diagnosed as depressed and 40% as having organic brain disease. Twenty-six of the 100 patients were misdiagnosed by the referring physician as depressed but were classified by the staff psychiatrist as suffering from organic brain syndrome. When referral was studied by primary site of cancer, only patients with breast cancer were referred at a significantly higher-than-expected rate ($p<.001$). The importance of the mental status examination as a routine procedure in all cancer patients is stressed so that an organic brain syndrome will not be missed.

7 Kaplan HI, Sadock BJ. Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences, Clinical Psychiatry. 8th ed. Baltimore: Williams & Wilkins; 1998.

8 Pirl WF. Evidence report on the occurrence, assessment, and treatment of depression in cancer patients. J Natl Cancer Inst Monographs. 2004;2004(32):32-39; full text.

Rates of major depressive disorder and depressive symptoms comorbid with cancer appear to be 10%-25%. Although multiple instruments are available for assessing depressive symptoms, a clinical interview using Diagnostic and Statistical Manual of Mental Disorders criteria is the standard to which assessments are compared.

9 Massie MJ. Prevalence of depression in patients with cancer. J Natl Cancer Inst Monographs. 2004;No.32:57-71; full text.

Although many research groups have assessed depression in cancer patients since the 1960s, the reported prevalence (major depression, 0%-38%; depression spectrum syndromes, 0%-58%) varies significantly because of varying conceptualizations of depression, different criteria used to define depression, differences in methodological approaches to the measurement of depression, and different populations studied. Depression is highly associated with oropharyngeal (22%-57%), pancreatic (33%-50%), breast (1.5%-46%), and lung (11%-44%) cancers. A lower prevalence of depression is reported in patients with other cancers, such as colon (13%-25%), gynecologic (12%-23%), and lymphoma (8%-19%).

10 Derogatis LR, Abeloff MD, McBeth CD. Cancer patients and their physicians in the perception of psychological symptoms. Psychosomatics. 1976;17(4):197-201. PMID: 1005638.

11 Lampic C, Wennberg A, Schill JE, Brodin O, Glimelius B, Sjoden PO. Anxiety and cancer-related worry of cancer patients at routine follow-up visits. Acta Oncol. 1994;33(2):119-125. PMID: 8204268.

Anxiety and cancer-related worry were assessed in 197 consecutive cancer patients attending follow-up visits. Results showed that while a majority of patients felt no or only mild anxiety in conjunction with the follow-up visit, about one-fifth reported moderate or strong anxiety. Many patients (46%) worry about suffering a recurrence and about overlooking symptoms of new cancer (33%). Patients who were not in complete remission reported higher levels of cancer-related worry concerning the follow-up visit than did patients in remission. Among patients in remission, those who had recently terminated treatment reported more overall distress than patients who were 2 or more years since treatment termination.

12 Rathbone GV, Horsley S, Goacher J. A self-evaluated assessment suitable for seriously ill hospice patients. Palliat Med. 1994;8(1):29-34. PMID: 7514069.

In an attempt to measure quality of life in these patients, a simple assessment was piloted (PEPS-patient-evaluated problem score) in which patients were asked to identify and grade major problems as they perceived them and also to grade problems previously identified by the medical and nursing staff. Overall, a mean of 5.6 problems per patient were identified, of which 14% were psychosocial. Of those patients who completed questionnaires, 58% identified problems not picked up by the nursing and medical staff; 52% of these were psychosocial problems. PEPS has proved useful in the management of patients, enabling the identification of previously unrecognized or underrated problems, particularly of a psychosocial nature, and also as a means of evaluating progress.

13 Barnett MM. Does it hurt to know the worst? Psychological morbidity, information preferences and understanding of prognosis in patients with advanced cancer. Psychooncology. 2005 Mar 7; [Epub ahead of print] PMID: 15750997.

One hundred six patients with advanced cancer were interviewed at home. When understanding of prognosis was compared with psychological distress, a significant difference was observed between those with realistic versus unrealistic time scales. Although patients with deteriorating health are more likely to be psychologically distressed, awareness of prognosis does not itself cause depression.

14 Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression. Am J Psychiatry. 2000;157:1552-1562. PMID: 11007705.

15 Massie M, Holland J, Lesko L. Management of common psychiatric syndromes in elderly patients with cancer. In: Zenser T, Coe R, eds. Cancer and Aging. New York: Springer Publishing Company; 1998.

16 Passik SD, Breitbart WS. Depression in patients with pancreatic carcinoma. Diagnostic and treatment issues. Cancer. 1996;78(3 Suppl):615-626. PMID: 8681300.

Depression and anxiety occur more frequently in patients with cancer of the pancreas than they do in patients with other forms of cancer. Diagnosis and treatment of depressive disorders as they apply to patients with cancer of the pancreas are reviewed, and psychologic and pharmacologic treatment strategies to deal with these issues are outlined.

17 Trask PC. Assessment of depression in cancer patients. J Natl Cancer Inst Monographs. 2004;(32):80-92. PMID: 15263046; full text.

This review was designed to succinctly address and identify several areas for future research, including refining diagnostic criteria for depression in cancer patients; creating cancer-specific depression measures with appropriate cutoffs; focusing on the issues of age, race, ethnicity, subculture, and type and stage of cancer in creating depression assessment tools; and exploring the issues of clinical versus subclinical depression, who and when to assess, and timely and cost-effective assessment methods.

18 Endicott J. Measurement of depression in patients with cancer. Cancer. 1984;53(10 Suppl):2243-2249. PMID: 6704912.

The recognition or detection of depressive symptoms and syndromes in patients with cancer is of value to patients because their mental distress may respond to treatment, and to the clinician because clinical complications or difficulties in diagnosis and treatment of patients may be reduced. Many factors militate against the diagnosis of depressive syndromes in patients with cancer. These include problems with the application of standard sets of criteria for depression; the assumption on the part of medical staff, family, and patients that depression is a "natural" response and therefore not treatable; and the pressure on all involved to "think positive." Some ways of modifying the usual screening and diagnostic procedures for depressive disorders are suggested.

19 Chochinov HM, Wilson KG, Enns M, Lander S. "Are you depressed?" Screening for depression in the terminally ill. Am J Psychiatry. 1997;154(5):674-676. PMID: 9137124.

This study compared the performance of four brief screening measures for depression in a group of terminally ill patients. The methods included: 1) a single-item interview assessing depressed mood, 2) a two-item interview assessing depressed mood and loss of interest in activities, 3) a visual analog scale for depressed mood, and 4) the Beck Depression Inventory-Short Form. Single-item interview screening correctly identified the eventual diagnostic outcome of every patient, substantially outperforming the questionnaire and visual analog measures.

20 Breitbart W, Cohen K. Delirium in the terminally ill. In: Chochinov HM, Breitbart W, eds. Handbook of Psychiatry in Palliative Medicine. New York: Oxford University Press; 2000:435.

21 Fisch M. Treatment of depression in cancer. J Natl Cancer Inst Monographs. 2004;2004(32):105-111. PMID: 15263050; full text.

Depression occurs in about 15% of the general population and is at least two to three times more common in patients with cancer. Depression is often difficult to diagnose in these patients because of the complexity and constraints of cancer care, patient and family reluctance to acknowledge distress, and the presence of multiple other symptoms. Both antidepressants and psychotherapy are effective in treating depression in patients with cancer, much as in patients with other significant medical problems. Precise assessments of the benefits of treating depression in these patients are important in weighing them against the costs and potential adverse effects. There is an emerging trend toward simplifying the assessment of depression in outpatient cancer care settings and studying depression therapies in cohorts of patients with cancer other than those with fully characterized depressive disorders.

22 American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry. 2000;157(4 Suppl):1-45. PMID: 10767867.

23 American Medical Directors Association. Clinical Practice Guideline: Depression. Columbia, MD: AMDA; 2003. Available at http://www.amda.com/tools/cpg/depression.cfm. Accessed February 20, 2006.

24 Edmonds CV, Lockwood GA, Cunningham AJ. Psychological response to long-term group therapy: A randomized trial with metastatic breast cancer patients. Psychooncology. 1999;8(1):74-91. PMID: 10202785.

Research has demonstrated that short-term psychological interventions improve the quality of life of cancer patients. However, there is much less evidence for the efficacy of long-term interventions. The authors report the psychometric results from a randomized clinical trial (n=66) assessing the effects of an 8-month, weekly psychological intervention on 30 metastatic breast cancer patients. Results demonstrated little psychometric difference between the control (n=36) and intervention groups over this length of time, in spite of the fact that when intervention subjects attended a weekend of support and training in coping skills, the usual significant, short-term changes were observed. However, profound clinical changes were observed by the therapists, similar to those noted by Spiegel et al. (1981). The authors conclude that many of the psychological changes made by subjects in long-term interventions may elude conventional psychometric assessment.

25 Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. A randomized outcome study. Arch Gen Psychiatry. 1981;38(5):527-533. PMID: 7235853.

The effects of weekly supportive group meetings for women with metastatic carcinoma of the breast were systematically evaluated in a 1-year, randomized, prospective outcome study. Eighty-six patients were tested at 4-month intervals. The treatment group had significantly lower mood disturbance scores on the Profile of Mood States scale, had fewer maladaptive coping responses, and were less phobic than the control group. This study provides objective evidence that a supportive group intervention for patients with metastatic cancer results in psychological benefit.

26 Spiegel D, Bloom JR. Group therapy and hypnosis reduce metastatic breast carcinoma pain. Psychosom Med. 1983;45(4):333-339. PMID: 6622622.

The pain and mood disturbance of 54 women with metastatic carcinoma of the breast were studied over the course of 1 year. A random sample was offered weekly group therapy during the year, with or without self-hypnosis training directed toward enhancing their competence at mastering pain and stress related to cancer. Both treatment groups demonstrated significantly less self-rated pain sensation ($t=2.5$, $p<0.02$) and suffering ($t=2.17$, $p<0.03$) than the control sample. Those who were offered the self-hypnosis training as well as group therapy fared best in controlling the pain sensation ($F=3.1$, $p<0.05$). Changes in pain measures were significantly correlated with changes in self-rated total mood disturbance on the Profile of Mood States and with its anxiety, depression, and fatigue subscales.

27 World Health Organization. Essential Medicines Library. [WHO medical information Web site.] Available at: http://mednet3.who.int/EMlib/index.aspx. Accessed February 20, 2006.

28 Schatzberg AF, Cole JO, DeBattista C. Manual of Clinical Psychopharmacology. 4th ed. Washington, DC: American Psychiatric Pub; 2003.

29 Fernandez F, Adams F, Holmes VF, Levy JK, Neidhart M. Methylphenidate for depressive disorders in cancer patients. An alternative to standard antidepressants. Psychosomatics. 1987;28(9):455-461. PMID: 3432548.

30 Bruera E, Watanabe S. Psychostimulants as adjuvant analgesics. J Pain Symptom Manage. 1994;9(6):412-415. PMID: 7963794.

Psychostimulants have multiple roles in the adjuvant treatment of pain. Studies are discussed that demonstrate the efficacy of these drugs in potentiating opioid analgesia, counteracting opioid-induced sedation and cognitive impairment, allowing dose escalation in difficult pain syndromes, and alleviating symptoms of depression. Practical guidelines are suggested and areas for future research are indicated.

31 Bruera E, Driver L, Barnes EA, et al. Patient-controlled methylphenidate for the management of fatigue in patients with advanced cancer: A preliminary report. J Clin Oncol. 2003;21(23):4439-4443. PMID: 1464534.

The article provides an assessment of the effects of patient-controlled methylphenidate for cancer-related fatigue. In this prospective open study, 31 patients with advanced cancer and fatigue who scored ≥4 on a scale of 0 to 10 received methylphenidate 5 mg by mouth every 2 hours as needed for 7 days (maximum, 20 mg/d). Anxiety, appetite, pain, nausea, depression, and drowsiness all improved significantly (P<.05). All patients took afternoon or evening doses, and 28 patients (93%) took three or more doses daily. All patients chose to continue taking methylphenidate after 7 days of treatment. No serious adverse effects were reported.

32 Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry. 2005;66(1):85-93. PMID: 15669893.

Up to one-half of depressed patients have partial or no response to antidepressant monotherapy. This multicenter, placebo-controlled study evaluated the efficacy of modafinil augmentation in major depressive disorder (MDD) patients with fatigue and excessive sleepiness despite selective serotonin reuptake inhibitor (SSRI) monotherapy. Findings suggest that modafinil is a well-tolerated and potentially effective augmenting agent for SSRI partial responders with fatigue and sleepiness.

33 DeBattista C, Lembke A, Solvason HB, Ghebremichael R, Poirier J. A prospective trial of modafinil as an adjunctive treatment of major depression. J Clin Psychopharmacol. 2004;24(1):87-90. PMID: 14709953.

Preliminary evidence indicates that modafinil may improve fatigue and excessive sleepiness associated with a variety of conditions. The purpose of this study was to investigate the utility of modafinil as an adjunctive treatment of depressed patients. All subjects endorsed complaints of significant fatigue and/or excessive sleepiness on clinical assessment. Modafinil was added to their existing regimen at a dose of 100 to 400 mg/d for 4 weeks. Significant improvements were seen across all three measures of depression (HDRS, BDI, CGIS) and both measures of fatigue (VASF, FSI). Modafinil may be a useful and well-tolerated adjunctive agent to standard antidepressants in the treatment of major depression.

Self-Assessment

Module 3h: Depression

5. Mr. Arlinson is a 32-year-old man who has advanced AIDS and Kaposi's sarcoma. He has been nonadherent with HAART and has a multiple resistance strain of HIV. He has lost weight and reports a poor appetite. He sleeps poorly. He reports a lack of energy and spends most of his time at home. During a visit to his physician, he reports feeling hopeless and helpless. He is comfortable talking about the fact that he will die. A clinical suspicion of major depression is most supported by:

   - a). changes in appetite and sleep patterns
   - b). feelings of hopelessness and helplessness
   - c). lack of energy
   - d). comfort in talking about the prospect of death

6. To treat a diagnosis of major depression for Mr. Arlinson, with a goal of response within a few days, the best initial drug of choice would be:

   - a). methylphenidate
   - b). amitriptyline
   - c). fluoxetine
   - d). lorazepam

Self-Assessment Answers

Question 5. The correct answer is: b)

This question is aimed at understanding the diagnosis of depression in patients with advanced illness. Psychological symptoms such as hopelessness and helplessness are the most sensitive and specific. Changes in appetite and sleep, and lack of energy are common to both depression and the advance stages of most illnesses. Talking about the prospect of dying is a healthy response to the situation; it is not *de facto* evidence of depression.

Question 6. The correct answer is: a)

This question is aimed at understanding the pharmacologic treatment of depression. The psychostimulant methylphenidate acts within days without excessive or worrisome side effects. Amitriptyline is associated with unwanted side effects. Fluoxetine is likely to be effective, but will take several weeks to see an effect. Lorazepam is an anxiolytic sedative, not an antidepressant.