Diagnosis and Treatment of Depression in the Cancer Patient

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ABSTRACT

Cancer patients often experience depressed mood which can be serious if left untreated. Psychotherapy, pharmacotherapy, or a combination of the two represents the primary treatment options for the diagnosis of major depression. The choice of antidepressant pharmacotherapy is dependent on the nature of the depressive symptoms, current comorbidities, adverse side effect profile, and the potential to interact with other medications. Selective serotonin reuptake inhibitors (SSRIs) have limited side effects, proven efficacy, and safety in overdose which makes them first-line agents for treatment of depression in the cancer patient. Finally, treatment of depression can improve quality of life and may also facilitate cancer treatment.

INTRODUCTION

Depression is recognized as a serious and chronic illness which is often under-recognized and insufficiently treated. The diagnosis of depression is made in approximately 50% of patients suffering from depressive illness, and only half of those diagnosed will receive adequate therapy. Depression left untreated can cause prolonged hospitalizations, poor compliance with medical care, increased morbidity, and mortality.[1-3]

It is estimated that 25% of all cancer patients will experience major depression at some time in their illness.[4-7] Oncology patients are three times more likely than the general population and about two times more likely than other hospitalized medical patients to develop depression.[8,9] Cancer patients who are the most critically ill, with the highest level of disability, and distressing physical symptoms (especially poor pain control) have the highest prevalence of depression.[8,9] Moreover, oncology patients are more likely to commit suicide or request euthanasia than any other depressed population.[10,11] Therefore, it is extremely important that patients with cancer be routinely screened for concomitant depressive illness.

MAJOR DEPRESSION DIAGNOSIS

Table 1 outlines the diagnostic criteria for major depressive episode from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition *(DSM-IV)*.[12] In order to meet the *DSM-IV* criteria for major depression, one of the symptoms must be either depressed mood or loss of interest/pleasure. Additionally, the patient must be suffering from distress or impairment in social, occupational, or other important areas of functioning.

Diagnosis of depression in the cancer patient population can be complicated by the fact that many of the neurovegetative symptoms of depression (especially loss of energy, loss of appetite, and sleep disturbance) overlap with the common symptoms of cancer or other medical illnesses, and with the adverse side effects of medications used in cancer pharmacotherapy. In these cases, alternative psychological criteria (eg, self-pity, brooding, crying spells, and pessimism) are often used.[13] Cognitive symptoms of depression such as depressed thoughts, hopelessness about appreciating any degree of quality in their lives, guilt or worthlessness, or persistent suicidal ideation may often be present. Finally, patients who are near death often become withdrawn and hypoactive and may exhibit neurovegetative symptoms. These symptoms are most likely a part of the dying process, not a depressive episode.[13]

The oncology patient must be routinely evaluated for the presence of depression throughout the course of their cancer-related illness. Predisposing factors such as previous history of psychiatric illness, early maladjustment to cancer, poor social support, and low performance status should be identified.[14] Assessment for depression with a rapid mental status examination should be completed at each visit to the healthcare provider. Table 2 provides a 5 to 10 minute questionnaire for this purpose.[15] There are primarily three areas assessed in the questionnaire: 1) the patient's mood, 2) the risk of suicide, and 3) any physical signs of

TALKING POINTS	Physicians	Pharmacy	Formulary	Cancer Nurses

Antidepressant medications and/or referral to psychotherapy is recommended for treatment of mild to moderate depression.

Dosage of pharmacotherapy should be carefully considered and monitored for any adverse effects, especially in the elderly and patients with liver dysfunction.

Oncology patients are three times more likely than the general population and about two times more likely than other hospitalized medical patients to develop depression.

Treatment of depression can improve quality of life and may also facilitate cancer treatment.

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depression. It is important that the healthcare provider clinically evaluate the physical signs of depression to determine whether symptoms such as fatigue, insomnia, and low libido are caused by depression, the cancer, or the cancer pharmacotherapy. Additionally, screening tools such as the Hospital Anxiety and Depression Scale, Primary Care Evaluation of Mental Disorders, and the Zung Self-Rating Depression Scale are currently useful in oncology settings.[16-18]

The risk of suicide must also be evaluated at each visit to the healthcare provider. As mentioned earlier, cancer patients are more likely to commit suicide or request euthanasia than other depressed patients.[10,11] Risk factors for suicide are outlined in Table 3.[15] If suicide ideation is present, a psychiatrist should be consulted. Patients who appear to be at high risk of suicide should be immediately taken to an emergency care unit for evaluation and possible hospitalization.

TABLE 1. DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, FOURTH EDITION, CRITERIA FOR MAJOR DEPRESSIVE EPISODE

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure.

Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful).

Note: Children, adolescents, and geriatric patients can be in irritable moods.

- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation by others).
- Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

Note: In children, consider failure to make expected weight gains.

- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The symptoms are not due to the direct physiologic effects of a substance (eg, a drug of abuse, a medication) or a general medical condition (eg, hypothyroidism).

Adapted from: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth ed. Washington, DC: American Psychiatric Association; 1994.

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DIFFERENTIAL DIAGNOSIS

Common medical problems and other psychiatric illness with similar symptomatology must be ruled out before the diagnosis of major depressive disorder can be made. Table 4 provides a list of causes of depressive symptoms often present in the cancer patient.

Uncontrolled pain is the most common reason for a depressed mood in the cancer patient.[15] Poor pain control is often accompanied by anxiety and a sense of anguish that life is intolerable. The depressed mood will remain unless the pain is relieved. Pain relief, or even acknowledgment of its existence along with an attempt to relieve it, often leads to an improvement in depressive symptoms.

The potential for dementia, delirium, and psychiatric disorders (eg, bipolar, adjustment, and personality disorders) exists in the oncology population, and should not be overlooked.[15] In both major depression and dementia, patients can present with memory and concentration difficulties making it difficult to discern the correct diagnosis. In these instances, a thorough medical evaluation using the Mini-Mental Status Examination should be performed. The onset, time course of depressive and cognitive symptoms, course of illness, and response to treatment, are often helpful in properly diagnosing depression.[12] Patients with dementia usually have a history of slowly declining cognitive function, whereas those with major depressive illness usually have an abrupt onset of cognitive difficulties. Neuropsychological testing is advised and may be helpful in distinguishing between "true" dementia and the "pseudo" dementia of depression. Patients with depression are usually able to do the cognitive tasks with a significant amount of encouragement.

The patient with delirium may present with a waxing and waning course of attention and cognitive disturbances, symptoms of crying and depressed mood, and complaints of visual hallucinations. Psychotic features are possible in depressed patients. In distinguishing between delirium and depression, it is important to note that depressed patients usually experience auditory hallucinations as

TABLE 2. QUESTIONS TO ASK IN THE ASSESSMENT OF DEPRESSIVE SYMPTOMS

Questions	Symptom(s) Assessed
Psychological Symptoms	
How are you coping right now? Well? Poorly?	Well being
How are your spirits? Down? Depressed? Blue?	Mood
Do you cry sometimes? How often?	
Have you lost anyone close to you recently?	Bereavement
Are there things you still enjoy doing, or have you lost pleasure in the things you used to do?	Anhedonia, loss of interest
How does the future look to you?	
Are you feeling hopeless?	Hopelessness
Do you feel that you can change things, or that they are out of your control?	
Are you feeling helpless?	Helplessness
Do you worry about being a burden?	Guilt
Do you feel guilty about things?	
Suicidal Risk	
Do you ever have thoughts of just giving up or wishing that you were dead?	Suicidal ideation
Do you ever have thoughts of suicide? If so, have you thought about or planned how you would kill yourself?	
Have you had a problem with alcohol or illicit drugs?	Substance abuse
Physical Symptoms[a]	
How much time do you spend in bed?	Energy level
Do you fatigue easily?	Fatigue
Are you rested by sleep?	
How are you sleeping?	Sleep disturbance
Do you have trouble falling asleep?	
Early awakenings?	
Are you sleeping too much?	
How is your appetite?	Appetite
Does food taste good?	
Have you experienced weight loss or gain?	
Do you think or move more slowly?	Psychomotor retardation
Do you feel restless?	Psychomotor agitation

a=evaluate in the context of cancer-related symptoms.

Adapted from: Roth AJ, Holland JC. Treatment of depression in cancer patients. *Prim Care Cancer.* 1994;14:23-29.

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opposed to visual hallucinations as seen in cases of delirium.[15]

Exacerbation of pre-existing coping abilities in patients with cancer can occur. Patients with personality disorders, particularly borderline personality disorder, are at high risk. These patients may also experience a comorbid depressive episode and require psychotropic pharmacotherapy. Personality disorders are frequently the most difficult to manage requiring regularly scheduled visits, good communication network between all caregivers, limit setting for poor behavior, and perhaps designation of a coordinator for care.

Adjustment disorder is defined as depressive symptoms that develop after an identifiable stressor such as a cancer diagnosis or recurrence which do not fully meet the criteria for major depressive episode.[15] Adjustment disorders can progress into a major depression. Therefore, cancer patients with severe or prolonged adjustment disorders may benefit from a trial of antidepressants.[15]

Medications commonly prescribed to oncology patients (eg, benzodiazepines, vincristine, vinblastine, procarbazine, and asparaginase) can also cause depressive symptoms (see Table 4). Prednisone and dexamethasone frequently induce alterations in mental status including symptoms of euphoria, irritability, severe depression, delirium, and psychosis. Cognitive deficits and depressive symptoms may occur from interferon-alfa and interleukin-2 administration. A reduction in dose or discontinuation of the causative medication will often reduce the depressive symptoms. However, if the dose cannot be tapered, antidepressant therapy may be necessary.

TREATMENT OPTIONS

Psychotherapy, pharmacotherapy, or a combination of the two represents the primary

TABLE 3. SUICIDE RISK FACTORS IN CANCER PATIENTS

- **Medical factors**
  - Poorly controlled pain
  - Advanced stage of disease
  - Mild delirium/mental status changes with poor impulse control
  - Depression
- **Personal risk factors**
  - Prior suicide attempt
  - Prior psychiatric history
  - Substance abuse (alcohol, drug abuse)
  - Recent bereavement
  - Few social supports
  - Hopelessness and/or helplessness
  - Family history of suicide

Adapted from: Roth AJ, Holland JC. Treatment of depression in cancer patients. *Prim Care Cancer.* 1994;14:23-29.

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TABLE 4. CAUSES OF DEPRESSIVE SYMPTOMS IN CANCER PATIENTS

- **Uncontrolled pain**
- **Initial reaction to cancer diagnosis**
- **Physical illness**
- **Metabolic abnormalities**
  - Hypercalcemia
  - Sodium/potassium imbalance
  - Vitamin B12 or folate deficiency
- **Anemia**
- **Endocrinologic abnormalities**
  - Hyperthyroidism or hypothyroidism
  - Hyperparathyroidism
  - Adrenal insufficiency
- **Neurologic problems**
  - Brain metastasis
  - Stroke
  - Parkinson's disease
  - Huntington disease unrelated to cancer
- **Psychiatric disorders**
  - Adjustment disorder
  - Bipolar disorder
  - Personality disorder
  - Dementia
  - Delirium
- **Medications**
  - Glucocorticoids (eg, prednisone, dexamethasone)
  - Interferon and interleukin-2
  - Chemotherapeutic agents (eg, vincristine, vinblastine, procarbazine, asparaginase)
  - Barbiturates
  - Benzodiazepines
  - Amphotericin B
  - Antihypertensives (eg, propranolol, methyldopa, reserpine)

Adapted from: Roth AJ, Holland JC. Treatment of depression in cancer patients. *Prim Care Cancer.* 1994;14:23-29.

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"A small starting dose increased gradually is recommended, particularly in advanced cancer cases which usually respond to lower antidepressant doses."

treatment options for the diagnosis of major depression. Additionally, some patients may benefit from self-help or professional support groups. Many healthcare providers utilize antidepressant pharmacotherapy as first-line treatment, and only refer to psychiatrists in complicated or severe situations. When pharmacotherapy fails, electroconvulsive therapy (ECT) may be considered.

Psychotherapy

Individualized or group psychotherapy is primarily directed towards addressing present problems or issues such as coping with changes of lifestyle, financial status, concerns about dying, dependency, disfigurement, and disability (See Table 5). Poor coping skills (eg, excessive self-expectations, inflexible standards, reluctance to compromise or ask for help, rigid outlook, use of excessive denial) must be identified. Depending on the level of functioning and personality of the patient, other psychotherapies, such as cognitive-behavioral and psychoanalysis may prove useful as well.

Pharmacotherapy Principles

Medications are often used in conjunction with psychotherapy to treat depression in cancer patients. Table 6 outlines pharmacotherapy utilized in the treatment of depression in the cancer patient.[15,19] Some improvement in symptoms can be expected after 2 weeks of antidepressant therapy, with the full effect seen at 4 to 6 weeks.[15,19,20] Dosage of pharmacotherapy should be carefully considered and monitored for any adverse effects, especially in the elderly and patients with liver dysfunction.[19,20] A small starting dose increased gradually is recommended, particularly in advanced cancer cases which usually respond to lower antidepressant doses.[19,20]

The choice of antidepressant pharmacotherapy is dependent on the nature of the depressive symptoms, current comorbidities, adverse side effect profile, and the potential to interact with other medications (See Tables 6 through 8, and Figure 1).[15,19-24] As an example, the depressed patient who is anxious, agitated, and/or has insomnia will benefit from an antidepressant with sedating side effects (trazodone, doxepin, nefazodone, mirtazapine, amitriptyline, or imipramine). Moreover, paroxetine has been shown effective in patients with anxiety, and is considered a first-line choice in the depressed patient with anxiety symptoms. Likewise, patients with

psychomotor slowing, fatigue, or sedation from opiate analgesics will benefit from the use of low sedating/stimulating antidepressants (eg, fluoxetine, bupropion, desipramine, methylphenidate). Patients suffering from stomatitis (secondary to chemotherapy or radiation therapy), or who have slowed intestinal motility or urinary retention should be prescribed an antidepressant with the least anticholingeric effects (desipramine, nortriptyline, SSRI, trazodone, nefazodone, bupropion, venlafaxine, or a psychostimulant). Medications with low gastrointestinal upset (mirtazapine, fluoxetine, paroxetine, citalopram, tricyclic antidepressant [TCA], bupropion, or trazodone are useful in cancer patients with nausea.

Low doses of TCAs (ie, amitriptyline or nortripyline 10 mg to 50 mg) or psychostimulants have proven useful as adjuvant pain medications in patients with neuropathic pain syndromes.[15,19] Patients with difficulty swallowing pills may be able to take an antidepressant available in an elixir formulation (paroxetine, fluoxetine, amitriptyline, nortiptyline, doxepin) or use the chewable psychostimulant pemoline.

Selective Serotonin Reuptake Inhibitors

Fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram are considered first-line

TABLE 5. NONPHARMACOLOGIC TREATMENT OF DEPRESSION IN CANCER PATIENTS

- **Emotional support from primary physician, oncologist, and nursing staff**
- **Supportive psychotherapy (individual or group):**
  Goals:
  - Strengthen coping skills
  - Improve self-worth
  - Relieve anxiety and depressed mood
  - View illness in the continuum of life experiences
  - Practice help in managing treatment side effects
- **Electroconvulsive Therapy**

Adapted from: Roth AJ, Holland JC. Treatment of depression in cancer patients. *Prim Care Cancer.* 1994;14:23-29.

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TABLE 6. MEDICATIONS PRESCRIBED FOR DEPRESSION IN CANCER PATIENTS

Medication	Starting Dose (Therapeutic Range)	Common Side Effects
Serotonin Specific Reuptake Inhibitors		
Fluoxetine (Prozac)	10–20 mg (20–60 mg)	Nausea, headache, insomnia, anxiety, nervousness, weakness, sexual dysfunction
Sertraline (Zoloft)	25–50 mg (50–150 mg)	Nausea, diarrhea, headache, sexual dysfunction, insomnia, tremor, dizziness
Paroxetine (Paxil)	10–20 mg (20–50 mg)	Nausea, sedation, headache, constipation, dizziness, sexual dysfunction
Fluvoxamine (Luvox)	50 mg (150–200 mg)	Nausea/vomiting, headache, insomnia, sedation, nervousness, weakness
Citalopram (Celexa)	20 mg (20–40 mg)	Nausea, dry mouth, sweating, sedation, sexual dysfunction
Tricyclic Antidepressants		
Amitriptyline (Elavil)	10–25 mg (50–100 mg)	Very sedating, tachycardia, arrhythmias, anticholinergic effects, seizures, hypotension
Imipramine (Tofranil)	10–25 mg (50–150 mg)	Hypotension, anticholinergic effects, sedation, tachycardia, arrhythmias, seizures
Desipramine (Norpramin)	25 mg (75–100 mg)	Nausea/vomiting, tachycardia, arrhythmias, minimal sedation and anticholinergic effects
Nortriptyline (Aventyl, Pamelor)	10–25 mg (75–100 mg)	Mild sedation and anticholinergic effects, weight gain, hypotension, seizures
Doxepin (Adapin, Sinequan)	25 mg (75–150 mg)	Very sedating, anticholingeric effects, hypotension, arrhythmias, seizures
Atypical Antidepressants		
Bupropion (Wellbutrin)	75 mg (150–450 mg)	Seizure risk, nausea/vomiting, no sexual dysfunction, agitation, insomnia
Trazodone (Desyrel)	50 mg (150–200 mg)	Very sedating, nausea/vomiting, hypotension, dizziness, priapsim
Nefazodone (Serzone)	100 mg (200–300 mg)	Sedation,nausea, dry mouth, dizziness, constipation, low sexual dysfunction,
Venlafaxine (Effexor)	37.5 mg BID (75–225 mg)	Nausea, constipation, anorexia, insomnia, sedation, sweating, hypertension, anxiety
Mirtazepine (Remeron)	15 mg (15–60 mg)	Sedation, dizziness, constipation, weight gain, dry mouth, no nausea
Stimulants		
Dextroamphetamine (Dexedrine)	2.5 mg (5–30 mg)	Insomnia, agitation, tachycardia, dry mouth, dependence, anorexia, nightmares, psychosis
Methylphenidate (Ritalin)	2.5 mg (5–30 mg)	Restlessness, insomnia, behavior changes, slurred speech, hallucinations, dermatitis
Pemoline (Cylert)	18.75 mg (37.5–150 mg)	Anorexia, insomnia, dizziness, liver function test abnormalities, hepatoxicity, Tourette syndrome
Monoamine Oxidase Inhibitorsa		
Phenelzine (Nardil)	15 mg (30–60 mg)	Orthostatic hypotension, hypertensive crisis, drowsiness, dizziness, mania, agitation
Tranylcypromine (Parnate)	10 mg (20–40 mg)	Palpitations, sedation, agitation, headache, hypertensive crisis

TRM= transplant-related mortality; CR=complete remission; EFS=event-free survival; OS=overall survival; Bu=busulphan; Cy=cyclophosphamide; TBI=total body irradiation; Mel=melphalan.

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agents for treatment of depression in the cancer patient.[15,19] The low incidence of side effects, proven efficacy, and safety in overdose make these agents less problematic in cancer patients. Unlike some of the TCAs, SSRIs do not have the same risks of cardiac arrhythmias, orthostatic hypotension, and anticholinergic effects.

Table 7 outlines the specific medication related interactions associated with SSRIs. Fluoxetine, fluvoxamine, and paroxetine are highly protein bound and therefore are likely to interact with warfarin, digoxin, anticonvulsants, and cisplatin. Sertraline and citalopram are better choices when the potential for protein binding interactions exists. Additionally, all SSRIs except citalopram are known to interact with the cytochrome P450 enzyme system (primarily at the 3A4 and 2D6 isoenzymes).[21-24]

Flu-like withdrawal symptoms in SSRIs with short half-lives (sertraline, paroxetine, fluvoxamine, and citalopram) are possible.[19,21-24] Therefore, careful dosage reduction over a period of time is recommended. Finally, SSRIs can be administered once a day to improve compliance, and, except for sertraline, require little titration to achieve the therapeutic effect.

TABLE 7. ANTIDEPRESSANT MEDICATION INTERACTIONS: CYP3A4 AND 1A2

Relative Rank	Inhibitors	Illustrative Substrates
		3A4
High	Nefazodone Fluvoxamine	Terfenadine,[a,b] astemizole[a] Protease inhibitors Cisapride[a]
Moderate to low	TCAs (high doses)	Ketoconazole, itraconazole Alprazolam, triazolam[a]
Low to minimal	Fluvoxamine (20 mg) Mirtazapine[c] Paroxetine Sertraline Venlafaxine Citalopram	Clonazepam, midazolam Verapamil, nifedipine, diltiazem Carbamazepine (inducer) Cyclosporine Corticosteroids Sex hormones Zolpidem
Other inhibitors	Grapefruit Protease inhibitors Antifungals Calcium blockers Macrolides	Tamoxifen Erythromycin Quinidine Lovastatin Fluoxetine, sertraline, TCAs Nefazodone, venlafaxine Quetiapine, ziprasidone
		1A2
High	Fluvoxamine Haloperidol	Caffeine,
Moderate to low	Fluoxetine (high doses) Paroxetine (high doses) Sertraline (high doses)	Clozapine Olanzapine Theophylline Tacrine
Low to minimal	Nefazodone Bupropion Mirtazapine[c] Citalopram Venlafaxine	Tertiary TCAs Phenothiazines β-blockers
Other inhibitors	Fluoroquinolones Grapefruit	

TCAs=tricyclic antidepressants.
a=contraindications; b=the Food and Drug Administration has withdrawn this medication due to fatalities; c=in vitro data only.

Adapted from: Ereshefsky L. Antidepressant pharmacodynamics, pharmacokinetics, and drug interactions. *Geriatrics.* 1998;53(suppl 4):S22-S33.

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Tricyclic Antidepressants

TCAs have been replaced by the SSRIs as the most common antidepressants prescribed in the oncology patient. TCAs are efficacious and the least expensive however their poor side effect profiles (ie, anticholinergic symptoms, orthostatic hypotension, tachycardia, arrhythmias), and overdose morbidity and mortality have limited their use.[15,19,20] Baseline and regular follow-up electrocardiograms are recommended with these agents. TCAs are known to interact with the cytochrome P450 3A4 and 2D6 enzyme system (see Tables 7 and 8).[21-24] For patients who have difficulties in swallowing pills, amitriptyline, doxepine, and nortriptyline are available in elixir. Intramuscular injectable formulations of amitriptyline and imipramine are also available.

Atypical Antidepressants

Buproprion is structurally related to amphetamine and has a mild stimulant effect.[20] As a result, the prescribing of buproprion has increased in the oncology population. The most common side effects include restlessness, insomnia, agitation, gastrointestinal upset, and possible appetite suppression.[19] Moreover, the dose of buproprion should not exceed 450 mg/day (risk of seizures with higher doses), and should therefore be avoided in patients with central nervous system cancers or seizure disorders.[19] Bupropion interacts with other medications, and is therefore contraindicated for use in patients on monamine oxidase inhibitors (MAOIs). It should be used with caution in patients taking selegiline and zolpidem.[21-24]

The sedative nature of nefazodone and trazodone make them useful in cancer patients with insomnia. Additionally, nefazodone is one of the few antidepressant medications that does not induce sexual dysfunction. Other side effects of nefazodone include nausea, dry mouth, dizziness, constipation, and blurred

vision.[19] Although nefazodone can cause nausea, there is some evidence that it actually helps lessen chemotherapy induced nausea.[25]

Trazodone is commonly prescribed for insomnia as a nonaddictive hypnotic.[19] It carries the least risk of serotonin syndrome and is the agent of choice in depressed patients taking procarbazine.[19] Additional side effects of trazodone include orthostatic hypotension, nausea, and vomiting. In rare cases, it can cause priapism and cardiac arrhythmias.[19]

Mirtazepine is quite useful in cancer patients because, unlike most antidepressants, it does not cause nausea or gastrointestinal distress.[19] Additionally, mirtazepine's propensity to increased appetite, produce weight gain, and cause sedation may be desirable side effects in the oncology population. Mirtazepine is more sedating at lower doses and is best administered before bedtime. Sexual dysfunction is not a common problem with mirtazepine. In premarketing clinical trials of mirtazapine, 2 out of 2,796 patients studied developed agranulocytosis (absolute neutrophil count [ANC] of less than 500 cells/mm3 with symptoms) and 1 patient developed severe neutropenia (ANC of less than 500 cells/mm3 without symptoms). All three patients recovered upon discontinuation of mirtazapine. The incidence based on these three cases was approximately 1.1 per 1,000 patients.[26] Therefore, the manufacturer recommends that mirtazepine therapy should be discontinued if the patient develops a sore throat, fever, stomatitis, or signs of infection, along with a low white blood cell count.[26]

Venlafaxine is usually a second-line agent, which is prescribed in patients who are not responding to other antidepressant medications. Venlafaxine commonly causes anxiety, insomnia, dizziness, constipation, and sweating.[19] Some patients may also experience drowsiness with this medication.[19] Most importantly, venlafaxine can cause hypertension at higher dosages.[19] Therefore, patients prescribed venlafaxine must have regular monitoring of their blood pressure.

Psychostimulants

Low doses of amphetamine, methlyphenidate, and pemoline are useful in targeting depressed mood, low energy, poor concentration, poor appetite, and apathy.[27,28] Stimulants may counteract the sedative side effects of opioid narcotics prescribed for pain. Most importantly, they produce rapid effect as compared to several weeks with TCA pharmacotherapy.[28] The most common side effects of these agents include anorexia, insomnia, euphoria, irritability, and mood lability.[28] High doses have been documented to induce nightmares and paranoid thoughts. Psychostimulants are best taken in the morning and at noon in order to avoid insomnia. Finally, pemoline should be used with caution in renal compromised patients, and can cause hepatotoxicity.[28] Therefore, renal and liver function tests should be monitored regularly in patients on pemoline.

TABLE 8. ANTIDEPRESSANT MEDICATION INTERACTIONS: CYP2D6, 2C19, AND 2C8/9

Relative Rank	Inhibitors	Illustrative Substrates
		2D6
High	Paroxetine Fluoxetine TCAs	Secondary TCAs β-blockers Codeine Hydrocodone
Moderate to low	Sertraline (150 mg)	Dextromethorphan Amphetamines Phenothiazines
Low to minimal	Fluvoxamine Mirtazapine[a] Nefazodone Citalopram Venlafaxine	Risperidone Sertindole Haloperidol Encainide Flecainide Chlorpheniramine
Other inhibitors	Thioridazine Haloperidol	Venlafaxine Fluoxetine Paroxetine Nefazodone Tramadol
		2C19[b]
High	Fluvoxamine (2C19 only) Fluoxetine (2C9 only) Fluvoxamine (2C9 only)	Omeprazole Diazepam Barbiturates Moclobemide
Moderate to low	Fluoxetine (2C19 only) Sertraline (2C19 only)	Tertiary TCAs Clozapine/olanzapine Propranolol
Low to minimal	Venlafaxine (2C19 only) Sertraline (2C9 only)	Citalopram Mephenytoin
		CYP2C8/9
Other inhibitors	Ketoconazole Omeprazole	NSAIDs Bupropion Tolbutamide Warfarin S-Warfarin Phenytoin

TCAs=tricyclic antidepressants; NSAIDs=nonsteroidal anti-inflammatory drugs.
a=in vitro data only;b=up to 20% of Asian- and African-Americans are poor metabolizers, compared with less than 7% of Caucasians.

Adapted from: Ereshefsky L. Antidepressant pharmacodynamics, pharmacokinetics, and drug interactions. *Geriatrics.* 1998;53(suppl 4):S22-S33.

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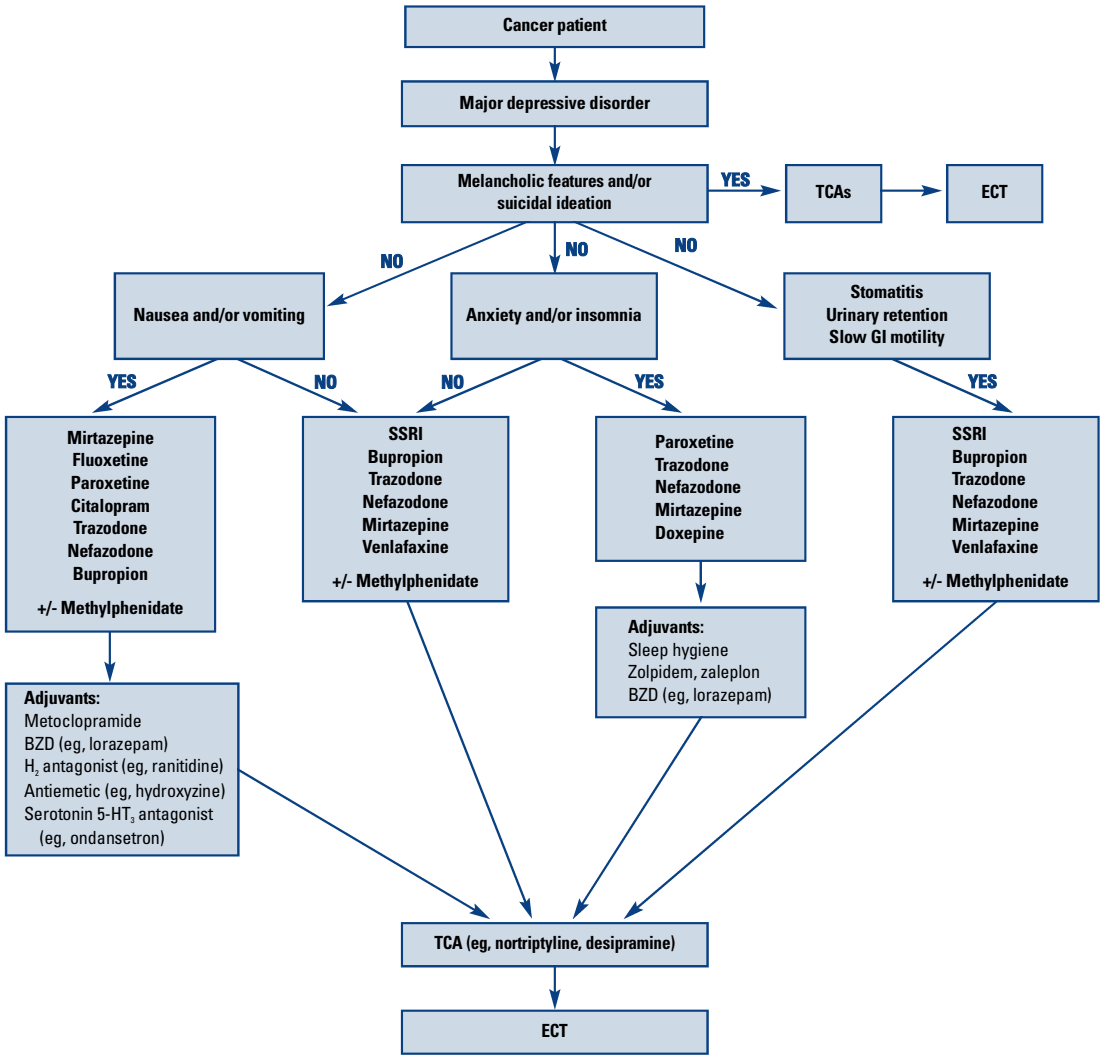
FIGURE 1. MAJOR DEPRESSION TREATMENT ALGORITHM FOR THE CANCER PATIENT



BZD=benzodiazepine; ECT=electroconvulsive therapy; GI=gastrointestinal; H2=histamine 2 receptor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

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Monoamine Oxidase Inhibitors

MAOIs are beneficial in patients diagnosed with atypical depression along with hypersomnia and increased appetite.[19] However, MAOIs have a large number of serious medication interactions, especially with meperidine, as well as, interactions with food, and are therefore not widely used to treat depression in cancer patients.[19]

Electroconvulsive Therapy

When antidepressant pharmacotherapy fails, an effective way to treat depression is through the use of ECT.[29] The ECT procedure has been perfected over the past few years, and patients no longer experience permanent cognitive deficits as seen in the past. ECT is indicated for patients with life-threatening weight loss secondary to depression, acute

suicidal thoughts, and severe intractable depression.[29] ECT is contraindicated in patients with severe cardiac abnormalities and those with central nervous system lesions. ECT is delivered in a series of 5 to 10 treatments. An improvement in depressive symptoms can be observed as early as the first treatment. Most patients will show improvement by their third to fifth ECT procedure.

CONCLUSION

Cancer patients often experience depressed mood which can be serious if left untreated. Primary care and oncology healthcare providers can assist their cancer patients by properly recognizing the signs and symptoms of depression, and by prescribing appropriate therapy. Antidepressant medications and/or referral to psychotherapy is recommended for treatment of mild to moderate depression. More severe complicated depression, especially if accompanied by suicidal ideation, is best treated by immediate referral to a psychiatrist. The choice of antidepressant pharmacotherapy is dependent on the nature of the depressive symptoms, current comorbidities, adverse side effect profile, and the potential to interact with other medications. SSRIs have limited side effects, proven efficacy, and safety in overdose which makes them first-line agents for treatment of depression in the cancer patient. Finally, treatment of depression can improve quality of life and may also facilitate cancer treatment.

"Primary care and oncology healthcare providers can assist their patients by properly recognizing the signs and symptoms of depression, and by prescribing appropriate therapy."

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