Management of psychiatric disorders in patients with cancer

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INTRODUCTION

Patients with cancer have a high rate of psychiatric comorbidity, approximately one-half exhibit emotional difficulties. The psychiatric complications generally take the form of adjustment disorder, unipolar depression, anxiety, diminished quality of life, or loss of self-esteem. The patients most at risk for depression and other psychiatric illness have advanced disease, a prior psychiatric history, poorly controlled pain, and other life stressors or losses.

In addition to these psychiatric conditions, nonspecific distress and anxiety are very common in cancer patients. Distress is the summation of multiple psychological, social, and spiritual factors. If severe enough, distress can interfere with the patient's ability to deal effectively with the illness, its symptoms, and the complications of treatment.

Specific issues regarding the management of psychiatric illness in patients with cancer are reviewed here. The diagnosis of these disorders is discussed separately. (See "Patients with cancer: Overview of the clinical features and diagnosis of psychiatric disorders".)

ADJUSTMENT DISORDER

The identification and diagnosis of adjustment disorder is not straightforward but is important since many of these patients will benefit from counseling. Physicians attempting to identify

individuals who could benefit from counseling should focus upon a lack of patient flexibility [1,2]. Those who develop adjustment disorder may be more rigid in their thinking and determined to address their cancer-related problems in the same manner as they have for prior stressors. If the old coping and problem-solving strategies fail, the person may begin to exhibit depressed mood and anxiety associated with adjustment disorder. In contrast, patients who successfully adapt typically have a flexible style [3].

People with adjustment disorder have positive outcomes when they are treated with brief psychotherapy [4]. Early treatment using counselors, nurses, and other staff is helpful before the problem expands to the point of requiring more intensive care.

Psychotherapy for adjustment disorder addresses cancer-related stressors directly by teaching enhanced coping skills, focusing upon immediate problems in living caused by the disease. Establishing social support networks and psychoeducation are also important [5,6]. Informal support groups and more formal group therapy are highly effective for improving quality of life and decreasing depression and anxiety symptoms [7,8].

DEPRESSION

The sections below discuss management and treatment of depression in patients with cancer. Treatment of major depression in the general population is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

Prevention — Pharmacotherapy can prevent onset of depression in patients with cancer. A 16-week randomized trail compared escitalopram (10 or 20 mg per day) with placebo in 125 patients who were about to commence treatment for newly diagnosed or recurrent stage II to IV epidermoid cancer of the head and neck, and were not receiving treatment for depression or anxiety, and did not meet criteria for major depression [9]. The incidence of depression (scores on the Quick Inventory of Depressive Symptomatology-Self Rated ≥11) was less in patients treated with active drug (10 versus 25 percent). However, there was a trend for a greater rate of dropout due to adverse effects of study medication in patients who received escitalopram. Although it is reasonable to prophylactically prescribe antidepressants for some patients (eg, those with a prior history of depression), we generally monitor patients instead, based upon our judgement that additional studies are needed to confirm the results.

Collaborative care — Outpatients with cancer and mild to moderate unipolar major depression can benefit when treatment of depression occurs within the context of collaborative care (also

called integrated care). Collaborative care involves treating patients with a team that usually includes a primary care clinician who prescribes antidepressants; a case manager, such as a nurse, who helps facilitate and implement treatment (which may include psychotherapy), as well as monitor treatment (using measurement-based care); and a mental health specialist, such as a psychiatrist, who provides consultation and supervision.

Evidence supporting the use of collaborative care for treating unipolar major depression in outpatients with cancer includes multiple randomized trials. As an example, a meta-analysis of five open-label randomized trials compared usual care plus collaborative care with usual care alone for treatment of depressive syndromes in patients with cancer (mixed type and stage; n >1700) [10]. Collaborative care interventions lasted 3 to 12 months and included antidepressants and psychotherapy (eg, problem solving therapy). The trials found that 12 months after treatment was initiated, improvement was greater among patients who received collaborative care, and the clinical benefit was moderate. However, heterogeneity across studies was substantial and involvement of primary care clinicians was minimal, with the care model more similar to “multidisciplinary care” [11].

Additional information about collaborative care is discussed in the context of treating adult depression in the primary care setting. (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments", section on 'Collaborative care'.)

Pharmacotherapy — Pharmacologic interventions are the mainstay of management for patients with moderate to severe levels of depression; antidepressants are safe and potentially effective in this setting. These drugs can alleviate depressive affect, emotional lability, irritability, and social withdrawal [12]. Medication also may help increase an individual's ability to participate in rehabilitation services and improve overall functioning.

Patients with early-stage cancer are similar to the typical patient who needs an antidepressant; patients with cancer can be safely and effectively treated with selective serotonin reuptake inhibitors (SSRIs) and other classes of antidepressants, using similar dose titrations as the physically healthy population. In patients with more advanced disease and increased levels of physical distress, the pharmacologic management is more complex and challenging. (See "Unipolar major depression in adults: Choosing initial treatment".)

Evidence supporting the use of antidepressants for depression in patients with cancer is minimal at best. Relatively few randomized trials have been conducted, and the patients were heterogenous for type of depressive syndrome, type and stage of cancer, and cancer treatment. One review concluded that antidepressants are relatively safe and effective for more severe

episodes of unipolar major depression [13]. By contrast, investigators who conducted a meta-analysis of seven trials that compared antidepressants with placebo (n = 511 patients), and found a clinically moderate effect for active treatment, were nevertheless more circumspect about the benefit because of the poor quality of the trials [14].

Antidepressant selection — Selection of an antidepressant depends upon a number of factors. Among the considerations are [15]:

- The type of depressive symptoms
- Current medical problems
- Side effect profiles

The depressed patient who is experiencing agitation or insomnia may benefit from the more sedating antidepressants (eg, tricyclic antidepressants [TCAs], trazodone, or mirtazapine) (table 1). A better choice for patients with fatigue or psychomotor slowing would be compounds with the least sedating effects (eg, SSRIs, stimulants).

Several coexisting medical problems may influence antidepressant selection.

- In addition to its antidepressant action, the serotonin-norepinephrine reuptake inhibitor duloxetine can be efficacious for neuropathic pain in cancer patients [16,17]. The TCAs also have analgesic properties and may potentiate the effects of opioid analgesics. Thus, patients who are experiencing pain, particularly neuropathic pain, may benefit from these agents alone or in combination with other drugs. (See "Cancer pain management: Role of adjuvant analgesics (coanalgesics)", section on 'Antidepressants'.)

  Despite evidence that venlafaxine may have analgesic effects in non-cancer patients, one study suggests it is inferior to duloxetine for chemotherapy-induced neuropathic pain [18].

- Patients with cardiovascular disease and older patients should take drugs that cause the least orthostatic hypotension (eg, fluoxetine, sertraline).

- Patients with slow intestinal motility or urinary retention, or with stomatitis secondary to chemotherapy or radiotherapy, should receive medications with the least anticholinergic effects (eg, selective serotonin reuptake inhibitors).

- Patients at risk for seizures or who may have a lower seizure threshold because of other medications are more safely treated with agents that will not exacerbate the problem (eg, neuroleptics). Virtually any antidepressant can have a small effect on lowering the seizure threshold. However, bupropion has been associated with the highest incidence of seizures and should be used cautiously in patients with central nervous system (CNS) disease.

- Liquid formulations are available for some antidepressants (fluoxetine, sertraline, paroxetine, citalopram, escitalopram, doxepin, and nortriptyline) and may be better options for patients who cannot swallow pills.

While attention to potentially upsetting or adverse effects of the different classes of antidepressants is warranted, many times side effects can be used to the patient's advantage (table 1). As an example, sedation may be useful to the agitated patient who is anxious and cannot sleep, while the side effect of activation may be useful to the hypersomnolent, withdrawn patient with lethargy. In addition, some antidepressants stimulate appetite, a useful effect when appetite is decreased.

Selective serotonin reuptake inhibitors — SSRIs have become the most widely used antidepressants (table 2). Their efficacy and side effect profiles in particular make them attractive agents for some patients with cancer. One study found that both fluoxetine and desipramine led to improvements in depression, anxiety, and overall quality of life in depressed women with advanced cancer, and were well tolerated [19]. A larger double-blind study suggested that fluoxetine (20 mg daily) was superior to placebo in improving depression and overall quality of life in outpatients with advanced cancer [20].

SSRIs cause fewer problems with cardiac arrhythmias, hypotension, and anticholinergic effects than the TCAs (table 1). In addition, the SSRIs generally have less sedative, autonomic, and anticholinergic effects.

The SSRIs may increase blood levels of other drugs by dislodging them from blood proteins. They also inhibit the cytochrome P450 isoenzymes. Thus, blood levels of any medications that are metabolized by the P450 system may be increased. This is an important consideration in the cancer population since many of these patients are on warfarin or cisapride, two medications that are substrates for the P450 system.

Additional information about the pharmacology, administration, and side effects of SSRIs is discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Tricyclic antidepressants — TCAs have been used frequently in the cancer setting (table 2). We typically begin TCAs at a low dose (10 to 25 mg at bedtime) and increased slowly by 10 to 25 mg increments every one to two days until a beneficial effect is achieved. This slow titration is especially important for debilitated patients with advanced disease. Patients with cancer may exhibit a therapeutic response to the TCAs at lower doses than physically healthy individuals [21]. Serial plasma drug levels can be utilized to monitor the effective and safe administration of the drugs, minimizing the risk of side effects or toxicity [22]. A cardiac history and

electrocardiogram should be obtained prior to prescribing TCAs since these drugs can have an adverse effect on cardiac rhythm [23].

The tertiary amines (eg, imipramine, amitriptyline, and doxepin) tend to sedate patients, stimulate appetite, and cause anticholinergic side effects (eg, dry mouth, blurred vision, constipation, nausea, urinary retention, and tachycardia). Their metabolites, the secondary amines (eg, desipramine and nortriptyline) are less sedating and less anticholinergic. Many times, patients can tolerate secondary amines in higher doses, allowing for greater therapeutic benefit.

Additional information about the pharmacology, administration, and side effects of tricyclics is discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

Other antidepressants — The other available antidepressants vary widely in their mechanism of action and side effects (table 1 and table 2).

- Bupropion is both an antidepressant and central nervous system stimulant that does not interact with other medications. It is very useful in depressed patients with psychomotor retardation and can be used in a wide variety of patients with few side effects. The drug is thought to act through the dopamine pathways, but its precise mechanism of action is not known. The immediate release formulation should be avoided in patients who have conditions (eg, CNS disease) that predispose them to seizures, and slow release formulations can be used with caution [24]. Additional information about the pharmacology, administration, and side effects of bupropion is discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Bupropion'.)

- Venlafaxine is a mixed serotonin and norepinephrine reuptake inhibitor that is well tolerated by cancer patients. It is not significantly active at the cytochrome P450 system and is somewhat less protein bound than the other antidepressants. Venlafaxine has been associated with safe but uncomfortable withdrawal symptoms (anxiety, nausea, insomnia) at discontinuation, suggesting that the drug should be tapered rather than stopped abruptly. Additional information about the pharmacology, administration, and side effects of venlafaxine is discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Venlafaxine'.)

- Mirtazapine is an antidepressant with a novel mechanism of action. The cell receptors that regulate production of norepinephrine and serotonin are blocked so that the neurotransmitters continue to be produced even when their concentrations might

normally shut down production by the cell. In addition, mirtazapine has 5HT2 and 5HT3 blocking action that may make it useful as a coanalgesic and antiemetic; clinical trials are underway to evaluate its potential in these two important areas for cancer patients. Mirtazapine also appears to block the H1 receptor in the CNS. It has some sedative side effects and stimulates appetite, side effects that may be very useful in some patients. It can be administered as a single dose at bedtime.

One open label pilot study of mirtazapine (15 to 30 mg at bedtime) suggests that patients with advanced cancer may derive benefit from this drug with regard to mood, weight loss and insomnia [25]. Treatment was well-tolerated at either starting dose.

Additional information about the pharmacology, administration, and side effects of mirtazapine is discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects", section on 'Mirtazapine'.)

- Trazodone and nefazodone are serotonin modulators. Trazodone is typically sedating and is used frequently to help with sleep disturbance; priapism is a rare side effect. Nefazodone has been withdrawn from many countries because of potential adverse effects on the liver. Additional information about the pharmacology, administration, and side effects of serotonin modulators is discussed separately. (See "Serotonin modulators: Pharmacology, administration, and side effects".)

Other options include the serotonin modulators vilazodone and vortioxetine, which may cause fewer sexual side effects.

Psychostimulants — The psychostimulants methylphenidate, dextroamphetamine, and modafinil are an alternative for depressed patients with cancer [26,27]. These drugs improve attention, concentration, and overall performance on neurologic testing in the medically ill [28]. Mood, appetite and sense of well-being can be improved for the patient at the same time the medication is decreasing feelings of weakness and fatigue. An additional benefit of methylphenidate and dextroamphetamine is reduction of the sedation caused by opioid analgesics; they also provide adjuvant analgesia in patients with cancer [29]. The psychostimulants may play a useful role in helping cancer patients feel energetic enough to engage in rehabilitation efforts until their energy level ultimately improves from the direct effects of such efforts.

Evidence regarding the efficacy of psychostimulants includes a small, 18-day randomized trial that compared methylphenidate with placebo in 28 patients with advanced cancer and unipolar major depression [30]. All patients received a selective serotonin reuptake inhibitor that was started prior to the trial or concurrently with the study drugs. Response (reduction of baseline

symptoms ≥50 percent) was relatively high with either methylphenidate or placebo (85 and 60 percent). Although the difference between active treatment and placebo was not statistically significant, a difference of this magnitude, if real, would be clinically meaningful (ie, the difference suggests that methylphenidate is beneficial).

The starting dose of methylphenidate and dextroamphetamine is 5 to 10 mg once or twice daily. Depending upon efficacy and tolerability, the dose can be increased every several (eg, three to five) days, up to 40 mg/day; however, some clinicians administer doses as high as 60 mg/day [31-34]. Typically, patients are maintained on the stimulant for one to two months or longer. Tolerance can develop and dose adjustment may be necessary over time. Most patients respond quickly to these agents and, if taken in the morning and early afternoon, they should not interfere with sleep. Side effects include anxiety, overstimulation, headache, increase in blood pressure, and tremors; however, these are rarely a problem with the typically low doses used.

Modafinil, a benzhydryl sulfinyl acetamide non-amphetamine "wake-promoting agent," was introduced to the world market in 1994 for the treatment of narcolepsy and idiopathic hypersomnia, and was approved for use in the United States in 1999 (see "Treatment of narcolepsy in adults"). Modafinil has not been directly compared with amphetamines in patients with narcolepsy, but early indications are that it is better tolerated and has less abuse potential. It is usually administered in a single morning dose of 100 or 200 mg.

Modafinil may be a useful treatment for fatigue, depression, and opioid-induced sedation, and is well tolerated. Although modafinil may offer similar benefit to the amphetamines in patients with cancer, no published studies are available. (See "Cancer-related fatigue: Treatment".)

Combined therapy — Combined antidepressant therapy may provide certain advantages in select patients, particularly those experiencing distressing physical symptoms. Patients with depression and severe fatigue or psychomotor slowing, for example, may gain the most from the use of TCAs, SSRIs, or mirtazapine plus psychostimulants. Patients with depression and anxiety or insomnia may gain the most from the combination of TCAs and SSRIs, or an SSRI with mirtazapine.

Many antidepressants require weeks to reach peak efficacy. Thus, augmentation with another medication directed at the most distressful symptom not only leads to a quicker benefit to the patient, but also may improve compliance. This symptom driven approach is particularly helpful in patients with advanced cancer in whom treatment is often complex, but immediate relief of symptom distress is a priority.

Psychotherapy — Patients with cancer and depression are often reacting to the burden of the illness and the effect it has on their lives. Psychosocial interventions are used to help individuals, families, and groups. The general objective of this therapy is to improve coping skills through educational, behavioral, or psychodynamic approaches.

The benefits of psychotherapy in patients with advanced, incurable cancer were addressed in a Cochrane review [35]. In six trials (292 patients in the psychotherapy arm, and 225 in the control arm), psychotherapy was associated with a significant decrease in depression compared to usual care. Two more reviews of psychosocial interventions in patients with head and neck (21 studies) [36] and breast cancer (42 studies) [37] document efficacy in reducing symptoms of depression. Cognitive-behavioral therapy (CBT) showed the greatest effects in the head and neck cancer patients, while yoga and mindfulness-based therapies showed the greatest effects in the breast cancer patients. Another review of mindfulness-based psychotherapies (29 randomized trials with 3274 subjects) documented beneficial but small effects on depression, as well as anxiety, fatigue, pain, and sleep disturbances [38].

Crisis intervention — Clinicians working in oncology rely primarily upon short-term supportive psychotherapy based on a crisis intervention model to help patients with depressive symptomatology. Crisis intervention is a process of actively influencing psychosocial functioning during a period of disequilibrium. It is directed at alleviating the immediate impact of disruptive stressful events. The aim is to reduce emotional distress while working toward strengthening the patient's psychological and social resources. Crisis therapy is generally time limited and asserts clear-cut goals [39].

Supportive/crisis intervention psychotherapy involves clarifying information and answering questions about the illness and its treatment, correcting misunderstanding, and giving reassurance about the situation. Describing common reactions to illness may help the patient and family to normalize their experience. The patients' usual adaptive strategies should be explored, and strengths supported as needed in adjustment. Patients are encouraged to discuss how they feel about their lifestyle modifications, family role changes, and fears of dependency and abandonment. Themes of loss and anticipatory grief are also explored. Patients often experience loss of good health, body integrity, and self-esteem, along with losses secondary to cancer (eg, financial, social, and occupational). Therapy seeks to improve a sense of control and morale. When the focus of treatment changes from cure to palliation, it is important for patients to know that they will not be abandoned and that their comfort, pain control, and dignity will receive continued attention.

Cognitive-behavioral therapy — Cognitive-behavioral techniques are often integrated into depression therapy and are very useful and effective. These approaches explore patients' beliefs

about the cancer diagnosis and its treatment in order to elicit irrational or unhelpful thoughts that lead to feelings of helplessness and hopelessness. Therapy then leads to the correction of these maladaptive thoughts along with providing new coping skills (eg, relaxation). Both group and individual treatment are effective for reducing depressive symptoms and distress and improving quality of life [40-42].

The efficacy of CBT may depend upon the patient's cancer status. A 12-week randomized trial in 392 breast cancer survivors with depressive symptoms found that improvement of depression (and anxiety) was greater with CBT than either supportive care or usual care [43]. By contrast, a 16-week randomized trial in 230 patients with advanced (incurable) cancer and depressive syndromes compared usual care plus CBT with usual care alone, and found that improvement of depression was comparable in the two groups [44].

Cognitive-behavioral interventions help patients allay exaggerated fears by encouraging them to consider different possible outcomes for their situation. Helping the patient focus upon aspects of the disease and its treatment that they have control over and encouraging behavior modification that will keep them involved and positive could provide a better quality of life.

In addition, the benefits of cognitive-behavioral interventions appear to persist for years. As an example, a study examined patients who received surgery for early-stage breast cancer (n = 100) and participated in a randomized trial that compared cognitive-behavioral stress management (10 weeks of group therapy) with a psychoeducational seminar control condition (one day) [45]. Assessments several years (median 11 years) after treatment found that there were fewer depressive symptoms in the group that received active treatment, and the clinical difference was medium to large.

A randomized trial in 245 patients with cancer and psychological distress (symptoms of depression and anxiety) found that improvement of psychological distress was greater with mindfulness-based cognitive therapy, administered either face-to-face or digitally, than usual care [46].

Two randomized trials indicate that CBT delivered via the internet for cancer survivors can reduce both depressive and anxiety symptoms [47,48].

Problem-solving therapy — Problem-solving therapy (PST) is a behavioral treatment that can be efficacious for depressive syndromes in the general population. Two randomized trials in patients with cancer suggest that PST may be beneficial for depression in this population as well:

- A 12-week trial randomly assigned 134 patients with breast cancer (primarily early stage) and unipolar major depression to one of three psychotherapies: PST, interpersonal psychotherapy, or supportive psychotherapy [49]. Remission in the three groups was comparable, occurring in 25 to 30 percent of patients. However, lack of a nonactive treatment arm makes it difficult to interpret the results.

- A six-month randomized trial compared telehealth PST plus an internet resource with a waiting list control in 230 survivors of hematopoietic stem cell transplantation with impairment marked by depression, distress, and fatigue. Improvement of impairment occurred in more patients who received active treatment than controls (45 versus 20 percent) [50].

In a third randomized trial lasting five weeks, an internet-based, guided self-help program based upon PST was compared with a waiting list control group in 89 patients with glioma and depressive syndromes. Improvement of depression was comparable for the two groups; however, only 31 percent of the patients assigned to PST completed the five modules [51]. The results of the three trials suggest that in-person or voice contact may be necessary for PST.

Other modalities — Other modalities may be useful as adjunctive interventions for depression in patients with cancer:

- **Bright light therapy** – Bright light therapy is an accepted initial treatment for mild to moderate unipolar major depression with a seasonal pattern. In addition, the therapy has been studied in patients with nonseasonal depressive syndromes, including cancer-related depression. In a small, eight-week randomized trial that compared bright light therapy with a waiting list control condition in patients with breast cancer (n = 37) and depressive symptoms, improvement of depression was greater with active treatment [52].

- **Support groups** – Support groups are important adjunctive intervention modalities for cancer patients and family members who are distressed. Hospitals and community organizations will often sponsor groups that are professionally run and/or self-help. The professionally run groups usually use educational, supportive, or cognitive-behavioral methods, while lay groups focus upon education, practical advice and modeling, and serve as a source of mutual support and advocacy.

- **Creative arts therapy** – For cancer patients, adjunctive creative arts therapies (eg, art, dance, drama, music, and writing) appear to modestly reduce depressive symptoms during treatment, but the benefit dissipates during follow-up. A meta-analysis of 11 randomized trials compared creative arts therapies with a control condition (no treatment, waiting list, or usual care) as add-on treatment in 584 patients with cancer (primarily

breast or blood) [53]. There was a statistically significant but clinically small benefit favoring the active intervention. However, an analysis of posttreatment follow-up effects (five trials, 246 patients) found that depressive symptoms were comparable in both groups. A subsequent review of 40 studies concluded that music therapy may be helpful for depression in patients with cancer [54].

Relaxation techniques (eg, progressive muscle relaxation), breathing exercises, and meditation may enhance other therapeutic interventions. Pleasant imagery, such as visualizing a gentle stream flowing through a beautiful landscape, may also ease the tension that some patients feel.

ANXIETY

Treatment of anxiety in patients with cancer involves the combination of psychotherapy and a range of anxiolytic medications (see "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis"). Pharmacotherapy in patients with more advanced illness includes the judicious use of benzodiazepines, neuroleptics, antihistamines, antidepressants, and opioid analgesics [55,56].

Pharmacotherapy

Benzodiazepines — Benzodiazepines are frequently prescribed for short-term treatment of anxiety disorders [57]. The shorter-acting benzodiazepines such as lorazepam, alprazolam, and oxazepam, are safest in patients with cancer since they are least likely to lead to toxic accumulation due to impaired metabolism in debilitated patients [58]. Lorazepam and oxazepam are metabolized by conjugation in the liver and are therefore the safest choice in patients with hepatic disease.

The disadvantage of using short-acting benzodiazepines is that patients often experience breakthrough anxiety or end of dose failure. Alprazolam is particularly likely to do this because it is rapidly redistributed into fat tissues and out of brain resulting in rapid offset of effect. Such patients may benefit from switching to longer acting benzodiazepines such as diazepam or clonazepam; we have found clonazepam to be particularly useful in this setting. We also frequently switch patients from alprazolam to clonazepam when attempting to taper off the former. Clonazepam may have additional uses in patients with organic mood disorders who have symptoms of mania, and as an adjuvant analgesic in patients with neuropathic pain [59,60].

Fears of causing respiratory depression should not prevent the clinician from using adequate doses of benzodiazepines to control anxiety. The likelihood of respiratory depression is minimized with shorter acting drugs and small dose increments; ultimately the switch can be made to longer acting drugs. Common dose regimens include the short-acting drugs lorazepam 0.5 mg to 2 mg PO, IV or IM every three to six hours and alprazolam 0.25 mg to 1 mg PO three to four times daily, as well as the long acting drugs diazepam 2.5 mg to 10 mg PO, PR, IM, or IV every three to six hours and clonazepam 1 to 2 mg PO two to three times daily. However, clinicians should generally avoid using benzodiazepines in conjunction with opioids. (See "Use of opioids in the management of chronic non-cancer pain", section on 'Drug interactions'.)

Other anxiolytics — Low-dose second-generation antipsychotics such as olanzapine (eg, 1.25 to 2.5 mg once or twice per day) and quetiapine (eg, 12.5 or 25 mg once or twice per day) can be useful to treat anxiety when benzodiazepines are not sufficient for symptom control [57]. Antipsychotics are also indicated when psychotic symptoms such as delusions or hallucinations accompany anxiety. These medications are probably the safest class of anxiolytics in patients at risk for respiratory depression or compromised function. However, they also pose a potential risk of extrapyramidal side effects, which may rarely be problematic for cancer patients [61]. (See "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects".)

Methotrimeprazine (10 mg to 20 mg every four to eight hours, IM, IV, or SC) is a phenothiazine with unique analgesic and anxiolytic properties that is often used for the treatment of pain and anxiety in patients with advanced cancer [62,63]. Its side effects include sedation, anticholinergic symptoms, and hypotension. Intravenous administration by slow infusion is preferable to avoid problems with hypotension.

Hydroxyzine is an antihistamine with mild anxiolytic, sedative, and analgesic properties. It is particularly useful when treating anxious cancer patients with pain. A dose of 100 mg administered intramuscularly may have analgesic potency equivalent to 8 mg of morphine, and also potentiates the analgesic effects of morphine [64]. As an anxiolytic, 25 mg to 50 mg of hydroxyzine orally every four to six hours is effective.

The atypical antipsychotics are useful in the treatment of both "functional" and "organic" anxiety syndromes, especially in older and/or frail patients. (See "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Delirium and acute confusional states: Prevention, treatment, and prognosis".)

Although not extensively studied in patients with cancer, anecdotal experience suggests that low doses of olanzapine or risperidone are effective and well-tolerated for the treatment of delirium and organic mental phenomena in patients with cancer, improving anxiety related to confusional states, delusions, and nausea [65,66]. In addition, they offer the advantage of not causing extrapyramidal symptoms in the doses generally used, ranging from 2.5 to 10 mg of olanzapine one to two times daily, and for risperidone, 0.5 to 4 mg one to two times daily.

TCAs, SSRIs, and heterocyclic antidepressants are the most effective treatment for anxiety accompanying depression and also are helpful in treating panic disorder [67,68] (see "Management of panic disorder with or without agoraphobia in adults"). Guidelines for their use are discussed in the section on depression above.

Buspirone is a non-benzodiazepine anxiolytic that is useful along with psychotherapy in patients with chronic anxiety or anxiety related to adjustment disorders. The onset of anxiolytic action is delayed in comparison with the benzodiazepines, taking 5 to 10 days for relief of anxiety to begin. Buspirone is not a benzodiazepine; thus, it will not block benzodiazepine withdrawal, and caution must be used when switching from a benzodiazepine to this drug. The effective dose of buspirone is 10 mg PO three times daily [69]. Its delayed onset of action and indication for use in chronic anxiety states limit its usefulness in patients with cancer.

Investigational treatments — Investigational treatments for managing anxiety in patients with cancer include psychedelic drugs. As an example, a randomized crossover trial compared a single low dose of psilocybin (1 or 3 mg/70 kg) with higher active doses (22 or 30 mg/70 kg), given in counterbalanced sequence five weeks apart, in 51 patients with life threatening cancer (mixed type and stage) and symptoms of depression and anxiety [70]. High dose patients had larger decreases in depression, anxiety, and death anxiety, as well as improved quality of life, with persistence of effects in 80 percent of patients at the six-month follow-up assessment. Mystical-type experiences during the psilocybin session mediated the benefits. Other randomized trials have also found beneficial effects, but there is limited information on the optimal number of sessions and dosing, type of patient preparation, and whether and what type of accompanying psychotherapy is required [71].

Psychotherapy — Nonpharmacologic interventions for anxiety and distress include supportive psychotherapy and behavioral interventions used alone or in combination. Brief supportive psychotherapy is often useful in dealing with both crisis-related issues as well as existential issues [72]. Psychotherapeutic interventions can include both the patient and family, particularly as the patient with cancer becomes increasingly debilitated and less able to interact. In multiple studies of cognitive-behavioral therapy and mindfulness-based cognitive therapy

that demonstrated efficacy for depression, the treatments were also beneficial effects for anxiety. (See 'Psychotherapy' above.)

The goals of psychotherapy for the anxious patient are to establish a bond that decreases the sense of isolation, to help the patient face cancer with a sense of integrity and self-worth, to correct misconceptions about the past and present, to integrate the present illness into a continuum of life experiences, and to explore issues of separation, loss, and the unknown that lies ahead. As in the treatment of depression, the therapist should emphasize past strengths and support previously successful ways of coping. This helps the patient mobilize inner resources, modify plans for the future, and perhaps even accept the inevitability of death.

Relaxation, guided imagery, and hypnosis may help reduce anxiety and thereby increase the patient's sense of control. Most patients with cancer, even those with advanced disease, are candidates for behavioral techniques despite physical debilitation. In assessing the utility of such interventions for a given patient, the clinician should take into account the patient's mental clarity. Confusional states interfere dramatically with the ability to focus attention and thereby limit the usefulness of these techniques, although occasionally they can be modified to include the mildly cognitively impaired [73]. This often involves the therapist taking a more active role by orienting the patient, creating a safe and secure environment, and evoking a conditioned response to the therapist's voice or presence.

A typical behavioral intervention for anxiety includes a relaxation exercise combined with some distraction or imagery technique. The patient is first taught to relax with passive breathing accompanied by either passive or active muscle relaxation. Once in a relaxed state, the patient is taught a pleasant, distracting imagery exercise. In a randomized study comparing a relaxation technique with alprazolam in the treatment of anxiety and distress in cancer patients, both treatments were effective for mild to moderate degrees of anxiety or distress [74]. Alprazolam was more effective for greater levels of distress or anxiety and had a more rapid onset of beneficial effect. Relaxation techniques can be used in combination with anxiolytic medications for highly anxious patients.

It is not clear if stress management training relieves psychological distress during cancer treatment, due to conflicting results across studies [75,76]. In a trial of patients (n = 382) about to begin chemotherapy, clinician-administered stress management training was not effective compared to usual care, whereas self-administered training was found to be beneficial [75]. In a trial in 160 colorectal cancer patients posttumor resection, cognitive-behavioral stress management (two-hour sessions for 10 weeks) improved, anxiety, depression and quality of life [77]. By contrast, a previous trial of patients (n = 310) receiving radiation therapy found that self-

administered training did not relieve psychological distress compared to usual care, except in those cases with the highest levels of initial psychosocial distress [76].

An eight-week randomized trial in 70 patients with cancer (primarily early stage) found that improvement of anxiety was greater with yoga and meditation than a waiting list control condition [78].

For cancer patients, adjunctive creative arts therapies (eg, art, dance, music, and writing) appear to modestly relieve anxiety symptoms during treatment, but the benefit dissipates during follow-up. A meta-analysis of 25 randomized trials compared creative arts therapies with a control condition (no treatment, waiting list, or usual care) as add-on treatment in 1413 patients with cancer (primarily breast or blood) [53]. There was a significant but clinically small benefit favoring the active intervention. However, an analysis of posttreatment follow-up effects (5 trials, 246 patients) found that anxiety symptoms were comparable in both groups.

INSOMNIA

Cognitive-behavioral therapy (CBT) can help patients with cancer who have insomnia. A meta-analysis of eight randomized trials compared CBT with control conditions (eg, wait list control, usual care, or sleep education) in 752 cancer survivors with insomnia [79]. Self-reported sleep efficiency, sleep onset latency, wake after sleep onset, and insomnia severity each improved more with CBT, and the clinical effects favoring CBT ranged from small to large.

Additional information about CBT in the general population of patients with insomnia is discussed separately. (See "Cognitive behavioral therapy for insomnia in adults".)

DELIRIUM

The standard approach for managing delirium in the cancer patient includes a search for underlying causes, correction of those factors, and management of symptoms. Symptomatic and supportive therapies also are important [80], and fluid and electrolyte balance, nutrition, and vitamins may be helpful. (See "Delirium and acute confusional states: Prevention, treatment, and prognosis".)

Measures to help reduce anxiety and disorientation include a quiet, well-lit room with familiar objects, a visible clock or calendar, and the presence of family. Judicious use of physical restraints, along with one-to-one nursing observation may be necessary. When supportive techniques alone are not effective, symptomatic treatment with neuroleptic or sedative

medications are necessary. Sedation may be required to relieve severe agitation or insomnia [80].

Haloperidol is the drug of choice for treatment of delirium in the medically ill [80-82]. Low doses (1 to 3 mg) are usually effective for agitation, paranoia, and fear. Typically 0.5 mg to 1 mg haloperidol (oral, intravenous, or intramuscular) is administered, with repeat doses every 45 to 60 minutes titrated against symptoms [73,83]. In a randomized trial of haloperidol versus chlorpromazine versus lorazepam, lorazepam alone, in doses up to 8 mg in a 12-hour period, was ineffective in the treatment of delirium and contributed to worsening delirium and cognitive impairment [82]. Both neuroleptic drugs however, in low doses (approximately 2 mg of haloperidol equivalent/per 24 hours), effectively controlled the symptoms of delirium and improved cognitive function.

Lorazepam 0.5 mg to 1 mg every one to two hours oral or intramuscular, plus haloperidol, may be more effective than the latter alone in rapidly sedating the agitated delirious patient. A randomized trial in advanced cancer patients with agitated delirium (n = 90) showed that improvement of agitation at eight hours was greater with haloperidol plus lorazepam than haloperidol alone [84].

A reasonable alternative to haloperidol for managing delirium is a second-generation antipsychotic. A review found that the following mean doses were used [85]:

- Haloperidol – 2 to 7 mg
- Aripiprazole – 9 to 18 mg
- Olanzapine – 2 to 8 mg
- Risperidone – 1 to 2 mg

Evidence supporting the use of second-generation antipsychotics includes a retrospective study that examined treatment with haloperidol (mean dose 6 mg), aripiprazole (18 mg), olanzapine (7 mg), and risperidone (1 mg) in patients with cancer and delirium. Each drug was studied in 21 patients, and the mean age in the four groups ranged for 64 to 70 years [85]. Resolution of delirium within four to seven days of the initial assessment was comparable for the four groups (haloperidol 76 percent of patients, aripiprazole 76 percent, olanzapine 62 percent, and risperidone 86 percent). However, parkinsonism occurred in more patients who received haloperidol (19 percent) than other drugs, and sedation occurred more often with olanzapine (29 percent).

Delirium during treatment for malignancy has been associated with adverse outcomes. In patients undergoing hematopoietic stem cell transplantation, those who have experienced delirium have significantly worse symptoms of depression, fatigue, and anxiety at 30 days [86].

These signs and symptoms persisted at 80 days, including multiple impairment of neurocognitive function. It is not clear if more severe disease is associated with delirium [87-89]. Two studies found that delirium in cancer patients was associated with increased mortality [87,88].

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Delirium (Beyond the Basics)")

SUMMARY

- **Adjustment disorder** – Cancer patients with adjustment disorder may respond to brief psychotherapy that addresses cancer-related stressors by teaching coping skills and focusing upon immediate problems. Psychoeducation and social support are also important, and informal support groups and formal group therapy are effective for improving quality of life and decreasing symptoms of depression and anxiety. (See 'Adjustment disorder' above.)

- **Depression**

  - Collaborative care – Collaborative care involves treating patients with a team that usually includes a primary care clinician (who prescribes antidepressants), a case manager (eg, nurse) who helps facilitate, implement, and monitor treatment, and a mental health specialist (eg, psychiatrist) who provides consultation and supervision. Where collaborative care is available, multiple studies indicate that collaborative care is

beneficial for patients with cancer and unipolar major depression. (See 'Collaborative care' above.)

- Antidepressants – Many antidepressants are available to treat patients with cancer (table 2). The choice depends upon a several factors, including specific depressive symptoms, comorbid medical problems, and side effect profiles (table 1). As an example, patients with agitation or insomnia may benefit from more sedating antidepressants (eg, tricyclics, trazodone, or mirtazapine). By contrast, a better choice for patients with fatigue or psychomotor slowing may be a less sedating drug (eg, SSRIs, bupropion, duloxetine, and venlafaxine). (See 'Antidepressant selection' above.)

- Psychostimulants – The psychostimulants methylphenidate, dextroamphetamine, and modafinil are an option for depressed patients with cancer, either as monotherapy or adjunctive treatment with an antidepressant. (See 'Psychostimulants' above and 'Combined therapy' above.)

- Psychotherapy – Psychotherapy for depressed cancer patients includes crisis intervention, cognitive-behavioral therapy (CBT), and support groups. (See 'Psychotherapy' above.)

- **Anxiety**

  - Benzodiazepines – Benzodiazepines are frequently prescribed for anxiety disorders in cancer patients. Shorter acting drugs (eg, lorazepam, alprazolam, and oxazepam) are safest, but often lead to breakthrough anxiety or end of dose failure. Thus, some patients may benefit from longer acting benzodiazepines such as clonazepam or diazepam. (See 'Benzodiazepines' above.)

  - Other options – For cancer patients with anxiety that does not respond to a benzodiazepine, other options include antipsychotics, antihistamines (eg, hydroxyzine), and antidepressants. (See 'Other anxiolytics' above.)

  - Psychotherapy – Psychotherapy for cancer patients with anxiety includes supportive psychotherapy and behavioral interventions (eg, relaxation and guided imagery). (See 'Psychotherapy' above.)

- **Delirium**

  - Standard approach – The standard approach for managing delirious cancer patients includes determining and correcting underlying causes, and management of

symptoms. Low dose haloperidol is effective for treatment of delirium that includes agitation, paranoia, and fear. (See 'Delirium' above.)

- Patient information – We encourage clinicians to print or email the patient information topic about delirium. (See "Patient education: Delirium (Beyond the Basics)".)

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