Mood Disorders in Patients with CNS Metastases

11

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Abbreviations

AEDs	Antiepileptic drugs
CBT	Cognitive behavioral therapy
CNS	Central nervous system
DBT	Dialectical behavior therapy
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
HADS	Hospital Anxiety and Depression Scale
HPA axis	Hypothalamic-pituitary-adrenal axis
IL-2	Interleukin-2
IL-6	Interleukin-6
MBSR	Mindfulness-based stress reduction
MDD	Major depressive disorder
NCCN	National Comprehensive Cancer Network
NSAIDs	Nonsteroidal anti-inflammatory drugs
PHQ-9	Patient Health Questionnaire-9

Introduction

Patient distress is becoming more widely assessed as national agencies and credentialing bodies highlight the importance of monitoring patients' well-being. The National Comprehensive Cancer Network (NCCN) has developed guidelines to assist clinicians in assessing and managing patient distress. This guideline defines distress as "a multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment." By this definition, multiple factors contribute to one's sense of well-being as well as to the development of mood and anxiety disorders, and all of these factors warrant monitoring and intervention when appropriate [1]. As data is collected from studies using this definition and guidelines, the importance of addressing mood disorders in patients with cancer is becoming more apparent. In patients with intracranial involvement, quality of life is more closely tied to a patient's sense of emotional well-being than physical well-being [2]. Comorbid mood disorders are associated with increased patient distress, lower quality of life, higher healthcare costs, caregiver burden, other maladaptive health behaviors, and poorer cancer-related outcomes.

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Depressive Disorders

Etiology

Multiple factors have been studied as potential causes of depression with evidence suggesting that development and perpetuation of depression are multifactorial. There is increasing evidence linking depression and inflammation in the body. Similarly, there is evidence linking cancer and inflammation, perhaps providing a link between higher rates of depression observed in patients with cancer, particularly those cancer types associated with more systemic inflammation. Cancer cells can produce multiple pro-inflammatory mediators, including cytokines, chemokines, growth factors, and transcription factors. Cell death resulting from cancer treatments, like radiation therapy and chemotherapy, leads to production of cytokines that can trigger a cascade of immune responses [3, 4]. There is also a correlation between depression and elevated levels of interleukin-6 (IL-6) [5, 6]. In a study of women with breast cancer, there was a clear association between major depressive disorder and elevated IL-6 levels as well as consistent abnormalities on dexamethasone suppression testing, which suggests a link between IL-6 and the hypothalamic-pituitary-adrenal (HPA) axis [7]. The HPA access has been studied extensively in its relation to mood disorders. Growing evidence exists about how cancer might relate to HPA dysfunction. For example, women with ovarian cancer have been found to have higher evening cortisol levels than controls [8]. The degree of causation in this relationship remains unknown. Patients receiving immunotherapy with IL-2 and/or interferon-alfa were found to have lower levels of tryptophan, a precursor for serotonin, which suggests that cytokines might have a direct impact on the production of neurotransmitters implicated in mood regulation [9]. These shared mechanisms between depression and cancer raise questions about the potential interplay of these disorders and how depression can impact cancer occurrence and progression [10, 11].

Lesions involving the brain can disrupt important structures and pathways that also lead to the development of mood symptoms [12]. Depressive disorders are most frequently associated with lesions of the frontal and temporal lobes, though there is no clear connection between depression and lesion location [13, 14]. Several syndromes caused by pathway disruption can present with symptoms that overlap with mood disorders. A dysexecutive syndrome with frontal lobe lesions impacting the dorsolateral prefrontal circuit presents with impairments in executive functioning (perseveration, difficulty managing multiple and new tasks). Patients may also experience psychomotor slowing, flattened affect, and impairments in self-care that resemble depression. Disinhibition syndrome occurs with frontal lobe lesions impacting the orbitofrontal circuit and presents with emotional lability, impulsivity, and impaired judgment that can mimic mood disorders, including depression or a bipolar illness. Lesions of the anterior cingulate circuit can lead to apathy, which also commonly mimics depression [15]. Multiple primary psychiatric diagnoses have ties to dysfunction in these circuits as well. This includes attention-deficit hyperactivity disorder, obsessive compulsive disorder, Tourette syndrome, Huntington's disease, and schizophrenia [15–17].

Epidemiology

The prevalence rates for depressive disorders in patients with cancer vary and are often related to factors such as cancer type, disease stage, treatment modalities, time from diagnosis, physical symptom burden, and patient demographics [18–21]. For example, in patients with breast cancer, predictors of depression include being in the year following diagnosis, younger age, receiving adjuvant chemotherapy, experiencing an impact on fertility, and physical side effects from treatment [22]. These variables, along with inconsistent ways of defining and measuring depression, have made it difficult to fully appreciate the impact of depression on this patient population as a whole. Depressive symptoms as well as mixed anxiety/depressive symptom states have been found to be more common in certain cancer types, including stomach, pancreatic, oropharyngeal, lung, and

gynecologic, and those with intracranial involvement [20, 23]. To date, studies of prevalence generally focus on the impact of primary cancer type, and there is limited information specifically assessing the impact of central nervous system (CNS) metastases. Overall, approximately 25% of patients with cancer have a depressive disorder that warrants treatment, representing at least a threefold increase compared to the general population [20, 24–26].

Differential Diagnosis

The term "depression" now has a wide range of meanings, varying from more social uses to severely impairing symptoms that warrant intensive treatment. The Diagnostic and Statistical Manual of Mental Disorders, currently in its fifth edition (DSM-V), provides a framework for conceptualizing mental health diagnoses and details widely accepted diagnostic criteria for clinical syndromes. Major depressive disorder (MDD) is the most commonly referenced depressive disorder. To meet criteria for MDD, patients must have at least five symptoms present for at least 2 weeks with subsequent impairments in daily functioning. Symptoms of depression include depressed mood or predominant irritability, decreased interest in activities, significant change in appetite and/or weight, significant change in sleep, psychomotor agitation or retardation, low energy/fatigue, feelings of worthlessness or guilt, impaired attention and concentration, and suicidal ideation. The depression also cannot be due to the effects of a substance, illicit or prescribed, or other medical condition [27].

When working with patients with medical illness, particularly cancer, it can be a challenge to differentiate a physical complaint related to the illness from a somatic manifestation of a mood disorder. Consider a patient with cancer who suffers from nausea leading to weight loss, impaired sleep and irritability while on steroids, fatigue, and difficulty with concentration and short-term memory loss since starting chemotherapy. When providing a diagnosis for patients with cancer, greater stress might be placed on symptoms that are less closely tied to physical symptom burden. This includes a deeper assessment of sadness, tearfulness, social withdrawal, worthlessness, guilt, and suicidal ideation [28]. One must also keep an open mind regarding other possible causes or contributors to the patient's symptoms.

Persistent depressive disorder is another depressive disorder that has been studied less formally in the cancer population but should remain on the differential diagnosis. With persistent depressive disorder, formerly called dysthymia, patients experience a depressed mood more days than not for a period of at least 2 years. They also experience other symptoms of depression but have fewer requirements in order to meet criteria when compared to MDD. Patients can experience major depressive episodes superimposed on persistent depressive disorder. This should be considered in patients with periods of symptom exacerbation that improve but never fully resolve between episodes [27]. There are no studies specifically examining persistent depressive disorder in patients with CNS metastases and limited data on the general cancer population.

When depressive symptoms occur exclusively in the context of a stressor and cause impairment in daily life or functioning, an adjustment disorder would be the most appropriate diagnosis [27]. This is common in patients who have cancer and often warrants treatment approaches similar to that of MDD.

For patients whose symptoms of depression are directly due to a substance or other medical problem, the appropriate diagnosis may be substance-/medication-induced depressive disorder or depressive disorder due to a general medical condition [27]. Substances can be illicit, prescribed, over-the-counter, and/or supplements and include intentional and accidental ingestions. Depression in a patient with at least one CNS metastatic lesion would be appropriately diagnosed in this category if the lesion itself is believed to be causing the symptoms.

The differential diagnosis for depression in patients with cancer is broad, and the etiology is often multifactorial. Factors that might contribute to a depression-type picture and should be considered are as follows.

Potential contributors to depressed mood in patients with cancer

- Depressive disorder
- Bipolar disorder
- Substance/Medication use
  - Alcohol
  - AEDs
  - Interferon-alfa, IL-2
  - Corticosteroids
- Vitamin D deficiency
- Malnutrition
- Hypothyroidism
- Low testosterone
- Pain
- Cancer-related fatigue
- Sleep disorders
- Apathy
- Demoralization
- Delirium
- Dementia

Hypoactive delirium often masquerades as a depressive disorder. Symptoms can include blunted affect, emotional lability including tearfulness, apathy, decreased involvement in daily activities, apparent lack of motivation, low energy, decreased PO intake, decreased physical activity, and impairments in attention/concentration. A waxing and waning course, alterations in level of consciousness, and perceptual disturbances can be helpful in distinguishing delirium from depression. Risk factors for delirium in cancer include a number of factors commonly associated with patients with CNS metastases: history of delirium, advanced age, premorbid cognitive impairment, intracranial disease involvement, leptomeningeal disease, low albumin, dehydration, infection, hypoxia, recent surgery, cytokine release syndrome, comorbid bone or liver metastases, and use of steroids, benzodiazepines, and opioids [29–34]. There is limited evidence to guide the management of agitated delirium associated with new immunotherapy approaches [35, 36]. Delirium can be distressing for patients, family members, and members of the care team and continue to impact patients into the future. In a study of 154 patients with cancer who experienced delirium while hospitalized, 53.5% recalled their delirium, and the majority of these patients recalled this experience as being highly distressing after resolution [37]. Up to 90% of patients with cancer have delirium at the end of life [32]. When depression and delirium occur together, priority should be given to addressing the causes of delirium, which are typically multifactorial in patients with cancer [25, 34].

In patients presenting with predominant cognitive complaints and possible mood disorder, it is important to consider an underlying cognitive disorder in addition to other causes. A gradual onset of impairments can often allow patients to compensate in day-to-day functioning. With the increasing demands that come with a cancer diagnosis and treatment, such as managing new medications and frequent appointments, underlying symptoms can be unmasked and become more impairing.

Bipolar Disorders

Bipolar disorders are differentiated from depressive disorders by the presence of at least one episode of hypomania or mania in a person's lifetime. Although depressive episodes typically occur at higher rates than manic episodes, history of a depressive episode is not a requirement for a diagnosis of a bipolar disorder. As with depressive disorders, the DSM-V identifies multiple diagnoses that help further classify the symptom profile and guide treatment decisions. These include bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance-/medication-induced bipolar disorder, and bipolar disorder due to another medical condition. Hypomanic and manic episodes differ in their severity with hypomania lasting fewer days and having a noticeable, but less impairing, impact on daily functioning. Symptoms may include grandiosity, decreased need for sleep, increased and pressured speech, racing thoughts, distractibility, an increase in goal-directed activi-

ties, and involvement in activities that are likely to have negative outcomes (i.e., risky financial decisions, spending sprees, driving very fast, sexual indiscretion, etc.) [27].

Much as in depressive disorders, patients with a bipolar illness are at an elevated risk of negative health outcomes when compared to the general population. This includes some factors that are associated with cancer, such as tobacco and alcohol use. However, there is no evidence that a patient with a bipolar illness is at a higher risk of developing cancer than others. There is also limited data specifically looking at cancer-related outcomes in patients with an underlying bipolar disorder.

There are examples of hypomania/mania being caused by a medical condition. Some of the most well-studied include stroke, traumatic brain injury, multiple sclerosis, and disorders of adrenal functioning [27, 38].

Some medications and other substances can lead to hypomania/mania and might be part of a patient's treatment while targeting cancer. Perhaps the most well-known example is that of corticosteroids. As previously mentioned, interferon-alfa also has rarely caused mania and should be monitored. Treatment-related mood symptoms are discussed later in this chapter.

Anxiety Disorders

Although the focus of this chapter is on mood disorders, we cannot discuss mood disorders without some mention of anxiety. Like depression, anxiety presents in patients with cancer at significantly higher rates than in the general population. When depression and anxiety symptoms occur together, they are associated with more severe depression, less robust response to treatment, lower quality of life, poorer adherence to mental health treatments, slower recovery, higher suicide rates, and higher overall healthcare costs [23]. Studies also suggest that patients with brain metastases have higher rates of anxiety than depression, particularly at specific points in treatment, such as prior to initiating radiation therapy [39].

Suicidality

Suicidal thoughts, attempts, and completions are more common in patients with cancer compared to those without. Rates have also been found to be higher in the cancer population when compared to those with other medical illness, even when controlling for expected prognosis [40]. Rates vary widely across studies and highlight the challenges of studying this heterogeneous patient population [41]. In general, the risk factors for suicidality that apply to the general population also apply to patients with cancer. Risk factors specific to patients with cancer include hopelessness independent of depression, impaired physical functioning, poor health overall, increasing stage of disease, and specific primary cancer types such as CNS malignancy [42–45]. There are mixed results on the impact of gender in this population as a whole [41].

There are no studies looking specifically at suicidality in patients with CNS metastases, but advanced stage of disease and involvement of a primary CNS lesion both suggest that this population is at increased risk. The highest rates occur close to the time of diagnosis [46]. Although there is consensus that suicidality generally decreases over time following cancer diagnosis, providers should always keep in mind that suicidality can occur at any time. In a study of more than 720,000 breast cancer survivors, participants continued to demonstrate elevated risk of suicide compared to the general population, even 25 years after cancer diagnosis [42]. Similarly, multiple studies show continued elevated risks in adult survivors of childhood cancers [43].

Mood Symptoms Related to Cancer Treatments

The side effects of specific chemotherapy agents will not be discussed in this chapter, but it should be noted that numerous neuropsychiatric side effects are possible with cancer treatments. In fact, receiving chemotherapy independently correlates with rates of depression in the breast cancer population, regardless of the agent being used

[47]. This reinforces the importance of monitoring for mood disorders in all patients receiving treatment.

Hormonal Agents

The use of hormonal agents also increases the risk for depression. There are clear links between hormones and depressive symptoms in healthy individuals. For example, mood disorders in women can have cyclical patterns related to menses, and women are at higher risk for depression in the postpartum period and surrounding menopause. There is mixed evidence about tamoxifen's effect on depression risk [47–50]. Perhaps unsurprisingly, patients with other risks factors for depression have higher rates of developing depression while on tamoxifen [50]. Increased depressive symptoms also correlate with other physical symptoms, such as hot flashes and sexual dysfunction, both of which are more common in women on tamoxifen compared to those who were not [51, 52].

Immunotherapy

As immunotherapies become more commonly used, there is increasing data about the neuropsychiatric side effects, particularly in the acute phase. Interferon-alfa is one of the most well-known examples of a medication causing depression and has warnings for the risk of suicidality. Depression occurs in up to 58% of patients receiving this medication. It should also be noted that there is a lower, but still significant, risk of mania associated with interferon-alfa use [53–55]. IL-2 has also been associated with higher depression rates [56].

Antiepileptic Drugs

The antiepileptic drug class (AEDs) as a whole has warnings about increased risk of depression, with rates varying between medications [56]. Clinical studies for oral levetiracetam show 13% of adults and 38% of those less than 18 years of age experience "behavioral symptoms" that might include depression, anxiety, mood lability, and agitation. One percent of adults developed psychotic symptoms [57]. On the other hand, many AEDs function as mood stabilizers and can be beneficial in treating mood disorders.

Steroids

Glucocorticoids have a clear association with the onset of multiple psychiatric side effects including depression, hypomania/mania, suicidal ideation, psychosis, delirium, and sleep changes [38, 56]. Onset is often within the first couple of weeks and dose-dependent but can occur after long-term use. A diagnosis of primary bipolar disorder does not increase the risk of steroid-related mania. However, patients who have a history of this response to steroids are at an increased risk, and prophylaxis with a mood stabilizer for future treatments should be considered. One should not underestimate the impact steroid-related sleep impairments can have on a patient's functioning and sense of well-being. This should be monitored closely and treated aggressively.

Radiation Therapy

Chapter 29 of this book discusses the potential neuropsychiatric impacts of radiation therapy in depth. These potential adverse outcomes cannot be overlooked. In a study of 170 patients with brain metastases undergoing whole brain radiation, self-reported measures of postradiation symptoms showed a high prevalence of symptom burden, most commonly fatigue, poor sense of well-being, anxiety, drowsiness, and poor appetite. They also found that symptoms tend to cluster together—anxiety and depression are frequent covariables [58]. Distress measures show similar patterns in patients undergoing whole brain or hypofractionated stereotactic radiotherapy compared to those without brain mets undergoing radiation to the breast [39]. Fatigue, a common side effect of radiation, can mimic depression in this phase of treatment.

When a medication suspected of contributing to a mood disorder is an integral part of a patient's cancer treatment, it is often not feasible to discontinue the medication. Providers should consider lowering the dose of the offending agent or transitioning to another agent in the same class, if possible. It is important to consider the benefit of psychiatric medications as adjuvant therapy, behavioral strategies, and lifestyle changes.

Impact of Mood Disorders on Cancer-Related Outcomes

Engagement in Treatment

Psychosocial stress has been linked to multiple factors that potentially play a role in cancer development or progression including inflammation, oxidative stress, decreased immune surveillance, and dysfunction of the HPA axis [10, 11]. Unsurprisingly, clinicians and researchers are interested in how these relationships can impact cancer-related outcomes in patients who struggle with mood disorders. Studies show that there are differences in how patients make decisions related to their cancer treatment. For example, in a study of women with breast cancer conducted by Colleoni et al., only 51.3% of women with comorbid depression accepted the recommendation of adjuvant chemotherapy compared to 92.2% of women without depression [59]. Treatment adherence rates also differ. Studies have found that patients with depression are up to three times more likely to be nonadherent with medication recommendations from their medical team [60]. Guilt is a common feeling in patients with cancer who may fear they are a burden on others or somehow deserve illness because of a perception of previous wrongdoings—this has been found to be an independent risk factor for treatment nonadherence [61]. As the treatment paradigm in cancer continues to shift toward managing a chronic disease, long-term follow-up and chronic medication use become more important. Kaul et al. noted that young adult cancer survivors are approximately twice as likely to report medication nonadherence as their peers and that mental distress is a significant risk factor for this behavior [62].

Morbidity

Cancer-related morbidity can similarly be impacted by the presence of a mood disorder. Depression rates correlate with levels of anxiety, fatigue, and pain [63, 64]. Distress is also associated with other maladaptive behaviors, some of which have their own associated cancer risks, such as tobacco use [65]. Current depression is a risk factor for future psychiatric comorbidities, which can negatively impact a patient's progress. Patients with depression during hospitalization following hematopoietic cell transplant were found to have higher rates of post-traumatic stress disorder and lower quality of life ratings at their 6-month follow-up visits [66]. In a study of 154 patients admitted to the hospital for surgery for thoracic and head and neck cancers, depression and fear of cancer recurrence were strongly associated with higher nicotine relapse rates [67]. El-Jawahri et al. compared 1116 patients with depression prior to allogeneic hematopoietic cell transplantation to 6317 patients without pretransplant depression and found higher rates of grade 2–4 acute graft-versus-host disease, lower overall survival rates, and fewer days alive and out of the hospital in the first 100 days posttransplant in patients with premorbid depression [68].

Mortality

It is challenging to study the impact of mood disorders on cancer-related mortality given the high number of confounding factors. However, studies have found that patients with higher depressive symptom burden have shorter survival times [69–73]. Also, having depression prior to cancer diagnosis correlates with lower survival compared to those without precancer depression. This difference is especially prominent for patients with depression and precancer physical limitations [74]. The etiology of this relationship is likely multifactorial with potential impact from cancer treatment nonadherence or maladaptive behaviors like comorbid substance use as discussed previously [10, 69].

Healthcare Utilization and Costs

The impact of comorbid mood disorders and cancer can also be felt on a systems level. With a shifting focus toward patient satisfaction, we see that depressive symptom severity inversely correlates with satisfaction in medical care [75]. Patient distress levels also correlate with the number of reported concerns during an outpatient oncology visit [76]. This translates to increased time spent with members of the treatment team, either through longer visits, more frequent visits, or increased utilization of urgent and emergency services [77]. Studies have clearly shown that mental health issues lead to higher healthcare costs as a whole. Implementation of appropriate treatment strategies that target mood disorders and anxiety lowers those costs [77, 78]. Also, studies show that proactive involvement of psychotherapy, particularly cognitive behavioral therapy (CBT) skills, can lead to higher quality of life reports, fewer psychiatric symptoms, and lower healthcare costs, even in patients who did not report elevated levels of distress at the time of diagnosis [78, 79]. This underscores the importance of addressing mental health needs in all patients.

Interactions with Caregivers

Caregivers can serve a wide range of functions, providing emotional, cognitive, spiritual, physical, and social support. The presence of brain metastases often corresponds with increasing care demands as patients develop new or worsening symptoms that impact daily life. The concept of caregiver burden has become a focus of research as patients with cancer live longer and the caregiver role has correspondingly become more fluid, transitioning in focus from end-of-life care to that of long-term survivorship. Being a caregiver correlates with higher levels of anxiety, depression, social isolation, and concerns about financial stress and stigma related to the cancer [80]. Studies have shown that caregivers of those with advanced cancer have higher rates of depression and anxiety compared to those caring for patients with earlier-stage disease. Studies specifically looking at caregivers of patients with CNS metastases are limited, but do show increased rates of depression and anxiety symptoms [81]. In addition to the vital role that caregivers play as part of the treatment team, evidence also reveals an association between high levels of caregiver distress and high levels of patient distress.

Role of Screening

Studies reveal that healthcare providers often fail to recognize patients who are experiencing emotional distress, highlighting the importance of routine screening for all patients [82]. As mentioned, confounding factors related to cancer, cancer treatment, and medical comorbidities can make screening for mood disorders more challenging. Many instruments are available, including some that have been validated for use specifically in patients with cancer, though no screening tools have been validated specifically in patients with CNS metastases. This validation occurs by comparing outcomes on the screening instrument with those of a gold standard tool, such as a standardized structured clinical interview [83]. Identifying the most appropriate screening tool requires assessing several factors including the symptoms of primary interest, patient population, clinic work flow, procedures for who will administer and follow-up when a patient screens positive, available technology for administration and/or interpretation, available time, etc. Systematic reviews of English instruments completed by Luckett et al. and Vodermaier et al. provide additional information on individual screening tools [84–86].

The Patient Health Questionnaire-9 (PHQ-9) is a self-report instrument with nine items that reflect the diagnostic criteria for MDD outlined in the DSM-V. Patients rate the severity of their symptoms in the past 2 weeks on a scale from 0 for "not at all" to 3 for "nearly every day" [87]. This was developed for use in primary care and since validated for use in patients with cancer [88].

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report tool commonly

used in research and clinical settings to screen for anxiety and depression symptoms in patients with medical illness. This has been validated in a wide range of patient populations, including those with cancer, and has proven to be particularly reliable in screening for depression in this population [89].

The NCCN Distress Thermometer has been validated for use in patients with intracranial tumors [82, 90]. It serves as a screening tool by asking patients to rate their distress on a scale from 0 to 10 with 10 representing the highest level of distress. Patients also have the opportunity to select areas in which they would like additional support and/or resources by checking off topics on a Problem List. Areas include practical problems, family issues, emotional stress, spiritual concerns, and physical ailments [1]. Although this instrument can gather information about a wider range of issues compared to the others discussed, results are less easily correlated with specific diagnoses, and studies show that the distress detected correlates with anxiety more than depression [91, 92].

Treatment Strategies

Comorbid mood disorders are best treated with a multidisciplinary approach that addresses patient needs while taking into account their inherent strengths and weakness and the environment in which they spend their time. Although therapy and medication have independently been shown to be effective for both unipolar and bipolar mood disorders, a comprehensive approach utilizing both tools should be encouraged.

Psychotherapy

Gathering comprehensive data on the effectiveness of different therapy modalities for patients with cancer has its challenges. Studies vary considerably in regard to the targeted symptoms, utilized treatment modality, training of those delivering the treatment, and the means of assessing effectiveness [41]. While numerous studies demonstrate benefit for patients in specific populations, data is limited in regard to patients with CNS metastases in particular.

Cognitive behavioral therapy (CBT), originally developed to target depression, is a widely used form of psychotherapy. It focuses on identifying dysfunctional patterns of cognition, which often occur automatically and without awareness, in order to change one's emotional response and behavior [93]. Evidence exists for using CBT in patients with cancer to target many symptoms, including depression, fear of cancer recurrence, pain intensity, and fatigue [94–96].

Mindfulness-based stress reduction (MBSR), developed by Jon Kabat-Zinn, has helped contribute to the rise in popularity of "mindfulness" practices in popular culture. Mindfulness is a form of meditation that refers to a purposeful and sustained focus on one's self and the immediate situation and/or surroundings to help bring focus and clarity [97]. When incorporated into formal treatment, this can involve multiple strategies, such as individual meditation, guided meditations in person or through the use of pre-recorded audio, body scans, and yoga [98]. This has been studied in patients with cancer and found to be helpful for many symptoms including overall anxiety, fear of cancer recurrence, quality of life, depression, cognitive symptoms, and physical tension [94, 98–100]. There is mixed evidence about the longevity of these benefits [99, 100]. Providers who teach these skills suggest they be incorporated as a lifestyle change rather than a time-limited therapy.

Motivational interviewing relies on a collaborative relationship between patient and provider to help illicit and build upon one's motivations for change while honoring patient autonomy [101]. Although this style has been most studied in patients with substance use disorders, it is being applied more widely over time. In patients with cancer, potential targets include optimizing diet, exercise, and lifestyle factors that impact sleep and fatigue, pain, mood, and substance misuse, among other aspects of daily life [102–104].

Similarly, dialectical behavior therapy (DBT) has seen a significant broadening of applications since the original skills training manual was pub-

lished in 1993 [105]. Originally developed to treat patients with borderline personality disorder, this therapy modality focuses on four sets of skills: mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance [106]. This modality typically requires a greater time commitment each week, but should be strongly encouraged.

Additional therapy modalities have been developed specifically to assist patients with chronic medical illness and those facing the end of life. Dignity therapy was developed to help patients find meaning and hope as they approach death [107]. Meaning-centered psychotherapy, both as individual and group modalities, is similarly focused on assisting patients in finding and sustaining meaning [108–110].

Medications

Before considering medication management to target mood disorders, it is important to evaluate and address other contributing factors. The impact of comorbid substance use disorders should not be overlooked, and incorporating screening for substance use is an integral part of mental health care. Impairments in sleep correlate with depression risk, and treating sleep disorders can result in lower depression symptoms [111, 112]. Rates of sleep apnea are higher in patients with cancer compared to the general public, and sleep-disordered breathing correlates with increased mortality in cancer patients, specifically [113]. It has also been found to correlate to increased rates of cancer development, though there are many confounding factors [114]. All patients should be screened for malnutrition, nutritional deficiencies, and hypothyroidism.

Antidepressants

There is a robust body of evidence for using antidepressants to treat depression, including specifically for patients with cancer. There is less evidence available to help guide treatment in patients who have symptoms of depression but do not fully meet diagnostic criteria for one of the depressive disorders. There is also less evidence specifically related to patients with CNS metastases. Despite this paucity in formal evidence, antidepressants are routinely used to manage both depression and anxiety symptoms in this patient population. In fact, rates of medication use for depression and anxiety in patients with cancer in the USA are typically about two times that of the general population, and these medications are used more frequently as disease progresses [115].

Choosing an appropriate medication to target depression in patients with metastatic cancer requires attention to a number of factors:

1. *Primary symptom of interest:* See Table 11.1 for information on the most commonly used antidepressants and considerations for their use. Of note, there is limited evidence for the use of stimulants as monotherapy to treat depression. If this is considered, it would be wise to involve a psychiatric provider to assist with proper use.
2. *Other potential targets:* While effective in treating depression, antidepressants have other effects that might be beneficial and should be considered. Sleep, appetite, nausea, hot flashes, sexual dysfunction, and neuropathic pain are the most common targets. See Table 11.1 for examples. In addition to those listed, trazodone is an antidepressant that is used off-label for insomnia. With less risk of tolerance or withdrawal and limited risk for a paradoxical reaction more common in patients with CNS pathology, trazodone is often viewed as superior to benzodiazepines for this purpose. Primary caution is with orthostasis.
3. *Potential problematic side effects*: Patients with intracranial pathology are often more sensitive to medication side effects. In general, starting at low doses and titrating slowly is the best approach. It should be noted that all serotonergic antidepressants have some risk for osteoporosis with long-term use, gastrointestinal bleeding through antiplatelet activity, and hyponatremia. Bupropion, which acts by increasing norepinephrine and dopamine, can be quite beneficial for some patients by increasing daytime motivation/energy,

Table 11.1 Most commonly used antidepressants and considerations for use in patients with cancer

	Primary mechanism of action	Reasons to consider	Cautions with use
Selective serotonin reuptake inhibitors (SSRIs)	Inhibition of 5-HT reuptake	Considered first-line Generally well-tolerated	Risk of headaches, GI upset, sexual dysfunction
Citalopram			
Escitalopram			
Fluoxetine			
Fluvoxamine			
Paroxetine			
Sertraline			
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Inhibition of 5-HT and norepinephrine reuptake	Helpful for neuropathic pain	Risk of HTN
		Activating impact of NE can increase motivation and daytime energy	Discontinuation syndrome is more prominent and requires slower taper
Desvenlafaxine		Venlafaxine for hot flashes	
Duloxetine			
Venlafaxine			
Bupropion	Inhibition of norepinephrine and dopamine reuptake	Helpful for smoking cessation	Risk of HTN, seizures
		Activating impact can increase motivation and daytime energy	Can exacerbate anxiety
		Off-label use for attentional issues	Can cause appetite suppression and weight loss
		Low risk of sexual side effects	Caution in psychotic disorders
		Less weight gain	
Mirtazapine	Inhibition of 5-HT_2 and 5-HT_3	Antiemetic properties	Risk of dry mouth, weight gain
	Increased serotonin and norepinephrine through alpha-2 adrenergic antagonism	Increases appetite	Rare risk of neutropenia through bone marrow suppression
		Sedating impact helpful for sleep	
Tricyclic antidepressants (TCAs)	Inhibition of 5-HT and norepinephrine reuptake	Helpful for neuropathic pain	Anticholinergic, anti-muscarinic, and anti-alpha adrenergic side effects
Amitriptyline		Sedating impact helpful for sleep	
Desipramine			
Doxepin			
Imipramine			
Nortriptyline			

improving attention, and aiding in smoking cessation. However, it should be used with caution in patients with CNS metastases or primary brain tumors due to a dose-dependent risk of seizures [116]. When combining medications, one should keep in mind the additive effects of side effect profiles. Use of anticholinergic medications is a common example in patients with cancer. As part of chemotherapy, pain, nausea, and psychiatric medication regimens, these medications can lead to the development of bothersome dry mouth and constipation as well as potentially more problematic effects like urinary retention, bowel ileus or obstruction, dental caries impacting oral intake, and cognitive impairment. There are also additional risks when combining multiple serotonergic medications, such as tramadol, fentanyl, triptans, and antiemetic agents, in addition to antidepressants. Serotonin syndrome can present with autonomic instability, altered mental status,

tremor, hyperreflexia, and myoclonus and can progress to seizures, coma, or death if not recognized and treated.

4. *Drug-drug interactions:* Providers should always assess for possible drug-drug interactions before prescribing a new medication. When working with patients who have cancer, it is important to consider what agents are typically used in the cancer treatment standard of care and make decisions accordingly. There are numerous potential interactions between psychiatric medications and other medications commonly used in cancer treatment. The most frequently discussed drug-drug interaction in this category is that of tamoxifen and paroxetine, a selective serotonin reuptake inhibitor (SSRI). Tamoxifen is an inactive prodrug metabolized through the liver by cyp2D6 into its active metabolites. Multiple antidepressants are inhibitors of this enzyme and pose a theoretical risk of decreasing the effectiveness of tamoxifen. Interestingly, studies have not shown this to be true in clinical practice. In the largest study to date, Haque et al. found that there was no correlation between antidepressant use and cancer recurrence or contralateral breast cancer diagnosis in patients taking both an antidepressant and tamoxifen [117]. The risks and benefits of using this combination should be considered for each individual case.
5. *Mechanism of delivery:* Patients with cancer often have temporary difficulty taking medications by mouth. In the USA, parenteral formulations are not as readily available [118, 119]. Patients may also have surgical interventions or other medical issues that impact bioavailability of medication. Psychiatric providers can be of assistance in these challenging cases.

Mood Stabilizers

There are multiple mood stabilizers that can be used in the treatment of bipolar illness. If a patient is currently stable on a psychiatric medication, it is advisable to avoid changes in this regimen as much as possible. This class of medication typically has more significant drug-drug interactions than other psychotropics and should be watched closely. Medication nonadherence can also be more detrimental. For example, lamotrigine is classically known for its risk of the life-threatening Stevens-Johnson syndrome during dose titration. If a patient misses approximately 5 consecutive days' dosing, regardless of the reason for this nonadherence, the dose must be re-titrated from the beginning of the titration schedule, which can have adverse effects on a patient's mood and behavior. Lithium can be a powerful mood stabilizer but it is very reliant on consistent body water status. Lithium toxicity, which can be fatal, occurs more frequently with dehydration, infection, and multiple medication interactions, including the use of low-dose nonsteroidal anti-inflammatory drugs (NSAIDs). Management with lithium in the context of cancer requires close monitoring and should involve a psychiatric provider.

Antipsychotic medications also have mood stabilizing properties. Although most are used for psychotic disorders and bipolar mania, there is evidence to support off-label use for many indications benefitting patients with cancer. This can include use as an antiemetic, benzodiazepine-sparing sleep aid, appetite stimulant in failure to thrive, treatment for agitation or severe irritability related to intracranial disease, and to treat steroid-related mood disorders, anxiety, and insomnia [120].

Conclusion/Summary

Patients with CNS metastases are at an increased risk for mood disorders. This correlation is multifactorial, with contributions from shared mechanisms on a cellular level, involvement of specific brain regions linked to the processing and generation of emotions, and side effects of cancer treatment to name a few. Comorbid mood disorders are linked to a number of poor cancer-related outcomes and problematic behaviors, including medication nonadherence, comorbid substance misuse, higher healthcare utilization and costs, and even mortality. Screening and early interventions are important and often involve collabora-

tion with mental health professionals to provide medications, psychotherapy, and other behavioral strategies. Although a wide range of treatment strategies are used in clinical practice, the body of literature for this specific patient population is small. Additional research is needed to provide evidence-based management recommendations for patients with CNS metastases.

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