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Authors

Kruse, Jennifer L
Strouse, Thomas B

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Sick and Tired: Mood, Fatigue, and Inflammation in Cancer

Jennifer L. Kruse · Thomas B. Strouse

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Abstract Cancer patients commonly experience depression and fatigue before, during, and after treatment. Symptoms can be debilitating, and the risks associated with unrecognized or inadequately treated depression are substantial. Inflammation may be important in the genesis of depression and fatigue in cancer patients; potential neurobiological mechanisms of inflammation-related behavioral symptoms are reviewed. Randomized studies of pharmacologic treatments for depression in cancer populations are limited, but available data are generally encouraging. Studies of pharmacologic treatments for cancer-related fatigue have been more numerous but with mixed results. A practical approach to pharmacologic treatment of depression and fatigue in cancer patients involves weighing the potential risks and benefits of specific agents, including potential for adverse or advantageous side effects. Progress in understanding the neurobiological mechanisms underlying inflammation-related behavioral symptoms will provide opportunities for the development of novel and targeted treatments.

Keywords Cancer · Inflammation · Depression · Fatigue · Cytokines · Kynurenine pathway

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J. L. Kruse (✉)
Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, 300 Medical Plaza, Rm 2273, Los Angeles, CA 90095, USA
e-mail: jkruse@mednet.ucla.edu

T. B. Strouse
Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California, Los Angeles, 757 Westwood Plaza, Rm 4230B, Los Angeles, CA 90095, USA
e-mail: tstrouse@mednet.ucla.edu

Introduction

Depression is common and debilitating. According to World Health Organization estimates, unipolar depressive disorders are the leading worldwide cause of work years lost due to disability. Among US adults, the 12-month prevalence rate of major depressive episodes is 6.9 %; women are affected roughly 1.6-fold more than men [1]. In patients diagnosed with cancer, depression is even more common. A 2011 meta-analysis found pooled prevalence rates of major depression of 16.5 % among cancer patients in palliative care settings and 16.3 % in non-palliative care settings; prevalence rates for depressive disorders did not differ among men and women [2•].

In addition to suffering and disability, depression in patients with cancer is associated with specific health risks. Depressed cancer patients may be less likely to pursue recommended treatments [3], have longer hospital stays [4], higher mortality rates [5], and higher likelihood of reporting desire for hastened death [6].

Fatigue is also exceedingly common among cancer patients—occurring before, during, and after treatment. Fatigue may be related to the disease itself, to cancer therapies (e.g., chemotherapy, radiation), or to comorbid disorders such as depression. Studies of fatigue among cancer patients demonstrate wide variability in prevalence, ranging from ~30–100 %. Cancer-related fatigue adversely affects psychological, social, and physical well-being, impairs functioning, and prevents patients from pursuing activities that they would normally enjoy [7]. Severe fatigue may even predict shorter recurrence-free survival [8]. Given that fatigue and depression frequently occur together, these symptoms may act synergistically among cancer patients to worsen quality of life, impair function, and threaten health outcomes.

Efforts are underway to understand the neurobiology of depression and fatigue in cancer. It is attractive to pursue a

unifying hypothesis that might explain the etiology of cancer-related depression and fatigue in the context of immune activation and inflammation in response to tumor immunogenesis. The “sickness” response associated with systemic inflammation has been described repeatedly in mammalian species and may manifest as depression and fatigue. Improved understanding of the pathophysiology of these phenomena may one day differentiate the treatment of depression and fatigue in patients with high levels of inflammation from routine treatment in medically well populations. Additionally, opportunities for novel and targeted treatment development may emerge to address the significant public health concerns related to the prevalent and troubling behavioral symptoms so often suffered by cancer patients.

This review aims to: 1) Review sickness behavior, its relevance in cancer, and the role of inflammation in sickness behavior, depression, and fatigue; 2) Review putative pathophysiologic mechanisms of inflammation-associated behavioral symptoms; 3) Review pharmacological treatment studies for depression and fatigue in cancer populations and outline a practical approach to the pharmacologic treatment of depressive symptoms and fatigue in cancer patients.

Inflammation and Sickness Behavior

Initially described by Hart in 1988, sickness behavior is a well-recognized set of signs and symptoms observed in ill animals and humans. “Sickness syndrome” was posited to reflect the survival benefits of a depressed behavioral response for overcoming febrile infectious illness [9]. Behavioral symptoms of sickness include social withdrawal, diminished interest in pleasurable activities, anorexia, fatigue, and somnolence. Anyone who has suffered from an acute viral illness, such as influenza, has experienced the symptom cluster that constitutes sickness behavior. In the right setting, these symptoms may be adaptive. By limiting activities, an ill animal will conserve energy needed to fight infection; anorexia may protect the ill and weakened animal from predators, as it will forego foraging that may put it in harm’s way [9].

The sickness response is associated with elevations in systemic inflammatory markers, and there is strong evidence that sickness behavior is driven by increases in pro-inflammatory cytokines (PICs). Indeed, multiple studies in both animals and humans have demonstrated that administration of PICs is sufficient to induce the sickness response and conversely that PIC antagonists can block that response [10].

Though initially described relative to febrile infectious illness, systemic inflammation and sickness behavior also occur under other conditions. Immune cells secrete PICs in the context of infection as well as tissue injury. In cancer, PICs may be secreted by the tumor itself, by the host in response to the tumor, or in response to tissue injury caused by the tumor or

treatments directed toward the tumor (surgery, radiation, chemotherapy). Many of the behavioral comorbidities typical of cancer patients (e.g., fatigue, anorexia/cachexia, sleep disturbance) squarely fall under the umbrella of “sickness behavior” and may be inflammation-associated phenomena [11]. In the remainder of this section, we will review diagnostic issues that arise when major depression occurs in the context of the sickness response. We will also review evidence that links inflammation to depression and fatigue.

Sickness and Major Depression—Diagnostic Issues

There is considerable overlap between the syndrome of major depression and sickness behavior. For example, medically ill patients may experience anorexia, fatigue, and sleep disturbance as a consequence of the primary disorder. Because the sickness response includes many of the core symptoms of depression, accurate diagnosis of major depression in the context of illness becomes more challenging. It may become difficult to determine whether a particular patient meets criteria for a bona fide major depressive episode, or whether there are symptoms that should be excluded from the diagnosis based on a determination that they are attributable to medical illness.

Given these concerns, some investigators have developed alternate measures which de-emphasize somatic symptoms of depression. These include the Hospital Anxiety and Depression Scale (HADS) [12] and the Endicott “substitutive” criteria for diagnosing depression [13]. In the Endicott schema, symptoms that may be attributable to medical illness (fatigue, weight loss, poor concentration) are replaced by other symptoms including fearful or depressed appearance, social withdrawal or decreased talkativeness, and brooding, self-pity, or pessimism. In a study of depression in patients with cancer, however, standard DSM-III criteria and the Endicott criteria yielded very similar results [14], suggesting the possibility that specialized criteria may provide a distinction without a difference. Others have suggested an exclusive approach, in which anorexia and fatigue are eliminated from the diagnostic criteria for depression [15]. The DSM 5 includes a notation that symptoms “clearly attributable to another medical condition” should not be counted toward the diagnosis of a major depressive episode. However, determining the etiology of a particular symptom requires causal inferences, and a symptom may have multiple etiologies. In a study of medically ill patients, exclusion of weight loss and fatigue from the diagnostic criteria for major depression resulted in greater specificity and greater ability to detect the most severe and persistent depressions, but an inclusive approach (using DSM criteria without etiologic determinations or substitutions) was more sensitive [16]. Thus, an exclusive or etiologic approach increases diagnostic specificity for severe and persistent depression among

medically ill patients but also decreases sensitivity. As the risks of untreated or undertreated depression are increasingly recognized, and the tolerability of antidepressant medications has improved, a trial of treatment may be warranted when an attempt to definitively exclude symptoms “clearly attributable” to a medical condition leads to diagnostic uncertainty [17].

Inflammation and Depression

As described above, there is strong evidence that inflammation elicits sickness behavior. There are also multiple overlapping symptoms between sickness behavior and major depressive disorder. More generally, the notion that inflammation plays a role in the pathophysiology of depression has been an emerging hypothesis in mood disorders research over recent decades [18–20]. This hypothesis is informed by a number of observations demonstrating that depressive-like behavior is induced by administration of PICs. Interferon alpha (IFN- α) studies indicated that 28 % of hepatitis C patients developed a new onset major depressive episode during treatment with IFN- α [21]; the rate reported in malignant melanoma patients is 45 % [22]. Treatment with paroxetine prevents depressed mood, anxiety, and cognitive dysfunction, but not neurovegetative symptoms, associated with IFN- α treatment. Among malignant melanoma patients undergoing IFN- α therapy, only 11 % of paroxetine-treated patients developed symptoms consistent with a major depressive episode, compared to 45 % of placebo-treated patients [23].

Administration of immunogenic stimuli also induces sickness behavior. Lipopolysaccharides (LPS) found on the cell membranes of Gram-negative bacteria elicit a strong immune response. In a pre-clinical model of depression, LPS is used to induce depressive-like behavior in rodents; treatment with various antidepressants can prevent or ameliorate LPS-induced depressive-like behavior in animals [24, 25, 26•]. Similarly, studies of LPS administration in humans demonstrate subsequent increases in PICs as well as emotional symptoms, including depressed mood [27]. Microglia produce PICs in the brain in response to LPS. In mice, pretreatment with minocycline inhibits LPS-induced cytokine production by microglia and lessens behavioral changes [28]; similarly, peptides that interfere with LPS-induced activation of toll-like receptor 4 (TLR4) prevent microglia cytokine production as well as sickness behavior [29].

The inflammatory hypothesis of depression is additionally informed by epidemiological evidence demonstrating that patients with inflammatory disorders have elevated rates of depression comorbidity. Indeed, depression is highly comorbid in patients with immune-mediated diseases such as multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis [30–32].

Given these observations, as well as evidence from multiple studies identifying elevations in circulating PICs in depressed patients who are otherwise medically healthy [33], there has been interest in targeting depressive disorders with drug therapies typically reserved for immune-mediated disorders. For example, infliximab, a monoclonal antibody directed at tumor necrosis factor alpha (TNF- α), was studied compared to placebo, as a therapy for treatment-resistant depression. Though the overall results of the study were negative, there was a positive association between baseline concentrations of high sensitivity C-reactive protein (hs-CRP) and improvement in depressive symptoms with infliximab, suggesting that depressed patients with higher levels of inflammation may have differential improvements in depressive symptoms with antibody targeting of TNF- α [34•]. Similarly, a study of etanercept (another TNF- α antagonist) in psoriasis patients led to improvement in depressive symptoms over placebo; this improvement was not strongly correlated with improvement in overall disease severity and is suggestive of a direct effect of TNF- α antagonism on depressive symptoms [35]. A recent meta-analysis in JAMA Psychiatry summarizes antidepressant effects of anti-inflammatory treatments in randomized placebo-controlled trials to date, finding decreases in depressive symptoms with anti-inflammatory agents compared to placebo [36•]. In a recent trial of escitalopram vs. nortriptyline for major depression, patients exhibited differential responses to treatment depending upon baseline CRP. This suggests that one day, inflammatory burden may inform treatment decisions even among currently established antidepressant therapies [37•].

In summary, there is compelling evidence that inflammation may play a role in the pathophysiology of depression in a subset of patients; intriguing evidence suggests that inflammation may also play a role in treatment responsiveness.

Inflammation and Fatigue

Fatigue is a frequent symptom of depression; indeed, it is one of the nine symptoms of depression that constitute criterion A of the DSM 5 criteria for major depressive disorder. Additionally, it is a well-recognized symptom of a variety of medical illnesses, cancer included. Fatigue is also perhaps the most intuitively understood symptom among the “sickness syndrome” cluster. Nearly all humans have experienced this symptom in relation to one illness or another. Given its clear association with sickness behavior and the close linkage of sickness behavior with inflammation, the relationship between fatigue and inflammation may seem straightforward. However, given the nonspecific nature of fatigue and its association with multiple and varied conditions, the neurobiology of fatigue is far from well understood.

Multiple studies of cancer-related fatigue have demonstrated correlations with inflammatory markers—before, during,

and after cancer treatment. Results have not always been consistent, however, and studies in a variety of cancer populations have demonstrated associations between different inflammatory markers or different aspects of fatigue. A recent comprehensive review of mechanisms of cancer-related fatigue in *Nature Reviews Clinical Oncology* provides an excellent and nuanced summary of the current literature, with an emphasis on studies evaluating inflammatory hypotheses of fatigue in cancer [38•].

Newly diagnosed acute myelogenous leukemia patients showed close correlations between levels of multiple inflammatory markers and fatigue [39]. Similarly, in preoperative patients with ovarian cancer, there was an association between IL-6 levels and fatigue [40]. Multiple studies have further demonstrated that both during treatment and well into the so-called survivorship period, levels of inflammatory markers correlate with fatigue. Confusingly, however, specific markers are not consistently identified [38•]. A large epidemiologic study in a non-cancer population demonstrated that mild elevations in CRP and IL-6 predicted subsequent development of fatigue [41].

As noted earlier in this review, patients treated with IFN- α experience treatment-emergent depressive symptoms with significant frequency. Interestingly, fatigue and anorexia tend to emerge earlier in the course of IFN- α treatment than primary mood symptoms. Further, while paroxetine prevents onset of major depressive episodes in a substantial percentage of these patients, it is not as effective at preventing neurovegetative symptoms of depression, including fatigue [23]. This finding suggests that with the same trigger (IFN- α treatment), there may be different neurobiological pathways that lead to different symptom clusters. The specific mechanisms of IFN- α -induced fatigue remain elusive.

Given data supporting the hypothesis that inflammation plays a role in cancer-related fatigue, anti-inflammatory immune-modulating agents have been studied as potential treatments for fatigue in the setting of cancer. Small trials of anti-TNF agents have demonstrated reductions in fatigue in cancer populations [42, 43]. Similarly, the previously discussed etanercept trial for psoriasis patients not only reduced depressive symptoms but also reduced fatigue [35]. In advanced cancer, dexamethasone (4 mg PO twice daily, administered for 2 weeks) resulted in improvement in fatigue scale scores [44].

In summary, though fatigue is a nonspecific symptom that is likely to be the final common pathway of various pathophysiologic mechanisms, there is substantial evidence that inflammation indeed plays an important role in some patients' fatigue. In cancer-related fatigue, there are multiple studies supporting this hypothesis and some initial small treatment trials suggesting benefit with treatments that target the inflammatory response.

Neurobiological Mechanisms of Inflammation-Induced Behavioral Symptoms

We have reviewed sickness behavior and its relationship to inflammation, depression, and fatigue. We have outlined the relevance of these symptoms in cancer patients. In the current section, we review potential neurobiological mechanisms underlying inflammation-associated behavioral symptoms, focusing on a brief review of four topics: 1) effects of inflammation on monoamine neurotransmission, 2) effects of inflammation on glutamate neurotransmission, 3) effects of inflammation on neuronal plasticity and neurogenesis, and 4) functional neuroimaging data pertinent to anatomical networks that may be involved in inflammation-induced behavioral symptoms.

Effects on Monoamine Neurotransmitters

Serotonin has long been a molecule of interest in efforts to understand the pathophysiology of depression. Worldwide, SSRIs are the most often prescribed antidepressant medications and have in fact been demonstrated to prevent PIC-induced depression. Peripheral depletion of tryptophan and the attendant reduction in serotonin precursors is a possible mechanism to explain PIC-induced depression. Additionally, decreased synthesis or increased reuptake of monoamines, including serotonin, norepinephrine, and dopamine, may play a role in inflammation-associated behavioral symptoms. See Table 1.

Effects on Glutamate Neurotransmission

Glutamate is the most abundant excitatory neurotransmitter in the brain; it acts via stimulation of glutamate receptors, including the NMDA receptor. The role of glutamate neurotransmission in depression has been of increasing interest over recent years, particularly with multiple studies demonstrating the robust antidepressant effects of ketamine, an NMDA receptor antagonist [45, 46]. Endogenous NMDA receptor agonists and antagonists, influenced by PICs, may play a role in the pathophysiology of depressive symptoms. PICs have also been shown to increase the release of glutamate from astrocytes, which may lead to increases in glutamate neurotransmission at extra-synaptic NMDA receptors [47], decreased expression of brain-derived neurotrophic factor (BDNF), and neuronal damage via glutamate excitotoxicity [48]. In summary, altered glutamate neurotransmission, either through increased neuroactive kynurenine metabolites or through increased release of glutamate, is a potential mechanism through which inflammation may affect behavior. See Table 1.

Table 1 Potential neurobiological mechanisms underlying inflammation-associated behavioral symptoms

Effects on monoamine neurotransmitters	<p><i>Tryptophan depletion:</i> Tryptophan is the precursor molecule for the synthesis of serotonin. When PICs activate the enzyme indoleamine-2,3-dioxygenase (IDO), tryptophan is preferentially metabolized down the kynurenine pathway, possibly depleting stores of tryptophan available for metabolism to serotonin.</p> <ul style="list-style-type: none"> • Malignant melanoma patients undergoing IFN-α treatment had decreases in peripheral tryptophan over time and increases in kynurenine levels, suggesting that IDO is in fact activated in these patients. Further, there was a correlation between the average decrease in tryptophan concentration and severity of depressive symptoms [68]. • Tryptophan depletion in medically healthy patients with remitted depression can induce recurrence of depressive symptoms, but the mechanism by which tryptophan depletion is associated with relapse is not yet entirely clear [69, 70]. • Peripheral depletion of tryptophan and the attendant reduction in serotonin precursors is a possible mechanism to explain PIC-induced depression. <p><i>Diminished availability of the co-factor tetrahydrobiopterin (BH4)</i> is another potential mechanism of PIC-induced behavioral change. BH4 catalyzes the rate-limiting steps for the synthesis of serotonin, dopamine, and norepinephrine; scarcity of this essential co-factor might lead to decreased synthesis of monoamines. Elevations in PICs have been shown to decrease availability of BH4 by two potential mechanisms:</p> <ul style="list-style-type: none"> • Inflammatory states set the stage for generation of reactive oxygen species and reactive nitrogen species. BH4 is particularly sensitive to oxidative stress, and is readily oxidized to an inactive state in which it can no longer function as a co-factor for the metabolism of the monoamines [47]. • Inflammation can lead to increased synthesis of nitric oxide, through an enzymatic reaction for which BH4 is a co-factor. Thus, an inflammation-induced increase in the synthesis of nitric oxide may lead to decreased availability of BH4. <p><i>Increased expression and function of monoamine transporters:</i> Inflammatory stimuli, through activation of signaling pathways such as p38 mitogen-activated protein kinase (MAPK), may increase both the expression and function of monoamine transporters; most work in this area has focused on serotonin transporters [55•]. This may in turn lead to decreased synaptic concentrations of monoamines [47].</p>
Effects on glutamate neurotransmission	<p><i>Kynurenine metabolites:</i> Quinolinic acid (QUIN) is an NMDA receptor agonist and a metabolite of the kynurenine pathway of tryptophan degradation, regulated in part by PICs through activation of IDO [71, 72].</p> <ul style="list-style-type: none"> • Pre-clinical studies have demonstrated that LPS-induced depressive-like behavior is prevented by blocking IDO activation [73] • LPS-induced depressive-like behavior is accompanied by increased brain QUIN (NMDA receptor agonist) [26••]. • LPS-induced depressive-like behavior can be prevented or abolished by administration of ketamine (NMDA receptor antagonist) [26••]. <p><i>Increased glutamate release:</i> PICs have been shown to increase the release of glutamate from astrocytes, which may lead to increases in glutamate neurotransmission at extra-synaptic NMDA receptors [47], decreased expression of brain-derived neurotrophic factor (BDNF), and neuronal damage via glutamate excitotoxicity [48].</p>
Effects on plasticity/neurogenesis	<p><i>Decreased neurotrophic factors:</i> Studies have demonstrated that PICs may impact levels of neurotrophic factors.</p> <ul style="list-style-type: none"> • Decreased neurogenesis in the hippocampus, decreased hippocampal BDNF, and increased hippocampal TNF-α and IL-1β were observed in LPS treated animals [51]. • Inflammation-associated decrements in hippocampal neurogenesis are thought to be mediated by IL-1β. IL-1 receptor antagonists can block this effect in animals; IL-1 receptor knockout mice do not exhibit decreased neurogenesis in response to inflammatory stimuli [74, 75]. • In humans treated with IFN-α, serum BDNF levels decreased over time; however, this was not found to correlate with whether or not patients developed depressive symptoms, and variance may depend on other individual vulnerability factors [76]. <p><i>Alterations in glutamate neurotransmission</i> can lead to decreased production of BDNF [48].</p> <ul style="list-style-type: none"> • There is interest in ketamine's downstream mechanism of action as an NMDA receptor antagonist, thought to involve stimulation of neurogenesis and neuroplasticity via activation of signaling through the mTOR (mammalian target of rapamycin) pathway and release of neurotrophins, including BDNF [77].

Effects on Plasticity/Neurogenesis

The inflammatory hypothesis of depression may overlap with the neurotrophic hypothesis of depression. In the latter, it is hypothesized that deficits in neurotrophic factors such as BDNF lead to abnormalities in neurogenesis and neuroplasticity in brain networks important in mood regulation [49]. Indeed, meta-analyses have demonstrated that serum BDNF is low in depressed patients (not taking antidepressants) compared to healthy controls and that serum BDNF levels increase with antidepressant treatment [50]. Studies

have demonstrated that PICs may impact levels of neurotrophic factors [51]. See Table 1.

Effects on Regional Brain Activity

Functional neuroimaging studies in IFN- α -treated patients have helped define anatomical networks potentially involved in PIC-induced behavioral change. The most consistent and compelling data involves the basal ganglia and dopaminergic function [52, 53, 54••]. Functional MRI in IFN- α -treated patients revealed decreased activation of the ventral striatum

during a reward task; this decreased activation correlated with measures of fatigue, depression, and anhedonia. Additionally, IFN- α -treated patients had increased uptake and decreased turnover of radiolabeled fluorodopa in the ventral striatum, which correlated with behavioral changes including depression and fatigue [54••]. These findings suggest an inverse correlation between PICs and dopaminergic function in the basal ganglia, associated with depression and fatigue.

In summary, studies of inflammatory stimuli in animals and humans begin to outline the interaction between inflammation, neurotransmitter systems, neurogenesis, and the neurocircuitry that may be involved in inflammation-induced behavioral change. For more comprehensive reviews of these potential neurobiological mechanisms of inflammation-induced behavioral symptoms, please see Felger and Lotrich 2013 [55•] and Miller et al. 2008, 2009, and 2013 [11, 20, 47].

Pharmacologic Treatment of Depression in Cancer Populations

Emerging recognition of the role of inflammation in the development of depressive symptoms in cancer patients suggests possibilities for novel and personalized approaches to treatment. These might include assessment of biomarkers to inform treatment with immune-modulating agents or agents targeting specific downstream effects of inflammation. From a practical perspective, however, current treatment of major depression in cancer is best informed by established depression treatment guidelines.

There are limited data specifically evaluating pharmacological treatments for depression in cancer patients. A recent meta-analysis identified only six double-blind randomized placebo-controlled pharmacotherapy trials of depression in cancer patients. Treatment with SSRI antidepressants or mianserin led to greater benefit for depressive symptoms compared to placebo, but the studies were few and small, and additional research is needed [56••]. More generally, efficacy of antidepressants in medically ill populations was evaluated in a Cochrane review, and results are encouraging, confirming superiority of antidepressant medication over placebo in the depressed medically ill [57]. This work was extended to palliative care populations; results again confirmed the benefit of antidepressant medications over placebo [58]. The bulk of the available high-quality evidence suggests that antidepressant medications are effective in medically ill depressed patients.

In addition to studies of pharmacologic treatment for major depression, there has also been interest in depression prevention among cancer patients. Among cancer patients undergoing IFN- α therapy, which carries a high risk for development of severe depressive symptoms that may limit ongoing

treatment, evidence supports prophylactic antidepressant treatment [22]. But pharmacologic studies of depression prevention in cancer have not been limited to IFN- α therapy. A prevention trial for depression in head and neck cancer demonstrated lower rates of depression among escitalopram-treated patients compared to placebo [59•].

Thus, both clinical wisdom and the available research data demonstrate that there are situations in which prophylactic antidepressant treatment may be indicated. In particular, if patients are undergoing treatments known to induce major depressive episodes in substantial proportions of those treated, prophylaxis should be considered. In other high-risk patient populations, such as those with a pre-morbid history of major depression, re-initiation of a previously beneficial antidepressant therapy may be warranted prior to the development of recurrent depressive symptoms. This decision should be made in collaboration with the patient and the oncologic treaters, with due consideration to the psychological stressors and physical rigors of cancer diagnosis and treatment that may suffice to trigger a recurrent mood episode.

Antidepressant medication selection for the depressed cancer patient may require considerations distinct from those for an otherwise medically healthy depressed patient. Against the generic backdrop of general equivalent efficacy among all antidepressants, psychiatrists often recommend medications based upon potential adverse effects (or potentially beneficial side effects). For example, medications commonly associated with weight gain might be avoided in an obese patient but may be a good choice in a depressed patient who is losing weight. For a patient with insomnia, sedating agents might be favored, but for a hypersomnic depressed patient, a more activating agent is preferred.

Similar strategies may make sense for cancer patients, albeit with a few more considerations. There are multiple cancer-associated symptoms that can be targeted by particular antidepressant agents. Thus, in efforts to simplify pharmacology and maximize benefit, agents for depressed cancer patients should be selected while considering other potential target symptoms. Table 2 addresses some of these important considerations.

The usual cautions apply when it comes to treating depressed medically ill patients. Consider the patient's cancer therapies and other medications in order to avoid drug-drug interactions. Escitalopram, citalopram, sertraline, and venlafaxine are commonly prescribed antidepressant agents with few and generally mild drug interactions. In patients with particular vulnerability to the development of delirium (e.g., advanced age, comorbid cognitive disorder, severe medical illness), potentially anticholinergic antidepressants, such as tricyclic antidepressants, should generally be avoided. Anticholinergics are also best avoided in patients already afflicted by urinary hesitancy or constipation. For patients

Table 2 Psychotropic medications for symptom management

Cancer-associated symptoms, complications, or treatments	Psychotropic agent	Comments
Pain	SNRIs, TCAs, ketamine	Antidepressants can be effective adjuvant analgesics for neuropathic and other pain types. Effective agents include the tricyclic antidepressants as well as SNRIs such as duloxetine, venlafaxine, or levomilnacipran. For recalcitrant cancer pain, ketamine is sometimes used
Poor sleep	Mirtazapine, sedating tricyclic antidepressants, trazodone	As for any depressed patient, problems with initiating or maintaining sleep may call for a more sedating antidepressant agent such as mirtazapine, trazodone, or a sedating tricyclic.
Poor appetite/nausea	Mirtazapine, olanzapine, haloperidol (anti-emetic only), synthetic cannabinoids	For patients struggling with poor appetite, weight loss, and/or nausea, mirtazapine may have benefit for some patients. Appetite stimulation is a well-known side effect of mirtazapine, but mirtazapine has also been demonstrated to have anti-emetic effects, likely due to antagonism of 5HT-3; which is the same mechanism of action as ondansetron, granisetron, palonosetron, etc.
Fatigue	Bupropion, psychostimulants	For depressed patients with marked fatigue, stimulating agents such as bupropion should be considered. In addition to their modest efficacy for fatigue, there is some data supporting the use of psychostimulants for treatment of depressed medically ill patients under certain circumstances, particularly in advanced stages of disease where a more rapid antidepressant response is desired [78].
Pruritis	Doxepin	Depressed patients struggling with pruritis related to cancer or its treatment may benefit from treatment with doxepin, a tricyclic agent and potent anti-histamine.
Frequent infection with resistant Gram (+) bacteria	May need to avoid antidepressants if linezolid cannot be avoided	Linezolid is a reversible MAOI; serotonin syndrome has been reported when it is co-administered with some antidepressants (which should be avoided if linezolid is mandatory). If antidepressants are needed, consider selecting an agent with a short half-life that will wash out more quickly if serotonin syndrome develops, limiting risk. Given that linezolid is a reversible MAOI, severe reactions are less likely, but caution is advised.
Hepatic dysfunction	Avoid duloxetine, nefazodone. Dose adjust antidepressants per manufacturer guidelines.	Duloxetine and nefazodone have been rarely been implicated in drug-induced hepatic dysfunction
Renal impairment	Dose adjust antidepressants per manufacturer guidelines.	As for any depressed patient with renal impairment
CNS disease or history of seizure disorder	Avoid bupropion	Bupropion lowers seizure threshold
Constipation	Avoid anticholinergic antidepressants	Anticholinergic agents may worsen constipation. Constipation is common in cancer patients, given the frequent need for chronic opioid treatment for cancer pain, which slows GI motility. Less commonly, constipation may be related to the effect of some tumors on the GI tract
Cardiac conduction abnormalities	Avoid tricyclic antidepressants, citalopram, antipsychotics	In patients of advanced age or with comorbid risk factors for cardiac disease, attention to issues of cardiac conduction should be considered prior to initiating tricyclic antidepressants (TCAs), citalopram, or antipsychotic agents, all of which may worsen cardiac conduction abnormalities. If necessary to use these agents despite cardiac conduction abnormalities, monitor ECG and electrolytes (especially magnesium and potassium).
Tamoxifen treatment	Avoid potent 2D6 inhibitors; consider using venlafaxine, sertraline, citalopram or escitalopram	Tamoxifen's conversion to endoxifen depends upon CYP450 2D6
Meperidine treatment	Avoid MAOIs	Life-threatening serotonin syndrome is a risk when MAOIs are administered with any serotonergic agent. For this reason, MAOIs may be best avoided in cancer patients if possible, given potential for drug-drug interactions.

who have hepatic or renal dysfunction, usual precautions should be taken with regard to carefully selecting appropriate agents with appropriate dosage adjustments.

Eventually, evidence-based, highly personalized treatments may emerge from improved understanding of neurobiological mechanisms of depression in cancer patients. In the meantime,

a practical pharmacologic approach includes adapting usual depression treatment guidelines to particular circumstances of an individual's cancer and cancer-associated symptoms. Goals should include providing maximal benefit with the simplest medication regimen. Behavioral and psychosocial treatments, though not the focus of this review, may also have beneficial effects for cancer patients [60] and should be considered concurrently with psychopharmacology, based in part on patient preference and the availability of sub-specialty expertise.

Pharmacologic Treatment of Cancer-Related Fatigue

It is hoped that the quality and efficacy of pharmacologic treatments for cancer-related fatigue will improve concurrent with improved science regarding its underpinnings. In the meantime, we will review available pharmacologic treatment trials for fatigue and again outline a practical approach to treatment.

A 2008 systematic review and meta-analysis evaluated 24 studies of pharmacological treatments for cancer-related fatigue, 14 of which studied hematopoietic agents (and found a treatment benefit among cancer patients with fatigue and baseline anemia). Of the remaining studies, 4 evaluated progestational steroids (no benefit for cancer-related fatigue), 2 evaluated methylphenidate (and identified a treatment benefit over placebo), and 2 evaluated paroxetine (no benefit for cancer-related fatigue). Single studies reviewed within this meta-analysis included a small open label study of etanercept (tumor necrosis factor inhibitor) which demonstrated a statistically significant treatment effect over placebo and a randomized, placebo-controlled study of the bisphosphonate ibandronate, which also demonstrated a statistically significant treatment effect over placebo [61].

A subsequent study of modafinil demonstrated benefit for cancer patients with severe fatigue, but not for those with mild or moderate fatigue [62]. Overall, studies of psychostimulants for cancer-related fatigue have been mixed. A more recent meta-analysis of methylphenidate treatment for cancer-related fatigue included five studies ($n=426$) and demonstrated benefit of methylphenidate over placebo, though with a small effect size [63]. Subsequently, two larger studies of methylphenidate have failed to demonstrate benefit over placebo for cancer-related fatigue [64, 65]; but like the aforementioned modafinil study, a subset analysis demonstrated benefit for those patients with severe fatigue and/or advanced disease [65]. Thus, the data is limited regarding the efficacy of pharmacologic treatments for fatigue in cancer. As discussed above, small studies evaluating TNF- α antagonism, as well as a study of corticosteroid treatment, have found statistically significant benefits for cancer-related fatigue [42–44].

Regarding a practical approach for pharmacologic treatment of cancer-related fatigue, the available data generally

support the use of psychostimulants. Given subset analyses demonstrating greater psychostimulant efficacy among patients with severe fatigue and/or advanced disease, clinicians may wish to target pharmacologic interventions toward this population. Routine considerations apply when considering psychostimulant treatment. If patients have significant cardiac disease or uncontrolled hypertension, traditional psychostimulants are best avoided, but modafinil may be of benefit. Collaboration with the patient, the oncologist, and the cardiologist (when indicated) is recommended. Concerns regarding appetite suppression sometimes limit clinicians from initiating psychostimulants, but the data in cancer populations indicate that appetite suppression is not a usual side effect in these populations and that psychostimulants are generally well tolerated [66]. Further, psychostimulants may in fact improve appetite in some patients. In a retrospective chart review, 54 % of cancer in patients treated with dextroamphetamine or methylphenidate had improvement in appetite [67].

Regarding hematopoietic agents, while data supports the efficacy of these agents for cancer patients with both fatigue and anemia, there are also controversies surrounding these treatments; the risks and benefits of utilizing hematopoietic agents are best assessed by oncologic providers.

It should again be noted that behavioral and psychosocial treatments, though not the focus of this review, may also have beneficial effects for cancer patients and should be considered [38•].

Conclusions

While patients suffering from cancer and its treatments may have many reasons to feel sick and tired, major depression and cancer-related fatigue may work synergistically to increase suffering and threaten health outcomes. Systemic inflammation may play a role in driving behavioral symptoms in cancer patients, and personalized treatments may one day be available to target inflammation-induced behavioral symptoms. In the meantime, the available data support the use of pharmacologic, behavioral, and psychosocial strategies to target depression and fatigue in cancer populations, with the goal of providing maximal benefit with the simplest medication regimen.

Compliance with Ethics Guidelines

Conflict of Interest Jennifer L. Kruse and Thomas B. Strouse declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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