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REVIEW ARTICLE

Evidence-Based Treatment of Depression in Patients With Cancer

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ABSTRACT

Purpose
Depression is a common condition in patients with cancer, although there has been a relative paucity of research on the effectiveness of treatment in this population. This review summarizes the psychosocial and pharmacologic treatment of depression in patients with cancer based on a consideration of evidence regarding etiologic factors and treatment outcomes.

Methods
A review of the evidence base for psychosocial and pharmacologic interventions for depression in patients with cancer was performed, including original studies, systematic reviews, and meta-analytic studies in the literature.

Results
Recent evidence from randomized controlled trials has demonstrated the efficacy of psychosocial and pharmacologic treatments to alleviate depression in patients with cancer. Further research is needed to establish their relative and combined efficacy and their role in the treatment of depression that is less severe and occurs in association with more advanced disease. First-line recommendations for the treatment of depression in patients with cancer are difficult to derive based on current evidence, because comparative studies have not been conducted to support the superiority of one treatment modality over another in this population.

Conclusion
Both psychosocial and pharmacologic interventions have been shown to be efficacious in treating depression in cancer, but further research is needed to establish their relative and combined benefit. Future research directions include the development and evaluation of novel interventions targeted to specific biologic and psychosocial risk factors.

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INTRODUCTION

Depression is the most common psychological symptom in patients with cancer and may range in severity from nonpathologic sadness to clinical syndromes associated with marked distress and disability.[1] More severe symptoms of depression are of clinical concern because of their association with more prolonged hospital stays, physical distress, poorer treatment compliance, lower quality of life, increased desire for hastened death, and completed suicide.[2] This review addresses the treatment of depression in cancer based on a consideration of evidence regarding etiologic factors and treatment outcomes.

PREVALENCE OF DEPRESSION IN CANCER

The reported prevalence of depressive symptoms in cancer has been variable, depending on cancer type and stage, timing and method of assessment, diagnostic criteria applied, and demographics of the population studied.[3] Higher rates of depressive symptoms in cancer have been found toward the end of life[4] and in specific cancers, such as pancreatic, gastric, and oropharyngeal cancers as well as lung cancer.[3] Although depression has been reported to be two to three times more common in women than in men in the general population,[5] this disparity has not been observed in cancer, perhaps because the burden of disease may be equally distributed by sex.[6]

Depressive symptoms occur on a continuum, with nonpathologic sadness at the milder end, minor or subthreshold depression in the middle, and major depression at the more severe end of the spectrum. According to the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) of the American Psychiatric Association,[7] major depression refers to a syndrome characterized by at least five symptoms present for at

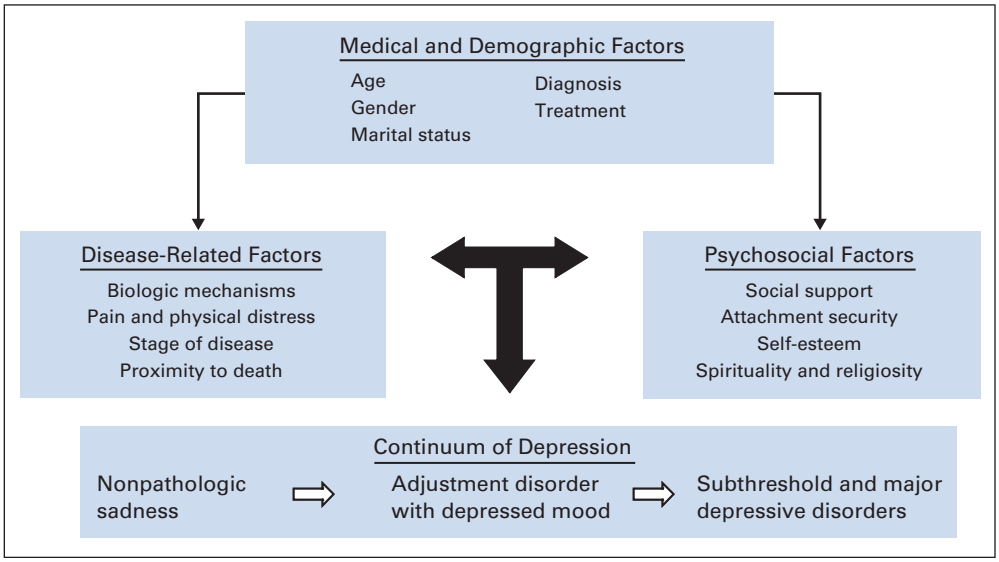

Fig 1. Pathways to depression. Reprinted with permission.[14]

least 2 weeks, one of which is depressed mood or anhedonia. The other symptoms include appetite or sleep disturbance, psychomotor agitation or retardation, decreased energy, feelings of worthlessness or guilt, difficulty concentrating, or suicidal ideation. Minor depression can be diagnosed when only two to four of these symptoms are present for at least 2 weeks; dysthymia, when 3 to 4 symptoms are present continuously for at least 2 years. Depressive symptoms may also be a component of a so-called adjustment disorder, which refers to a state of marked distress that is greater than expected from exposure to a stressor.[7] However, the lack of precision in this definition and the difficulty establishing what is normative distress in the context of cancer raise questions about its diagnostic validity.

Major depression has been found to occur in approximately 16% of patients with cancer, with minor depression and dysthymia combined reported in almost 22% of patients.[1] These rates are at least three times as common as those found in the general population.[8] A majority of patients with subthreshold or minor depression do not progress to major depression, although both major and minor depression are associated with significant impairment of well-being and quality of life.[9] A family history of psychiatric illness and the presence of chronic medical illness have been shown to be risk factors for conversion from minor to major depression.[10] A majority of depressive presentations in cancer are subthreshold and therefore may be underecognized and undertreated.

DIAGNOSTIC AMBIGUITY

Diagnostic challenges in cancer-related depression include the somewhat arbitrary and often ambiguous boundaries between realistic sadness and subthreshold and major depression. There is also frequent uncertainty about the diagnostic significance of physical and psychologic symptoms. Many symptoms of cancer and its treatment, such as fatigue, anorexia, insomnia, and cognitive impairment, overlap with those of depression. Furthermore, suicidality or the desire for hastened death may be a feature of depression, although it may also be found in states of demoralization in individuals who are not clinically depressed.[11] Cancer-related depression is also associated with fewer core depressive thoughts, such as sense of guilt and failure, dissatisfaction and self-dislike, than primary depression.[12] These observations raise the possibility that the phenomenology and etiology of depressive disorders in this population, and perhaps in other medical populations, may differ from those of primary depression.[13]

ETIOLOGIC MECHANISMS

We have suggested[14] that the emergence of depression in patients with cancer may be understood as a final common pathway resulting from the interaction of multiple disease-related, individual, and psychosocial factors (Fig 1). Individual and psychosocial factors that contribute to the risk of depression in this context include younger age, personal or family history of depression, less social support, greater attachment anxiety, poor communication with medical caregivers, and maladaptive coping strategies.[2] The physical burden of cancer, reflected in such variables as functional disability, stage of disease, and the number and severity of physical symptoms, is one of the strongest and most consistent predictors of depressive symptoms.[15] Individuals with both higher disease burden and greater psychosocial vulnerability are at most risk for becoming depressed as the proximity to death increases.[4]

Pancreatic cancer has long been considered to have a specific association with depression because of observations that the prevalence of depression is higher than in other cancer types.[16] There was early speculation that depression more often precedes the diagnosis of cancer of the pancreas than in other cancer types.[17] Recently, it has been suggested that the specificity of this association may have been overestimated and that depressive symptoms in this context are closely linked to pain and physical symptoms and could reflect shared biologic mechanisms.[18] In that regard, there is mounting evidence that tumor cell burden and treatment-induced tissue destruction, which release pro-inflammatory cytokines that alter neurotransmitter and neuroendocrine function, may contribute to depressive symptoms in patients with cancer, captured under the rubric of cytokine-induced depression.[19] Supporting this hypothesis is the finding that treatment of patients with cancer with specific cytokines, such as interferon-alfa

or interleukin-2, can induce depression in up to 50% of such patients.[20] Further elucidation of such pathophysiologic mechanisms may eventually lead to more targeted and effective treatments of depression in cancer.

TREATMENT

The treatment of depression in patients with cancer should address not only the depressive symptoms but also the disease-related and psychosocial factors that contribute to the emergence of depression in this context. These include the treatment of pain and other distressing physical symptoms, the relationship with oncologists and other medical care providers, the social support system, and the individual experience of illness. Antidepressant medications are most effective in those with more severe depression,[21] whereas psychotherapeutic approaches may be of value in both milder and more severe cases of depression.[22] Psychotherapy may be the only modality required in mild to moderate depression, although antidepressant medication may also be tried in such cases when depressive symptoms fail to respond to psychologic treatment. Further research is needed to establish the optimal treatment of minor depression and mild to moderate major depression.[9]

Pharmacologic and psychotherapeutic treatment studies of depression in cancer have provided mixed and ambiguous results. This may result in part from the methodologic limitations of published research, including small sample sizes and failure to specify severity of depression, and from other differences in inclusion criteria, demographic, disease-related, and treatment characteristics of the samples studied, and duration of follow-up.[23-27] Such indiscriminate recruitment can create a floor effect on outcome measures such that treatment effects are underestimated.[27]

PSYCHOTHERAPY

Psychologic interventions that may diminish or prevent depressive symptoms potentially include not only interventions delivered by specialists in psychosocial oncology but also the support provided by medical caregivers as part of routine cancer care. The impact of the latter needs to be established with regard to the outcome of depression, although relationships with health care providers who are perceived as supportive have been shown to be associated with less traumatic stress in patients with cancer.[28,29] The decline in clinical empathy that has been found to occur over the course of both undergraduate and postgraduate medical training raises concern that there may be insufficient attention to the acquisition and maintenance of such psychotherapeutic skills in both the formal and hidden curricula.[30] However, these findings are consistent with recent observations that oncologists tend to ignore the large majority of empathic opportunities in clinical interactions.[31,32] There is evidence that clinical empathy can be improved with training,[33] but the time and volume pressures in cancer treatment settings may not support the development or maintenance of such skills.

Types

A wide range of specific psychotherapies have been used in the treatment of depression in cancer. The type of psychotherapy that is optimal may depend on the severity of depressive symptoms, the stage of disease and functional status of the patient, patient motivation to participate in psychologic treatment, and patient interest in self-reflection. Recently diagnosed patients with cancer with mild to moderate depression may benefit from psychoeducation, cognitive behavioral therapy (CBT), relaxation strategies, and problem-solving approaches.[34,35] Patients who have more advanced disease may benefit from supportive-expressive psychotherapy that focuses on processing fears associated with death and other existential concerns[36] (summarized in Table 1). Targeted and manualized psychotherapies for those with advanced illness have recently been developed, including Meaning-Centered Group Therapy,[37] Dignity Therapy,[38] Mindfulness-Based Meditation Therapy,[39] and a brief supportive-expressive intervention referred to as CALM (Managing Cancer and Living Meaningfully).[40]

Effectiveness

An early meta-analysis of 20 trials by Sheard et al[41] yielded a negligible effect size for the psychosocial treatment of depression in cancer. However, a more recent review by Jacobsen et al[42] of nine systematic reviews and four meta-analyses of the effects of a wide range of psychological interventions for depression in cancer is more encouraging. They found positive results in 41% to 63% of the systematic reviews[23,43] and medium to large effect sizes in the meta-analyses.[44-46] In a systematic review focused on reductions of caseness of depression in patients with cancer, Williams et al[24] found only three positive randomized controlled trials (RCTs) of psychosocial interventions. Rodin et al[25] reported that only 50% of psychosocial intervention studies demonstrated significant reductions in depressive symptoms in patients with cancer who were

Table 1. Description of Psychosocial Interventions

Term	Description
Counseling	Generic term used to refer to supportive psychosocial care provided by a qualified professional
Psychoeducation	Provision of information designed to increase knowledge and reduce uncertainty and thereby enhance psychological well-being
Relaxation training	Teaches skills for releasing physical or mental tension using meditative activities, progressive muscle relaxation exercises, or use of guided mental imagery
Problem-solving therapy	Focuses on generating, applying, and evaluating solutions to identified problems
Cognitive behavioral therapy	Focuses on identifying, challenging, and changing maladaptive thoughts and behaviors to reduce negative emotions and promote psychologic adjustment
Interpersonal therapy	Focuses on problems within interpersonal interactions and relationships, emphasizing areas such as grief, role transitions, disputes, or interpersonal deficits to reduce distress and promote psychologic adjustment
Supportive-expressive (psychodynamic) therapy	Focuses on the communication and processing of subjective experience and on the joint creation of meaning within a therapeutic relationship to reduce distress and promote psychologic adjustment (eg, Meaning-Centered Therapy, Dignity Therapy, and CALM)

Abbreviation: CALM, Managing Cancer and Living Meaningfully.

diagnosed with depression based on a structured diagnostic interview or who scored above an established cutoff on a validated self-report measure of depression. A recent meta-analysis of 29 RCTs in which CBT was used to treat depression in people with comorbid somatic disease (including eight studies of patients with cancer) found CBT to be superior to control groups, with larger effect sizes in studies that restricted participation to participants who met criteria for a depressive disorder.[47] Similarly, in their meta-analysis of psychologic treatment outcomes in cancer studies, Linden et al[27] found treatment effect sizes to be roughly three times greater in studies in which patients were first screened for elevated distress at study entry. Interestingly, although demonstration of the effectiveness of psychologic interventions tends to depend on clinically significant pretreatment depression, Kissane et al[48] reported the first RCT, to our knowledge, to demonstrate an effect of supportive-expressive group therapy in preventing the emergence of major depression in women with metastatic breast cancer.

There is a paucity of research evidence on the effectiveness of psychosocial interventions to alleviate depression in the setting of advanced cancer. Although a meta-analysis of six studies in patients with incurable cancer found CBT, supportive-expressive psychotherapy, and problem-solving therapy to be effective in decreasing depressive symptoms in this population, no studies were identified that focused on major depression.[49] A preliminary prepost study of Dignity Therapy in patients with a life expectancy of less than 6 months demonstrated a significant improvement in depressive symptoms.[38] However, a subsequent multicenter RCT of 441 patients testing this intervention in a palliative care setting found no difference in distress levels between study groups, although the intervention was associated with subjective improvement in quality of life.[50]

In view of the variable and conflicting evidence base, Jacobsen et al[42] proposed deriving specific clinically relevant recommendations for various psychosocial interventions based on the number of RCTs that demonstrate efficacy in managing depression per intervention type and patient disease or treatment status. Such an approach would identify the need for further research in discrete populations and diminish discrepant interpretations of the literature.[27] An adapted and updated version of such a summary is provided in Table 2.[39,48,51-75]

Table 2. Evidence-Based Recommendations for Use of Psychosocial Interventions to Prevent or Relieve Depression in Patients With Cancer

Treatment Status	RCT Evidence	Level of Evidence[51*]	Major Depression	Subthreshold Depression
Relaxation techniques				
Newly diagnosed patients	Arakawa[52]	I	No	Yes
	Bindemann et al[53]		No	Yes
	Edgar et al[54]		No	Yes
Postsurgery	Fawzy et al[55]	I	No	Yes
	Petersen et al[56]		No	Yes
Undergoing chemotherapy	Ando et al[39]		No	Yes
	Burish et al[57]	I	No	Yes
	Burish et al[58]		No	Yes
	Jacobsen et al[59]		No	Yes
	Mantovani et al[60]		No	Yes
Undergoing radiotherapy	Decker et al[61]	I	No	Yes
Terminal phase of illness	Liossi et al[62]	II	No	Yes
Psychoeducation				
Newly diagnosed patients	McQuellon et al[63]	I	No	Yes
	Pruitt et al[64]		No	Yes
Undergoing surgery	McArdle et al[65]	II	No	Yes
Undergoing chemotherapy	Rawl et al[66]	II	No	Yes
Supportive-expressive therapies				
Postsurgery	Watson et al[67]	II	No	Yes
Undergoing chemotherapy	Mantovani et al[60]	II	No	Yes
Undergoing radiotherapy	Evans et al[68]	II	No	Yes
Patients with metastatic disease	Kissane et al[48]		Yes	Yes
	Edelman et al[69]		No	Yes
	Goodwin et al[70]	I	No	Yes
	Classen et al[71]		No	Yes
Cognitive behavioral therapies				
Undergoing chemotherapy	Pitceathly et al[72]	I	Yes	Yes
	Marchioro et al[73]		No	Yes
Patients with metastatic disease	Savard et al[74]	I	Yes	Yes
	Edelman et al[69]		No	Yes
Undergoing radiotherapy	Evans et al[68]	II	No	Yes
Completion of active treatment	Simpson et al[75]	II	No	Yes

Abbreviations: CANMAT, Canadian Network for Mood and Anxiety Treatments; RCT, randomized controlled trial.
*CANMAT levels of evidence: I, at least two RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow CIs; II, at least one RCT with adequate sample size and/or meta-analysis with wide CIs; III, nonrandomized, controlled prospective studies or case series or high-quality retrospective studies; IV, expert opinion/consensus.

PHARMACOTHERAPY

Table 3 lists the antidepressants most commonly used in the medically ill, their common adverse effects, and specific considerations for use within a cancer setting.[76-79] No particular antidepressant class has been shown to be most effective for treating depression,[80] although other factors may influence treatment selection. These include prior response to treatment in patients or their family members and the

Table 3. Medications Commonly Used in Treatment of Depression in Cancer

Drug	Main Adverse Effects	Major Interactions	Considerations/Toxicities
SSRIs	Sexual dysfunction, nausea, GI disturbance, sweating, anxiety, headache, sleep disturbance, tremor		Rare akathisia, gastrointestinal bleeding, hyponatremia, bruxism
Citalopram		No significant inhibition of cytochrome P450 enzymes	Generally first-line SSRI choice because well tolerated and few drug-drug interactions
Escitalopram		No significant inhibition of cytochrome P450 enzymes	Generally first-line SSRI choice because well tolerated and few drug-drug interactions
Fluoxetine	No discontinuation symptoms	Strong inhibitor of CYP2D6 and 3A4	Should be avoided in those taking tamoxifen because of 2D6 inhibition
Sertraline		Moderate inhibitor of CYP2D6	
Paroxetine	Discontinuation symptoms common	Strong inhibitor of CYP2D6	Should be avoided in those receiving tamoxifen because of 2D6 inhibition
Fluvoxamine		Moderate inhibitor of CYP2D6, 1A2, and 3A4	
Mixed action			
Venlafaxine (SNRI)	Sexual dysfunction, nausea, insomnia, dry mouth, anxiety, sleep disturbance, headache	No inhibition of cytochrome P450 enzymes	First-line choice for those receiving tamoxifen because of lack of 2D6 inhibition
	Discontinuation symptoms common		Beneficial in reducing hot flashes in women receiving chemotherapy or who have tamoxifen-induced menopause[76]
			May cause elevation of blood pressure at higher doses and should be avoided if risk of arrhythmia
Duloxetine (SNRI)	Similar to venlafaxine, but discontinuation symptoms less common; anorexia	Moderate inhibitor of CYP2D6	Also treatment for diabetic neuropathy and neuropathic pain[77]
			Monitoring required for risk of hepatic failure; contraindicated with significant liver disease
Mirtazepine (NaSSA)	Drowsiness, increased appetite, weight gain, headache, dizziness	Minimal effect on P450 enzymes	Good choice for depressed patients with cancer with loss of appetite and insomnia; less sedating at higher doses[78]
			Available in orally disintegrating tablet
			Minimal effect on sexual functioning
Bupropion (NDM)	Agitation, weight loss, constipation, headache, insomnia, nausea	Strong inhibitor of CYP2D6	Activating properties make it useful in cases of prominent fatigue, hypersomnia, or psychomotor retardation[79]
	Seizure risk (dose dependent)		Minimal effect on sexual functioning
			Also useful as aid in smoking cessation
TCAs	Sedation, postural hypotension, dry mouth, blurred vision, constipation, urinary retention, tachycardia, arrhythmia, delirium	Phenothiazines, some opioids, and SSRIs can increase plasma levels	Also used for neuropathic pain syndromes; poorer tolerability than other antidepressant medications; toxicity in overdose and anticholinergic effects are major drawbacks to their use in psychooncology
Amitriptyline			
Nortriptyline			
Desipramine			
Psychostimulants	Insomnia, agitation, euphoria, tremor, anxiety, hypertension, tachycardia, confusion, delirium	May increase levels of SSRIs, TCAs, and some antiepileptics	Stimulating properties have led to use in anergic, depressed patients with cancer with terminal or advanced disease; contraindicated in presence of significant cardiovascular disease; rapid onset of action (days *v* weeks)
Methlyphenidate			
Dextroamphetamine			
Modafinil (nonamphetamine)	Adverse effects less frequent		

NaSSA, norepinephrine and specific serotonergic antidepressant; NDM, norepinephrine-dopamine modulator; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

adverse effect profile and drug interactions of each medication. Because of both their adverse effect profiles and risk for lethality in overdose, tricyclic/heterocyclic antidepressants, monoamine oxidase inhibitors, and reversible inhibitors of monoamine oxidase A are rarely used in patients with cancer.

Medications

Among the selective serotonin-reuptake inhibitors, sertraline, citalopram, and escitalopram have the fewest drug-drug interactions and are well tolerated.[81] Antidepressant selection can also be guided by the dual benefit that several of these medications may provide in improving not only depression but also cancer-related symptoms such as anorexia, insomnia, fatigue, neuropathic pain, and hot flashes (Table 3). Atypical antipsychotic medications, such as quetiapine and olanzapine, have been proposed for multiple symptom palliation,[78] because they can improve insomnia, delirium, appetite, and chemotherapy-related nausea, in addition to their effects on anxiety and depression. However, the evidence for their efficacy in depression is derived from research on general psychiatric rather than cancer populations.[82]

Stimulants, such as methylphenidate and dexamethasone, have been used to alleviate depression in patients with cancer in the palliative setting because of their more rapid onset of action. However, they have not yet been proved to alleviate depression in these patients, and definitive conclusions are lacking, because of the small sample sizes and other methodologic limitations of the studies conducted thus far.[83] Recent European guidelines on the management of depression in the palliative care setting do not recommend the use of psychostimulants.[84]

Toxicity and Drug Interactions

There has been recent debate about the potential worsening of suicidality, particularly in adolescents and young adults, with all classes of antidepressant medication.[85,86] Because of this concern, careful monitoring for suicidality during the early treatment phase is warranted to assess for this possibility. As indicated in Table 3, each antidepressant medication is also associated with specific toxicities that must be considered in the context of cancer treatment.[87]

Drug interactions are important to consider with the use of antidepressants in patients with cancer because of their potential to alter the pharmacokinetics of other medications frequently prescribed for these patients.[88] For example, paroxetine, fluoxetine, and buproprion can all significantly decrease levels of the active metabolite of tamoxifen, as a result of the inhibition of the isoenzyme CYP2D6 (Table 2). This effect may increase the risk of breast cancer recurrence in those receiving tamoxifen who are prescribed such antidepressants.[89] Medications that have minimal or no effect on the 2D6 isoenzyme (eg, venlafaxine, citalopram) should therefore be used when pharmacotherapy for depression is indicated in this population.[90]

Effectiveness

Evidence for the efficacy of pharmacotherapy in the treatment of depressive disorders in patients with cancer remains limited. On the basis of nine RCTs, Jacobsen et al[23] found significant treatment effects in only 13 of 26 depression outcomes. Williams et al[24] found that only two of six RCTs demonstrated reductions in caseness for major depression, although five studies found reductions in depressive symptoms. In a systematic review of RCTs of pharmacologic treatment studies in patients with cancer for which clinically significant depression was an inclusion criterion, Rodin et al[25] identified only three of seven RCTs in which a significant reduction of depressive symptoms was reported, and Ng et al[26] reported positive findings for effectiveness in only three of eight studies of patients with clinically significant depression.

Three recent meta-analyses have provided more robust findings in favor of the effectiveness of pharmacotherapy for depression in patients with general medical conditions.[91-93] All three studies found a significant advantage for antidepressant use in terms of remission and response compared with placebo, although the subanalysis by Iovieno et al[93] of four cancer-specific trials did not find a specific benefit for antidepressant use in cancer (risk ratio for response, 1.26; $P = .19$). The meta-analysis reported by Rayner et al[92] demonstrated a greater effect size in the treatment of minor compared with major depression. However, these findings must be interpreted with caution, in view of the small number of trials and the inclusion of patients with milder depression in the major depression arm of the study.

The potential role of antidepressant medication in preventing the onset of depression in those with cancer has been investigated in a few studies. Musselman et al[94] demonstrated this effect in patients with melanoma receiving high-dose interferon-alfa who were pretreated with paroxetine. Another RCT of the use of citalopram to prevent depression in patients with head and neck cancer[95] revealed significantly less depression after 12 weeks in the treatment group compared with the placebo control group. Although these findings are intriguing, more research is needed to confirm that antidepressant medication can prevent depression in patients with cancer at high risk of depression.

The evidence for effectiveness of antidepressant medications to treat subthreshold depression in noncancer populations is mixed,[96,97] nor is it well established in patients with cancer. Navari et al[98] reported a placebo-controlled study demonstrating the efficacy of 6 months of fluoxetine in reducing subthreshold depressive symptoms in 357 patients with early-stage breast cancer. Significant improvements in quality of life and in completion of treatment with hormonal and/or chemotherapy were also demonstrated in fluoxetine-treated patients. However, in an advanced cancer setting, Stockler et al[99] failed to demonstrate an impact of sertraline on depressive symptoms in an RCT in which major depression was an exclusion criterion. Table 4 summarizes the current literature on pharmacologic treatments of depression in cancer according to level of evidence of the CANMAT (Canadian Network for Mood and Anxiety Treatments) guidelines,[51] on the basis of the trials included in the systematic reviews described, as well as on more recent randomized and open-label studies.[94,95,98,100-102,103-129]

BEST MANAGEMENT PRACTICES

In view of the limited evidence available from RCTs in cancer populations, first-line treatment guidelines for depression must be partly derived by research in psychiatric and other medical populations. In relation to pharmacotherapy, level I evidence is available from studies in cancer only for mianserin in the treatment of depressive symptoms and for paroxetine in the prevention of depression. However, mianserin is no longer available, replaced by its analog mirtazepine, for which positive open-label studies have been reported in cancer.[116,117]

Table 4. Effectiveness of Pharmacologic Intervention in Preventing or Relieving Depression in Patients With Cancer

Medication	Trials		Level of Evidence[51]*
	Positive	Negative	
Antidepressants			
Paroxetine	Morrow et al[100]	Pezzella et al[102]	I
	Musselman et al[94]	Musselman et al[103]	I
	Roscoe et al[101]		I
Fluoxetine	Navari et al[98]	Razavi et al[104]	II
		Holland et al[105]	II
		Fisch et al[106]	II
Citalopram	Lydiatt et al[95]		II
	Capozzo et al[107]		II
Escitalopram	Schilliani et al[108]		III
Sertraline	Torta et al[109]		III
	Schillani et al[110]		III
Reboxetine	Grassi et al[111]		III
Duloxetine	Torta et al[112]		III
Mianserin	Costa et al[113]	Tarrier et al[115]	I
	Van Heeringen et al[114]		I
Desipramine		Holland et al[105]	
		Musselman et al[103]	
Amitryptyline		Pezzella et al[102]	
Mirtazepine	Ersoy et al[116]		III
	Kim et al[117]		III
Buproprion	Moss et al[118]		III
Anxiolytics			
Alprazolam	Holland et al[119]	Wald et al[120]	II
Steroids			
Prednisone	Bruera et al[121]		II
Stimulants			
Methylphenidate	Fernandez et al[122]		III
	Homsi et al[123]		III
	Macleod[124]		III
	Olin et al[125]		III
	Natenshon[126]		III
Mazindol		Bruera et al[127]	
Modafinil	Lundorff et al[128]	Jean-Pierre et al[129]	III

Abbreviation: CANMAT, Canadian Network for Mood and Anxiety Treatments; RCT, randomized controlled trial.
*CANMAT levels of evidence: I, at least two RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow CIs; II, at least one RCT with adequate sample size and/or meta-analysis with wide CIs; III, nonrandomized, controlled prospective studies or case series or high-quality retrospective studies; IV, expert opinion/consensus.

Furthermore, caution should be exercised in the use of paroxetine in patients with cancer because of its strong inhibition of cytochrome p450-2D6[130] and its relatively pronounced anticholinergic adverse effects. The serotonin-reuptake inhibitors citalopram and escitalopram are the most common first-line drugs used in the treatment of major depression in cancer, but the optimal antidepressant for specific patients can be determined by each patient's depressive symptom profile and potential dual benefit for cancer-related symptoms and depression (Table 3).

First-line treatment recommendations for psychosocial interventions in depressed patients with cancer are similarly difficult to derive, because comparative studies have not been conducted to support the superiority of one treatment modality over another. A variety of psychosocial interventions have been shown to reduce depressive symptoms in patients with cancer, and preliminary evidence raises the possibility that psychologic treatment may help to prevent the emergence of depressive symptoms in these patients. Table 2 lists specific applications of effective psychosocial interventions, with the number of citations associated with each intervention indicating the strength of the evidence base; the citations themselves provide details about the conduct of the intervention.[39,48,51-75]

No difference has been found thus far between the effectiveness of psychotherapeutic and pharmacologic interventions for the treatment of major depression in cancer.[25] Several recent studies that combine case finding with problem-solving therapy and/or education, pharmacotherapy as required, and interprofessional care coordination have demonstrated effectiveness for the treatment of depression in cancer.[34,35] These types of interventions are reviewed in greater detail elsewhere in this special issue of *Journal of Clinical Oncology*. What may be most likely to be effective in this population is a multicomponent approach, with psychosocial interventions tailored to clinical features such as severity of depression and stage of disease, combined with pharmacotherapy for more severe depressive disorders (Table 5 summarizes treatment recommendations).

FUTURE DIRECTIONS

A variety of tailored novel interventions have recently been developed for patients at different stages of disease and with different cancer-related problems (eg, a geriatric-specific group psychoeducational

Table 5. Summary of Treatment Recommendations for Depression in Patients With Cancer

Severity of Depression	Recommendation
Subthreshold or mild	Assess and optimize physical symptom control
	Provide psychosocial assessment and offer help in addressing identified precipitating or perpetuating factors related to cancer care or to psychologic, social, or spiritual factors
	Supportive communication, psychoeducation, stress management, spiritual care, or volunteer or peer support may be of value
Moderate	Same as those for subthreshold or mild depression plus offer psychologic intervention and/or pharmacotherapy* via referral to specialist psychosocial services where available
	Psychologic intervention used may depend on skill set of psychosocial clinicians, preference of the patient, stage of disease, and nature of the personal and cancer-related problems; psychoeducational or cognitive behavioral therapy problem-solving approach may be suitable in the setting of early disease, whereas supportive-expressive therapy may be helpful in progressive or advanced disease
Severe	Pharmacotherapy* in combination with psychosocial interventions (same as those for mild and moderate depression); specialist psychosocial service involvement is imperative

*Antidepressant choice should be informed by the combination of patient symptom profile and medication factors (including adverse effect profile, tolerability, and potential for drug interactions). Patients should be reviewed for adverse effects of treatment within 1 week of commencing the antidepressant, and consideration given to discontinuing the drug or changing to an alternative class of drug if indicated.

intervention,[131] CALM[40] for patients with metastatic cancer, and Dignity Therapy[38] for patients near the end of life). Greater evidence will soon be available for their benefit in the prevention and treatment of depression in cancer. The identification of cytokine-mediated and other biologic pathways to depression in patients with cancer may also allow for the development and evaluation of more targeted pharmacologic interventions to treat depression in these patients. Future research should be directed toward characterizing the phenomenology of cancer-related depression as a unique clinical entity and evaluating collaborative care models of depression management, combining individually tailored psychosocial and pharmacologic approaches.

The routine application of distress screening in cancer treatment centers may allow earlier clinic-based interventions to relieve depression and other manifestations of distress. This will require more attention in oncology health care providers to the application of clinical empathy and to the development of skills in supportive communication and psychoeducation. Such approaches may help to diminish the risk of severe and persistent depressive symptoms and to identify early patients who may need and benefit from specialized psychosocial interventions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Madeline Li, Gary Rodin
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Final approval of manuscript: All authors

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