Management of Depression in Patients With Cancer: A Clinical Practice Guideline

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Abstract

Purpose

This report updates the Cancer Care Ontario Program in Evidence-Based Care guideline for the management of depression in adult patients with cancer. This guideline covers pharmacologic, psychological, and collaborative care interventions, with a focus on integrating practical management tools to assist clinicians in delivering appropriate treatments for depression in patients with cancer.

Methods

Recommendations were developed by synthesizing information from extant guidelines and reviews and searching for randomized controlled trials from the date of database inception (1964 for MEDLINE and 1974 for EMBASE) to January 2015. Quality assessment of guidelines and systematic reviews were conducted by using the Appraisal of Guidelines for Research and Evaluation II (AGREE II), Assessment of Multiple Systematic Reviews (AMSTAR), and Cochrane Risk of Bias tools. Final recommendations were developed through a standardized Program in Evidence-Based Care multidisciplinary expert and knowledge user review process.

Results

Two high-quality relevant clinical practice guidelines, eight pharmacologic trials, nine psychological trials, and eight collaborative care intervention trials composed the evidence base upon which the recommendations were developed. Eight specific recommendations were made to establish a standard of care for the management of depression in patients with cancer. The recommendations and practical management tools were reviewed as being well organized and helpful, although systemic barriers to implementation were identified.

Conclusion

This updated guideline supports the previous general recommendation that patients with cancer who have depression may benefit from psychological and/or pharmacologic interventions, without evidence for the superiority of any specific treatment over another. New recommendations for a collaborative care model that incorporates a stepped care approach suggest that multidisciplinary mental health care restructuring may be required for optimal management of depression.

ASSOCIATED CONTENT

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INTRODUCTION

Depressive disorders are a significant comorbidity in cancer, with an estimated prevalence of major depression in more than 16% of patients with cancer, and minor depressive disorders, including dysthymia and adjustment disorders, reported in up to 22% of patients with cancer,[1] although prevalence varies widely with cancer type, treatment phase, and method of diagnosis.[2] Depression has been associated with more prolonged hospital stays, increased physical distress,[3] poorer treatment compliance,[4] lower quality of life,[5] and increased desire for hastened death.[6] More severe depression in cancer has also been shown to be a risk factor for death, independent of medical variables.[7] However, as with other medical illnesses, the mediating mechanisms are unknown, and evidence that treatment of depression improves survival rates is lacking.[8]

The literature on treating depression in cancer presents many challenges, including the diagnostic complexity across this severity continuum, in which the clinician must distinguish physical symptoms of cancer from neurovegetative symptoms of depression, existential distress and grief from emotional and cognitive symptoms of depression, functional impairment from decreased activities as a result of anhedonia, and rational thoughts of death from suicidality. Treatment complexity is further compounded by medical and psychosocial factors, such as pain or inadequate social supports that contribute to depression and often need to be addressed before or concurrently with treatment for depressive symptoms. Clinicians must also consider detrimental adverse effects from pharmacotherapy, adverse drug interactions, and treatment compliance issues unique to the cancer context. Practice guidelines on the management of depression in cancer have been based on extrapolation from evidence on the treatment of depression in populations without cancer and limited to general statements on the overall effectiveness of antidepressants and psychological therapies, with few specific recommendations to guide practice for depression in patients with cancer.

This update to a previous Cancer Care Ontario Program in Evidence-Based Care (PEBC) guideline[9] presents recommendations for management of depression in adult patients with cancer who are at any stage in their treatment and have also been diagnosed with a major depressive disorder on the basis of a structured diagnostic interview, or who have a suspected depressive disorder because they met a threshold on a validated depression rating scale. It incorporates the most recently published literature and includes, for the first time, recommendations based on newer studies of collaborative care interventions, and it integrates practical management tools to assist clinicians in selecting appropriate specific treatments for depression in patients with cancer. This guideline was based on the results of a systematic review that explored this clinical research question: What is the efficacy of treatment (pharmacologic and/or psychological) for depression in adult patients with cancer?

GUIDELINE DEVELOPMENT METHODS

Literature Search Strategy and Quality Assessment

The working group, which consisted of individuals with expertise in nursing, health research methodology, psychiatry, and psychology, carried out a systematic review of Web sites of guideline developers, relevant cancer agencies, and MEDLINE and EMBASE from January 2005 to January 2015 using search terms related to depression and cancer. English language systematic reviews of randomized controlled trials (RCTs) or individual RCTs that reported at least one of the primary outcomes of interest were eligible for inclusion. Guideline quality was assessed with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[10] Systematic reviews were assessed for quality by using the Assessment of Multiple Systematic Reviews (AMSTAR) tool,[11] and quality was assessed by using the Cochrane Risk of Bias tool and other quality indicators.[12]

Literature search results

The literature search located two relevant clinical practice guidelines that scored well on the AGREE II instrument.[13,14] These guidelines were based on systematic reviews that scored highly on the AMSTAR tool. Twenty-five RCTs from database inception (1964 for MEDLINE and 1974 for EMBASE) to January 2015 met the inclusion criteria and composed the evidence base. Studies were categorized as pharmacologic interventions (n = 8), psychological interventions (n = 9), or collaborative care interventions (n = 8).

Synthesis of Evidence and Development of Recommendations

Data were extracted by a project methodologist (E.B.K. or H.K.) and verified by a project research assistant. A summary of the evidence base appears in Table 1, and detailed results of the systematic review and meta-analyses will be published separately (Li, manuscript submitted for publication). High-quality evidence was found for collaborative care interventions because

Table 1. Summary of Key Evidence for Recommendations 1 to 8

Recommendation	Evidence Base	Level of Evidence*	Strength of Consensus
1. Screening of patients with cancer for distress or depression	Screening for Distress, the 6th Vital Sign,[15-21] (literature not systematically reviewed).	II	High
2. General management principles	Two CPGs[13,14] (literature not systematically reviewed)	IV	High
3. Pharmacologic or psychological/psychosocial interventions	Meta-analysis of eight pharmacologic[22-29] and nine psychological therapy RCTs[30-38] (Li, manuscript submitted for publication), two CPGs[13,14]	I	High
4. Depression severity and a stepped care approach	One CPG[13]	IV	High
5. Collaborative care interventions	Meta-analysis of results of four RCTs[39-46] (ref to original meta-analysis to be added)	I	Moderate
6. Specialist referral	Two CPGs[13,14]	IV	High
7. Selection of psychological therapies	One CPG and relevant systematic reviews[13,14,47,48]	I	High
8. Use of antidepressant medication	One CPG[13] and relevant systematic reviews[47,49-54]	I	High

Abbreviations: CPG, clinical practice guideline; RCT, randomized controlled trial.
*According to the Canadian Network for Mood and Anxiety Treatments levels of evidence: I, at least two placebo-controlled RCTs and/or meta-analysis; II, at least one RCT with placebo or active comparison group; III, uncontrolled trial; IV, anecdotal reports or expert opinion.

of the larger sample sizes for their RCTs, larger effect sizes, and consistency of results. Lower-quality evidence was found for studies of pharmacologic and psychological interventions because the studies had smaller sample sizes, risk of bias because of lack of blinding, and heterogeneity in interventions and methods of measuring outcomes. Consensus-based recommendations were largely based on low-quality evidence; however, the consensus for these recommendations was high, given their low potential for harm and perceived high potential for benefit. There was a high level of consensus among the working group members for other recommendations, except for collaborative care, which had a moderate level of consensus because of concerns about the feasibility of implementation, given that it would require a substantial reorganization of care delivery. The included Practical Tools (Data Supplement) are based on the consensus opinion of the guideline development group.

Internal Review

The recommendations draft was circulated to a nine-person expert panel that included individuals with expertise in psychology (two), psychiatry (one), nursing and/or psychosocial oncology (two), or service delivery (four). Seven respondents voted to approve the document, and responses were not received from two members of the group. The report was also circulated to the PEBC Report Approval Panel, a three-person panel with clinical, methodologic, and oncology expertise, who approved the document with minor suggested revisions.

External Review

The external review process included a targeted peer review by three clinical and/or methodologic experts to obtain direct feedback on the draft report and a professional consultation that was intended to facilitate dissemination of the final guidance to practitioners.

Targeted peer review

During the development process, three clinical and/or methodologic experts identified by the working group were approached, and they agreed to participate. They were located in Canada, the United Kingdom, and Australia. The draft report and an evaluation questionnaire were sent via e-mail on January 29, 2015. Written comments were invited. The working group reviewed the results and made changes to the draft guideline.

Professional consultation

The professional consultation, conducted between February 3, 2015, and March 2, 2015, asked potential users of the guideline to rate the quality of the guideline, whether they would use and/or

recommend it, whether they perceived barriers or enablers to implementation, and for other comments. Nurse practitioners, nurses, primary care physicians, psychologists, psychiatrists, members of relevant professional organizations, and those with an interest in palliative care were contacted by e-mail to inform them of the survey. Comments and feedback were obtained from 51 practitioners that included family practitioners, nurses, nurse practitioners or advanced practice nurses, a psychologist, a palliative care physician, a program manager, and representatives from professional organizations. Several respondents commented that the guideline was well organized and that the algorithm (Fig 1) was helpful. Some respondents commented on barriers to implementation, including the lower level of evidence for pharmacologic and psychological therapy options, and they also mentioned implementation issues related to inadequate resources.

RECOMMENDATIONS, KEY EVIDENCE, AND QUALIFYING STATEMENTS

The eight recommendations developed in this guideline have been synthesized into a quick reference guide for the initial management of depression in patients with cancer (Fig 1). This management algorithm provides a general approach and practical guidance tool for health care providers treating patients with cancer who present with a depressive disorder. Most of the steps in the algorithm are described in more detail within the recommendations. A summary of the evidence base, level of evidence, and strength of consensus is provided in Table 1.

Recommendation 1. Screening of Patients With Cancer for Depression

Patients with cancer should be screened for depression. Many cancer programs incorporate depression screening into Screening for Distress programs. A clear diagnosis of depression is required to guide treatment. The psychological features that distinguish the continuum of depressive symptoms, ranging from normal sadness to subthreshold depression to major depression, are described in the Data Supplement. To improve health outcomes, screening must be linked to effective interventions.[55]

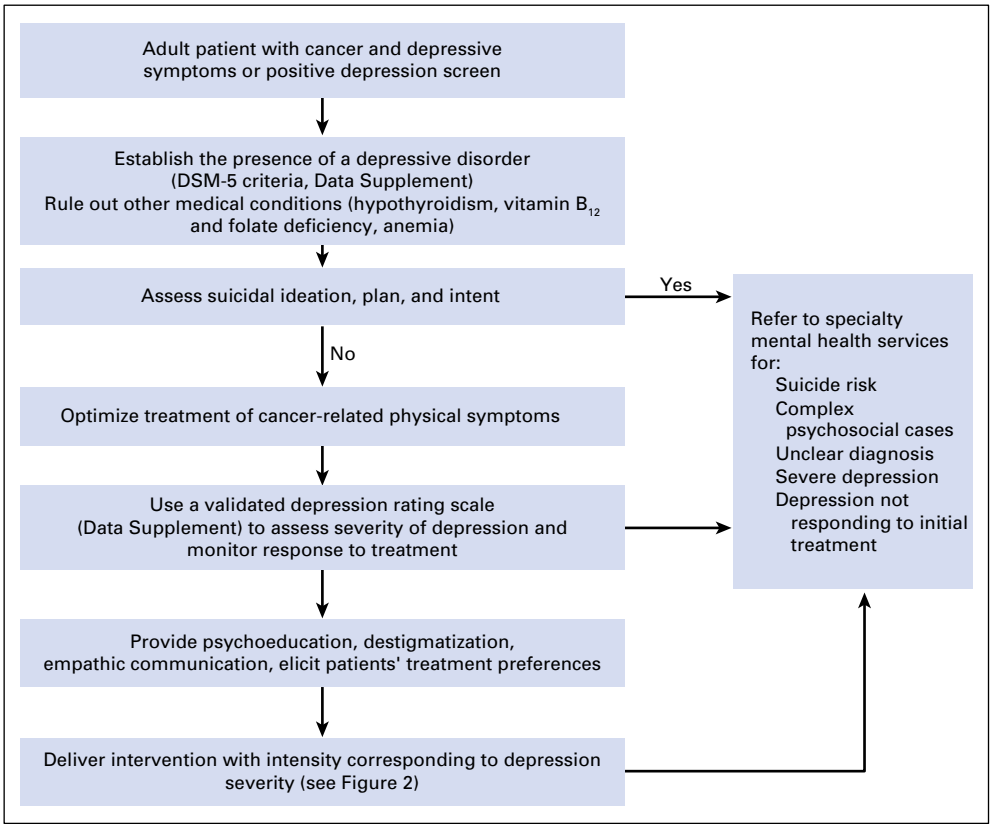

FIG 1. Quick reference algorithm for the initial management of depression in patients with cancer. DSM, *Diagnostic and Statistical Manual of Mental Disorders*.

Qualifying statement for Recommendation 1

The evidence base for the effectiveness of depression screening in reducing depression outcomes in cancer is lacking and is a topic of much debate in the field of distress screening.[13,14] Review of this literature is beyond the scope of this guideline; however, it is the opinion of the members of the working group that lack of evidence is not equivalent to lack of effectiveness.

Recommendation 2. General Management Principles

The following general management principles are recommended:

- Provide psychoeducation about the nature of depression to patients with cancer and consider providing handouts such as those published by the National Cancer Institute.[56]
- Inform patients about the impact of depression on cancer outcomes, including reduced quality of life, intensification of physical symptoms, longer hospital stays, and reduced survival rates.
- Destigmatize clinical depression in cancer by framing it as a serious problem requiring treatment rather than as a personal weakness or failure to cope.
- Investigate medical contributors to depression such as hypothyroidism, or vitamin B12, folate, or iron deficiency.
- Assess and optimize cancer-related physical symptom control.
- Encourage family members' involvement and education, communication with family members regarding prognosis, and resolution of problems within the support network.
- Discuss treatment options, attending to patients' preferences and previous treatment experiences.

Examples of validated scales can be found in the Data Supplement.

Recommendation 3. Pharmacologic or Psychological/Psychosocial Interventions

Patients with cancer who are diagnosed with major depression may benefit from pharmacologic or psychosocial interventions either alone or in combination (Li, manuscript submitted for publication).

Qualifying statements for Recommendation 3

- Psychosocial and pharmacologic interventions for moderate depression are equally effective.[57]
- Pharmacologic interventions are most effective for more severe depression.[58]
- Combined psychosocial and pharmacologic interventions should be considered for severe depression in patients with cancer.[59]

Recommendation 4. Depression Severity and a Stepped Care Approach

Interventions for depression in patients with cancer should be delivered according to a stepped care model. This involves assessment of the severity of depression for each patient (Data Supplement), provision of support and psychoeducation to all patients, and delivery of lower-intensity interventions for persistent subthreshold and mild-to-moderate depression followed by progression to higher-intensity interventions for nonresponsive or moderate-to-severe depression (Fig 2). Low-intensity psychosocial interventions include structured group physical activity programs, group-based peer support or self-help programs, and guided self-help programs based on cognitive behavioral therapy (CBT), behavioral activation, or problem-solving techniques. High-intensity psychosocial interventions include individual or group CBT, behavioral couples' therapy, and individual or group supportive-expressive psychotherapies.

Qualifying statement for Recommendation 4

Antidepressant medication should be reserved for moderate-to-severe depression but can be considered for subthreshold or mild depressive symptoms that persist after initial interventions or that interfere with engagement in cancer treatment.

Recommendation 5. Collaborative Care Interventions

Collaborative care interventions should be considered for patients with cancer who are diagnosed with major depression. Collaborative care involves active collaboration between the oncologist or primary care provider and a patient care manager (nurse, social worker, psychologist), with pharmacologic treatment supervised by a consulting psychiatrist as needed. The care manager provides psychoeducation, delivers structured psychosocial interventions such as behavioral activation or problem-solving therapy, and monitors progress. Weekly case review meetings are held to adjust treatment plans for inadequate improvement. These are multicomponent interventions that can be offered at a range of intensity levels, depending on the presentation of the patient and local resources. The interventions typically include measurement-based care and involve increases in the level or intensity

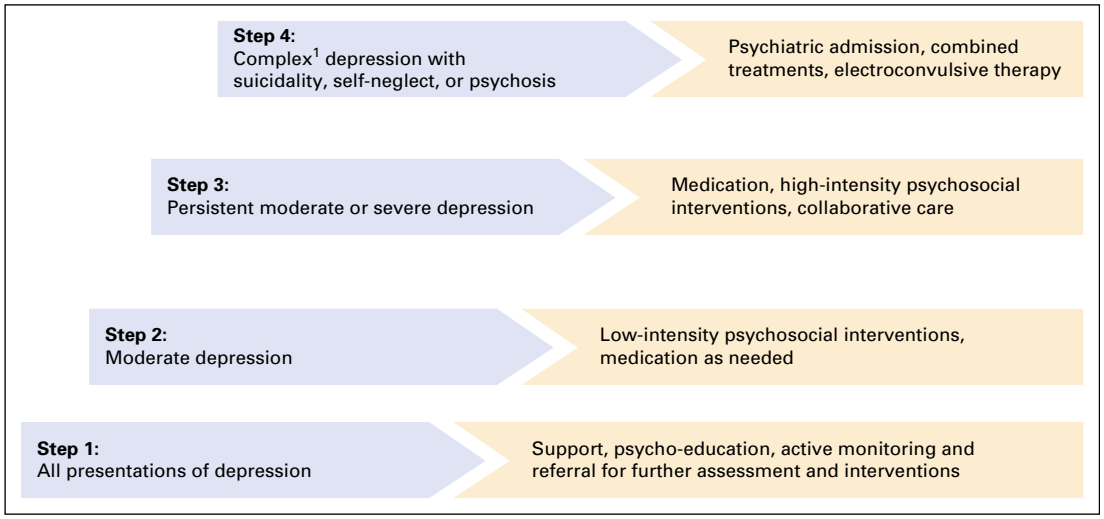

FIG 2. Delivery of intervention corresponding to the Stepped Care Model. *Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors. The stepped care algorithm was adapted from the National Institute for Health and Clinical Care Excellence (NICE) CG91, p.110.[13]

of intervention as needed according to the principles of stepped care.

Qualifying statements for Recommendation 5

- Within a stepped care approach, collaborative care interventions may be most appropriate for patients with cancer and with subthreshold or mild depression persisting after other interventions or with moderate-to-severe depression.
- Implementation of a collaborative care model may require significant reorganization of mental health care service delivery in cancer treatment facilities. Details regarding implementation of a collaborative care model of service delivery are outside the scope of this guideline, but information can be obtained at http://www.teamcarehealth.org/ or http://impact-uw.org/

Recommendation 6. Specialist Referral

In a stepped care model, referral to psychosocial specialists, including mental health specialists, should occur in the following instances:

- When there is risk of harm
- In complex psychosocial cases
- When the patient experiences persistent symptoms after initial intervention
- When diagnosis is unclear
- For delivery of specific psychotherapies that require specialized training

Recommendation 7. Selection of Psychological Therapies

Because there is insufficient evidence for superiority of one modality over another, consensus-based opinion of the members of the working group is that selection of psychological therapy should be based on patient factors and local resource availability.

- Among patients with cancer who present with depressive symptoms, most have mild-to-moderate depression. In the stepped care model, it is recommended that low-intensity interventions (eg, self-help materials such as books or computer programs) be considered first for mild-to-moderate depression.[13]
- Psychological therapies should be delivered by health care professionals competent in the modality, but non–mental health specialists can be trained in basic psychosocial interventions.

Examples of psychological therapies and further details on these therapies are provided in the Data Supplement.

Qualifying statements for Recommendation 7

- Delivery of therapy:
  - Empathic communication, psychoeducation, problem-solving, and behavioral activation are therapeutic

techniques that may be delivered by trained health care professionals.
  - Supportive-expressive and structured psychotherapies (eg, CBT, interpersonal therapy, psychodynamic therapy) require specially trained therapists.
- Patient factors that guide selection:
  - CBT may be useful for patients who want a symptom-based approach.
  - Supportive-expressive therapies may be of value with more psychologically minded patients (ie, patients with the capacity for self-reflection and introspection and the ability to gain insight into their motivations and behaviors).
  - Individual therapies may be more practical for patients who are in the palliative phase.

Recommendation 8. Use of Antidepressant Medication

Do not use antidepressants routinely to treat subthreshold depressive symptoms or mild depression because of the higher risk-benefit ratio at this level of depression severity. Antidepressant medication should be considered first for severe depression. The Data Supplement provides practical guidance on selecting commonly used antidepressants for patients with cancer, including further guidance on antidepressant prescribing practices, classes of antidepressants for use in patients with cancer, and information on antidepressant drug interactions. In clinical practice, selective serotonin reuptake inhibitors such as citalopram or escitalopram should be the first resort because they have the best tolerability and the least potential for drug interactions.

Qualifying statements for Recommendation 8

- Despite the limitations of the evidence base, the members of the working group recognize that both antidepressants and antipsychotic agents are widely prescribed for patients with cancer[60]; this is especially the case for patients with advanced illness.[61] Only case series and open trials have been published for newer antidepressants, such as escitalopram, citalopram, venlafaxine, desvenlafaxine, mirtazapine, bupropion, and duloxetine, which are routinely used in patients with cancer. Indications for these agents include not only depression but also anxiety and hot flashes in the case of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors,[62] neuropathic pain with serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants,[63] and nausea, sleep disturbances, and appetite enhancement with mirtazapine and atypical antipsychotics.[64]
- The members of the working group discussed concerns about interactions between tamoxifen and antidepressants that inhibit cytochrome P450 2D6 (CYP2D6), thus reducing the conversion of tamoxifen to the active metabolite endoxifen and increasing the risks of recurrence and mortality. However, meta-analyses have suggested that the reductions in endoxifen do not translate into increased breast cancer recurrence rates or mortality rates, possibly because the therapeutic dosing of tamoxifen fully saturates the estrogen receptor.[65,66] Existing recommendations are conservative and caution against using potent CYP2D6 inhibitors (eg, paroxetine, fluoxetine, high-dose sertraline, bupropion) with tamoxifen. Although these antidepressants are not recommended as first-line agents, clinical judgment can be exercised in their use with patients for whom safer alternatives are not an option, after discussion with the treating oncologist has occurred and informed consent has been obtained. More potent CYP2D6 inhibitors may be safer to use in postmenopausal women or women with a known extensive metabolizer CYP2D6 genotype.[67] When possible, it is prudent to prefer antidepressants with low CYP2D6 inhibition (eg, citalopram/escitalopram, venlafaxine/desvenlafaxine, low-dose sertraline [< 100 to 150 mg/day] or mirtazapine) as first-line agents.

DISCUSSION

This guideline does not include recommendations for the management of depressive symptoms in the normative or nonpathologic range of severity. Studies that address this level of depression have been highly heterogeneous, group-as-a-whole studies and were beyond the scope of this systematic review. Such studies have been extensively reviewed previously,[64] with management recommendations provided in other guidelines.[68]

Recommendations for the management of threshold depressive disorders are integrated into the quick reference guide provided in Figure 1. This management algorithm includes steps not fully articulated in these recommendations because they represent accepted standard of care and have been extensively reviewed elsewhere.[69] For example, assessment for suicidality requires either direct inquiry or the use of

depression rating scales that contain items assessing suicidal ideation (eg, Patient Health Questionnaire 9, Beck Depression Inventory II). Further guidance on the management of suicidal ideation in patients with cancer is available through the International Psycho-Oncology Society's core curriculum Webcast series.[70] Empathic communication by health care providers is an important component of management at all levels of depression severity in patients with cancer. The significance of good patient-provider communication has been extensively reviewed in other guidelines,[71] and excellent online training resources for cancer care providers are available.[72] More specific management tools, including strategies for the management of depression in patients who do not respond to initial treatments, are provided in Appendices 1 to 7 in the Data Supplement. These tools were developed according to consensus by the members of the working group. The working group for this guideline did not include patient representatives. For future updates of this guideline, it would be advisable to include a patient representative in the working group in addition to clinical and methodologic experts.

There has been a dearth of new and high-quality individual pharmacotherapy or psychotherapy research in this field since the previous version of this guideline was published.[9] Investigators who conduct antidepressant trials in patients with cancer have reported lack of success in recruiting subjects[73] and numerous potential barriers to study completion, including patient and clinician refusal to consider placebo trials for medications that are already in widespread clinical use.[73] As a result, the literature continues to accumulate modestly powered open-label nonrandomized pilot studies. Psychological intervention studies are similarly hampered by difficulties in establishing appropriate nonintervention control groups in a population with both depression and cancer and strong placebo effects in comparative control groups.

The recommendations in this updated guideline imply a significant restructuring of care delivery for patients with cancer who are experiencing depression, including routine screening to improve access to services, intervention based on a stepped care approach, delivered within a multidisciplinary collaborative care model, and ongoing monitoring to ensure timely intervention. This level of reorganization may be a significant challenge for institutions; practitioners who responded to our feedback survey reported that barriers to implementation included the lower level of evidence for pharmacologic and psychological therapy options and inadequate resources to fully implement organizational components of the recommendations. A renewed research agenda to strengthen the evidence base around these specific components is urgently needed to justify the investment of resources for this reorganization. Effective management of depression in cancer is required to optimize patient quality of life, improve cancer outcomes, and support a person-centered model of cancer care delivery. JOP

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Depression in Patients With Cancer: A Clinical Practice Guideline

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