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Guideline #19-4 IN REVIEW

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Management of Depression in Patients with Cancer

M. Li, E.B. Kennedy, N. Byrne, C. Gerin-Lajoie, E. Green, M. R. Katz, H. Keshavarz, S. M. Sellick, and the Management of Depression in Patients with Cancer Expert Panel

Report Date: May 11, 2015

An assessment conducted in November 2024 placed Evidence-based Series (EBS) 19-4 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 19-4 consists of 3 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/176

Section 1:	**Guideline Recommendations**
Section 2:	**Systematic Review**
Section 3:	**Guideline Development and External Review**

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Guideline #19-4: Section 1

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Management of Depression in Patients with Cancer: Guideline Recommendations

M. Li, E.B. Kennedy, N. Byrne, C. Gerin-Lajoie, E. Green, M. R. Katz, H. Keshavarz, S. M. Sellick, and the Management of Depression in Patients with Cancer Expert Panel

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GUIDELINE OBJECTIVE

To improve the quality and consistency of the management of depression for patients with cancer in Ontario.

TARGET POPULATION

Adult patients with cancer who are diagnosed with a major depressive disorder based on a structured diagnostic interview, or who have a suspected depressive disorder based on meeting a threshold on a validated depression rating scale.

INTENDED USERS

This guideline is intended to be used by mental health care providers (psychiatrists, psychologists), palliative care professionals, oncologists, oncology nurses, nurse practitioners, psychosocial intervention providers, primary care providers, and community nurses.

RESEARCH QUESTION

What are the effective treatments (pharmacological and/or psychological) for depression in the adult population with cancer?

INTRODUCTION

Knowing of the significant prevalence of depressive disorders in patients with cancer and of the clinical relevance of depression to health outcomes, the Program in Evidence-based Care (PEBC) developed an initial guideline for the management of depression in patients with cancer, which was published in 2007 [1]. The recommendations contained in this section are an update of the 2007 recommendations, based on the results of an updated systematic review (Section 2) and the consensus opinion of the members of the project Working Group. While this guideline summarizes the best available evidence to guide the management of depression in patients with cancer, members of the Working Group acknowledge the challenge of conducting research in an area of diagnostic complexity across the depression severity continuum. Clinicians must distinguish physical symptoms of cancer from neurovegetative symptoms of depression, functional impairment from decreased activities due to 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 prior to or concurrently with depressive symptoms. Clinicians must also consider potential detrimental pharmacotherapy side effects, drug interactions, and treatment compliance issues unique to the cancer context.

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 (Figure 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 tool are described in more detail within the recommendations. Recommendations and Practical Tools can be found at the following locations within Section 1:

TAXONOMY

Depressive disorders consist of a continuum of symptoms that mental health researchers have classified into categories. This remains an area of ongoing debate and modifications, as evidenced by revisions in the *International Classification of Diseases, 10th edition (ICD-10) Classification of Mental and Behavioural Disorders* [2] and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-4) [3] of the American Psychiatric Association classification systems. Also, various guidelines have adopted pragmatic subdivisions of dimensions that may not be perfectly aligned with each other.

While the target population of this systematic review is interview diagnosed major depression or depression severity above threshold on depression rating scales, the recommendations have been adapted from the National Institute for Health and Care Excellence (NICE) Clinical Guideline 91 (CG91), *Depression in Adults with a Chronic Physical Health Problem* [4], which are based on DSM-4-TR and include other mood disorders. The NICE stepped care model describes five steps based on depression severity, duration and course, which can be aligned with the care pathways mapped out the Canadian Association of Psychosocial Oncology's depression symptom management guideline (SMG), *A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer* [5], accordingly:

NICE stepped care model [4]	SMG care pathways [5]
Step 1	Mild
Step 2	Moderate
Step 3-4	Severe

Figure 1. Quick reference management algorithm.

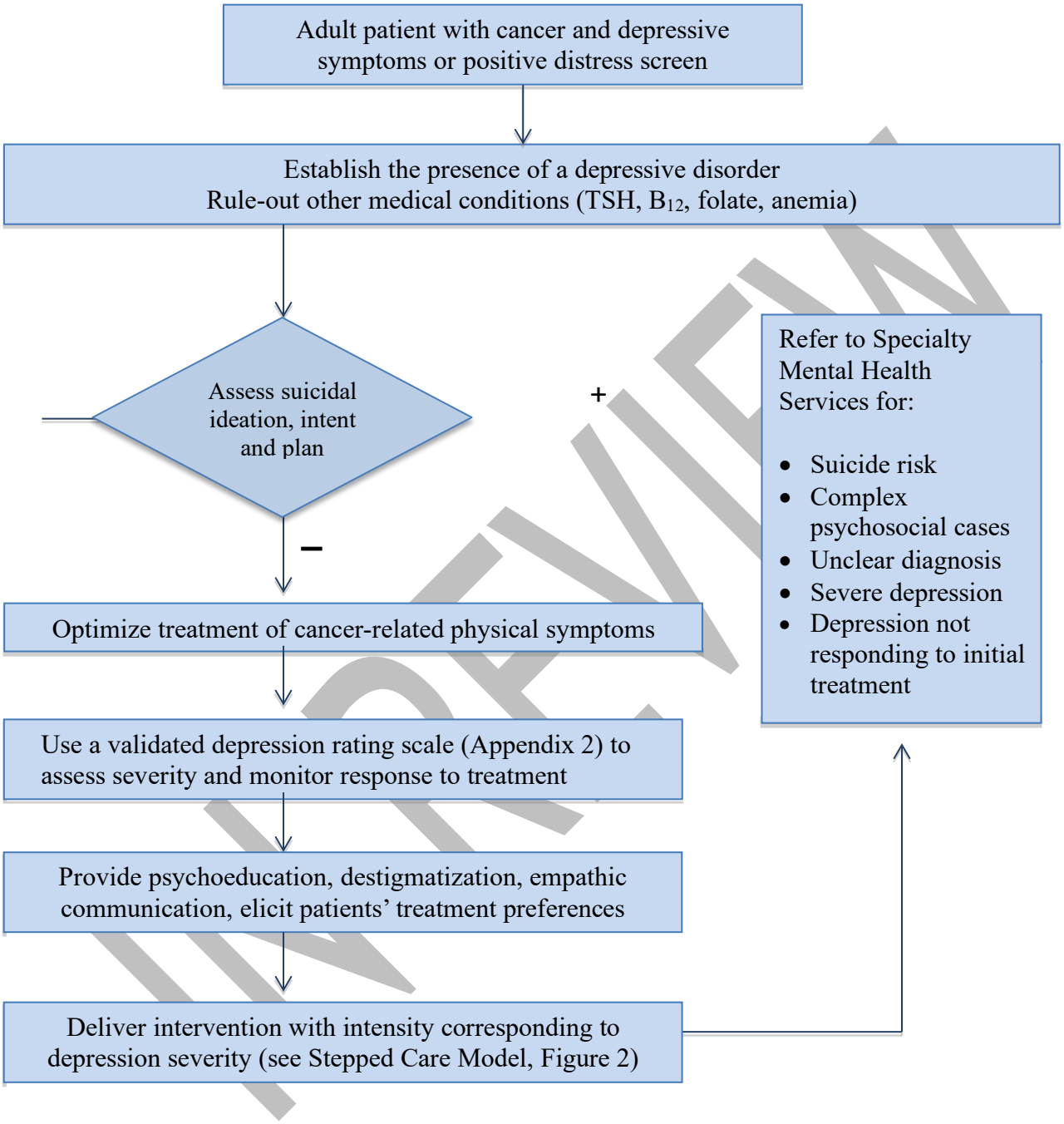
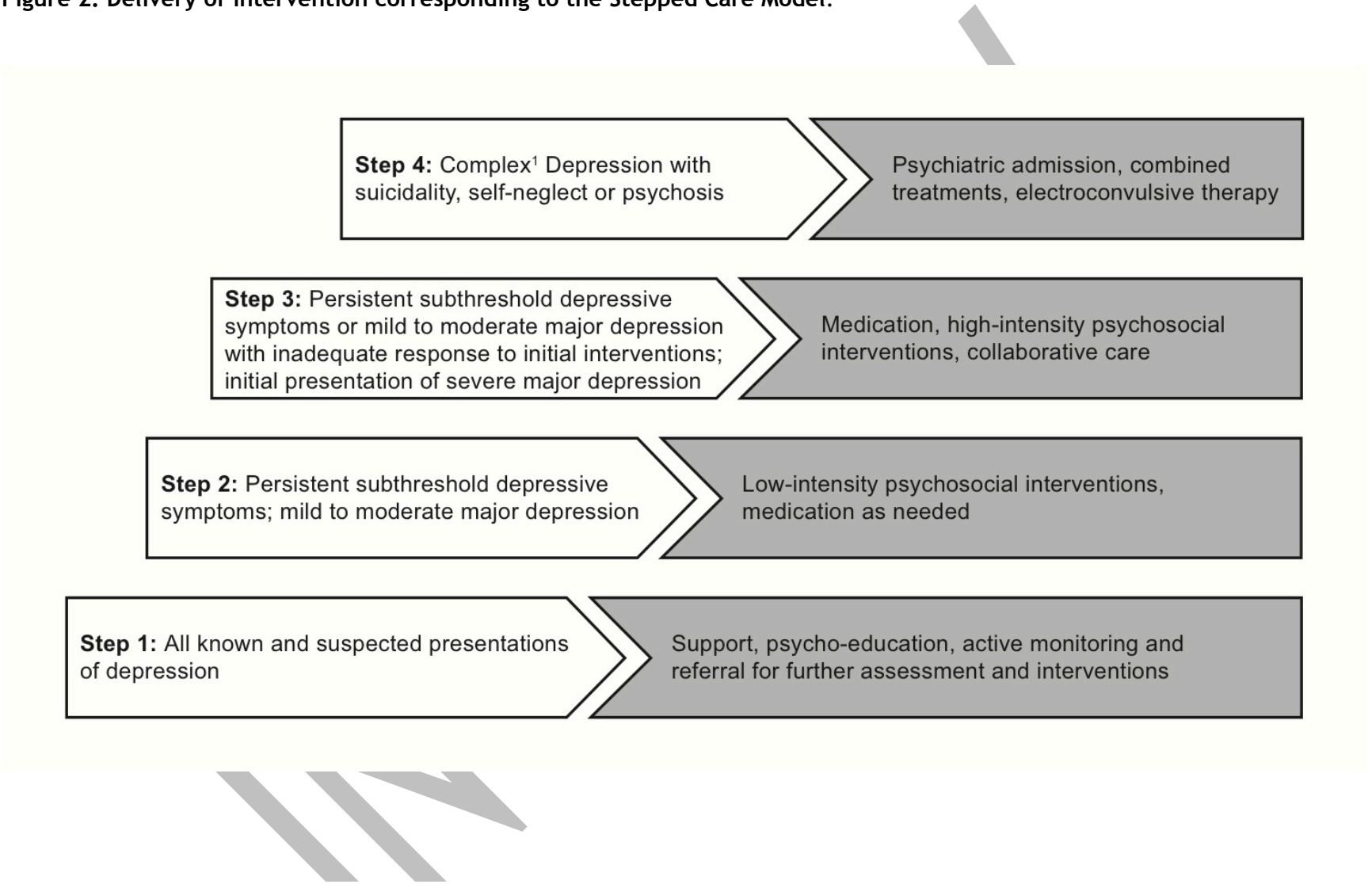


Figure 2. Delivery of intervention corresponding to the Stepped Care Model.



[1]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. Stepped care algorithm adapted from NICE CG91, p.110 [1].

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1. Screening of patients with cancer for distress or 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. See Appendix 3 for psychological features that distinguish the continuum of depressive symptoms. To improve health outcomes, screening must be linked to effective interventions [6].

Summary of Key Evidence for Recommendation 1

Screening for Distress, the 6th Vital Sign [7] is a standard of care in multiple cancer care guidelines. This recommendation is the suggestion of the members of the Working Group, based on recommendations contained within these publications: the NICE *Guidance on Cancer Services* [8]; the National Comprehensive Cancer Network's *Distress Management* [9]; the Institute of Medicine's *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs* [10] Canadian Association of Psychosocial Oncology, *Standards of Psychosocial Health Services for Persons with Cancer and their Families* [11]; and Cancer Care Ontario, *Psychosocial Health Care for Cancer Patients and Their Families* [12].

Qualifying Statements for Recommendation 1

It is recognized that the evidence base for the effectiveness of depression screening in reducing depression outcomes in cancer is lacking and is a topic of much recent 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.

These guidelines apply to patients who are in the moderate to severe care pathways according to *A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer* [5].

Recommendation 2. General management principles

The following general management principles are recommended:

1. Provide psychoeducation about the nature of depression in patients with cancer and consider providing handouts such as those published by the National Cancer Institute [15].
2. 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 [16].
3. Destigmatize clinical depression in cancer by framing it as a serious problem requiring treatment, rather than as a personal weakness or failure to cope.
4. Investigate medical contributors to depression such as hypothyroidism, or vitamin B_{12}, folate, or iron deficiency.
5. Assess and optimize cancer-related physical symptom control.
6. Encourage family members' involvement and education, communication with family members regarding prognosis, and resolution of problems within the support network.
7. Discuss treatment options, attending to patients' preferences and previous treatment experiences.
8. Consider use of a validated depression rating scale to monitor change over time (Appendix 2).

Summary of Key Evidence for Recommendation 2

Recommendations for general management are the consensus-based opinion of the members of the Working Group and are adapted from the NICE Clinical Guideline 91 (CG91), *Depression in Adults with a Chronic Physical Health Problem* [4], and from the European Palliative Care Research Collaborative (EPCRC) guideline *The Management of Depression in Palliative Care* [17].

Recommendation 3. Pharmacological or psychological/psychosocial interventions

Patients with cancer who are diagnosed with major depression may benefit from pharmacological or psychosocial interventions either alone or in combination.

Summary of Key Evidence for Recommendation 3

Insufficient new evidence was found in this updated systematic review to alter the conclusions of the previous version of this guideline regarding pharmacological therapies for patients with both cancer and depression. The evidence derived from the small number of placebo-controlled randomized trials conducted in patients with cancer demonstrates a significant overall beneficial effect of antidepressants on depression (odds ratio, 1.91; 95% confidence interval, 1.09 to 3.36). In the absence of a strong cancer-specific evidence base, this recommendation is the consensus of the members of the Working Group, and is consistent with NICE CG91 [4] and EPCRC guidelines [17] on the management of depression in patients with medical comorbidity and palliative care, respectively.

A significant difference was found between means for psychological interventions evaluated after two to 13 weeks (standardized mean difference [SMD] –1.40 [95% CI –2.50 to –0.29]), but the difference did not remain statistically significant when the effects were evaluated after longer time periods, ranging from six to 12 months (SMD –0.55, [95% CI –1.14 to 0.04]). The level of heterogeneity in these analyses was high, with I^2 values of 96% and 80%, respectively.

Qualifying Statements for Recommendation 3

- The effectiveness of psychosocial and pharmacological interventions for moderate depression is equal [18].
- Pharmacologic interventions are most effective for more severe depression [19].
- Combined psychosocial and pharmacologic interventions should be considered for severe depression in patients with cancer [20].

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 (Appendix 3), provision of support and psychoeducation to all patients, 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 (Figure 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 behavioural therapy (CBT), behavioural activation, or problem-solving techniques. High-intensity psychosocial interventions include individual or group CBT, behavioural couples' therapy, and individual or group supportive-expressive psychotherapies.

Summary of Key Evidence for Recommendation 4

This recommendation is based on NICE CG91 [4]. For more information on stepped care models for treatment of depression in patients with a physical illness, see NICE CG91, Chapter 6.

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 persisting 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 pharmacological treatment supervised by a consulting psychiatrist as needed. The care manager provides psychoeducation, delivers structured psychosocial interventions such as behavioural activation or problem-solving therapy, and monitors progress. Weekly case review meetings are held to adjust treatment plans for inadequate improvement. These are multi-component interventions, which can be offered at a range of intensity levels, depending on the presentation of the patient and local resources. They typically include measurement-based care, and involve increases in the level or intensity of intervention as needed according to the principles of stepped care.

Summary of Key Evidence for Recommendation 5

A meta-analysis of six reports of four randomized trials of collaborative care interventions in patients with major depression and cancer found that patients receiving the collaborative care intervention (compared with usual care or enhanced usual care) were significantly more likely to experience a 50% reduction in score on a validated depression rating scale, had lower mean scores, and were significantly more likely to experience remission of depression at time periods ranging from three to 24 months (Section 2, Figures 4 to 6, Section 2, Appendix 7, Figures 1 to 14). Most of the patients in these studies had at least moderately severe depression at baseline.

Qualifying Statements for Recommendation 5

- Within a stepped care approach, collaborative care interventions may be most appropriate for patients with cancer and with subthreshold/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:

1. When there is risk of harm,
2. In complex psychosocial cases,
3. Where the patient experiences persistent symptoms after initial intervention,

4. When diagnosis is unclear,
5. For delivery of specific psychotherapies requiring specialized training.

Summary of Key Evidence for Recommendation 6

This recommendation was adapted by the Working Group from EPCRC recommendation 2.6 (Refer to a mental health specialist if) [17] and NICE CG91 recommendation 5.6.1.12 (Risk assessment and monitoring) [4].

Recommendation 7. Selection of psychological therapies

Because there is insufficient evidence for superiority of one modality over another, selection of psychological therapy should be based on patient factors and local resource availability.

- Among patients with cancer presenting with depressive symptoms, most are mild to moderate. The stepped care model recommends that psychological interventions be considered first for mild to moderate depression [21].
- 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.

Summary of Key Evidence for Recommendation 7

This recommendation is the consensus-based opinion of the members of the Working Group. Examples of psychological therapies are provided in Appendix 4.

Qualifying Statements for Recommendation 7

- Delivery of therapy:
    - Empathic communication, psychoeducation, problem-solving, and behavioural activation are therapeutic techniques that may be delivered by trained health care professionals.
    - Supportive-expressive and structured psychotherapies (e.g., CBT, interpersonal therapy, psychodynamic therapy) require specially trained therapists.
- Patient factors guiding selection:
    - CBT may be useful for patients wanting a symptom-based approach.
    - Supportive-expressive therapies may be of value with more psychologically minded patients (i.e. patients with the capacity for self-reflection and introspection, and the ability to gain insight into their motivations and behaviours).
    - Individual therapies may be more practical in 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, due to the higher risk-benefit ratio at this level of depression severity. Antidepressant medication should be considered first for severe depression. Table 1 provides practical guidance on selecting commonly used antidepressants for patients with cancer (see Appendix 5, Appendix 6, and Appendix 7 for further guidance on antidepressant prescribing practices, classes of antidepressants for use in cancer patients, and information on antidepressant drug interactions, respectively). In clinical practice, a selective serotonin

reuptake inhibitor (SSRI) such as citalopram/escitalopram should be the first resort due to best tolerability and the least potential for drug interactions.

Table 1. Standard first-line antidepressants for patients with cancer.

Generic Name	Standard Adult Dose	Therapeutic Considerations
Citalopram/ Escitalopram	Start: 10 to 20 mg daily (od) / (5 to 10 mg nightly [qhs]) Goal: 20 to 40 mg / (10 to 20 mg) Max: 40 mg od / (20 mg qhs)	• May help with hot flashes • Escitalopram may have more rapid onset than other SSRIs (1 to 3 weeks)
Venlafaxine/ Desvenlafaxine	Start: 37.5 to 75 mg mornings (qam)/ (50 mg) Goal: 75 to 225 mg / (50 to 100 mg) Max: 300 mg qam / (100 mg)	• Optimal choice for patients on tamoxifen (see qualifying statement below) • Consider for prominent hot flashes
Bupropion XL	Start: 150 mg qam Goal: 150 to 300 mg Max: 450 mg qam	• Consider for prominent fatigue • Aids sexual function • Smoking cessation aid • Weight neutral
Duloxetine	Start: 30 mg qam Goal: 30 to 60 mg Max: 120 mg qam	• Separate indications for neuropathic and chronic pain
Mirtazapine	Start: 7.5 to 15 mg orally (po) qhs Goal: 15 to 45 mg Max: 60 mg po qhs	• Consider for prominent insomnia, anorexia/cachexia, anxiety, nausea, diarrhea, pruritus • Rapid dissolve formulation available

Summary of Key Evidence for Recommendation 8

This recommendation is based on the consensus opinion of the members of the Working Group, supported by NICE CG91 [4] and other guidelines and reviews on pharmacotherapy in medical and cancer populations [22]. 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 [23,24]; this is most particularly the case for patients with advanced illness [25]. 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 cancer patients. Indications for these agents include not only depression but also anxiety and hot flashes in the case of SSRIs and serotonin-norepinephrine reuptake inhibitors [26,27], neuropathic pain with serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants [28], and nausea, sleep disturbances, and appetite enhancement in the case of mirtazapine and atypical antipsychotics [27].

Qualifying Statement for Recommendation 8

Some studies have raised concerns about interactions between tamoxifen and antidepressants that inhibit cytochrome P450 2D6 (CYP2D6), reducing the conversion of tamoxifen to the active metabolite endoxifen and, thereby, increasing the risks of recurrence

and mortality [29,30]. 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 [31,32]. Existing recommendations have been conservative, cautioning avoidance of potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, high-dose sertraline, bupropion) with tamoxifen. Although these antidepressants are not recommended as first-line agents, clinical judgement 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 been obtained. More potent CYP2D6 inhibitors may be safer to use in postmenopausal women or women with a known extensive metabolizer CYP2D6 genotype [33]. When possible, it is prudent to prefer antidepressants with low CYP2D6 inhibition (e.g., citalopram/escitalopram, venlafaxine/desvenlafaxine, or mirtazapine) as first-line agents.

DISCUSSION

This guideline does not include recommendations for the management of depressive symptoms in the normative or nonpathological range of severity. Studies addressing 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 in previous publications [34,35], with management recommendations provided in other guidelines [5].

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. For example, assessment for suicidality requires either direct inquiry, or the use of depression rating scales that contain items assessing suicidal ideation (e.g., 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 [36]. 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 [37] and excellent online training resources for cancer care providers are available [38]. 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 accompanying this guideline. These tools were developed by consensus by the members of the Working Group.

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. Investigators conducting antidepressant trials in patients with cancer have reported lack of success in recruiting subjects [39] and report numerous potential barriers to study completion, including patient and clinician refusal to consider placebo trials for medications that are already in widespread clinical use [39]. As a result, the literature continues to accumulate modestly powered open-label nonrandomized pilot studies, such as a 2014 study of citalopram and mirtazapine [40]. Psychological intervention studies are similarly hampered by difficulties establishing appropriate nonintervention control groups in a population with both depression and cancer and strong placebo effects in comparative control groups.

Despite the decades-long history of psychosocial oncology research, little has changed over the past decade and high-quality pharmacotherapy or psychotherapy studies on the treatment of depression in patients with cancer are still lacking. As a result, clinical practice must be guided by the existing evidence base and must be extrapolated from evidence of treatment efficacy in primary psychiatric and other medical populations. Recent research in this field has shifted to the study of more effective models of interprofessional collaborative care delivery.

Effective management of depression in cancer is required to optimize patient quality of life, improve cancer outcomes, and support a person-centred model of cancer care delivery.

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PRACTICAL TOOLS (APPENDICES 1-7)

Appendix 1. DSM-5 Diagnostic Criteria for Major Depressive Episode.

I. DSM-5 diagnostic criteria for a major depressive episode (A and B criteria only)	
A. At least five of the following symptoms, present during the same two-week period, representing a change from previous functioning, each present nearly every day; and at least one of the symptoms is either (1) or (2). Note: Do not include symptoms that are clearly attributable to another medical condition. **1.** Depressed mood most of the day **2.** Markedly diminished interest or pleasure in almost all activities most of the day **3.** Significant weight loss or gain (change of >5% in a month), or decrease or increase in appetite **4.** Insomnia or hypersomnia **5.** Psychomotor agitation or retardation **6.** Fatigue or loss of energy **7.** Feelings of worthlessness or excessive or inappropriate guilt **8.** Diminished ability to think or concentrate, or indecisiveness **9.** Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation, or a suicide attempt or plan **B.** Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	
II. DSM-5 depression severity criteria	
Subthreshold depressive symptoms	Fewer than five symptoms of depression
Mild depression	Few, if any, symptoms in excess of the minimum required to make the diagnosis and symptoms result in only minor functional impairment
Moderate depression	Symptom number/intensity or functional impairment are between 'mild' and 'severe'
Severe depression	Most symptoms and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms

DSM-5 = the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [41]

Appendix 2. Select Validated Depression Screening Scales.

Measure	Scoring, Cut score in Cancer (Sensitivity/Specificity)	Comments
Hamilton Rating Scale for Depression (HRSD) [42]	Mild: 7 to 17 Moderate: 18 to 24 Severe: >25 Cut score: 10 (100/67) [43]	• 24-item measure, 17 items scored • Clinician-rated • Measures low mood, anxiety, insomnia, and somatic domains
Center for Epidemiologic Studies Depression Scale (CES-D) [44]	Range: 0 to 20, higher scores indicating greater severity Cut score: 16 (100/67) [43]	• 20-item self-report • Measures negative affect, well-being, somatic and interpersonal symptoms • Not congruent with DSM-5
Patient Health Questionnaire 9 (PHQ-9) [45]	Mild: >5 Moderate: >10 Moderately Severe: >15 Severe: >20 Cut score: 8 (93/81) [46]	• Nine-item self-report • 100% concordant with DSM-5 diagnostic criteria • Includes diagnostic algorithm
Hospital Anxiety and Depression Scale (HADS) [47]	Normal: 0 to 7 Mild: 8 to 10 Moderate: 11 to 14 Severe: 15 to 21 Cut score on depression subscale: 7 (86/81) [48]	• 14-item self-report • Separate anxiety and depression subscales • Separate scoring ranges for total HADS • Excludes somatic symptoms which may falsely elevate scores in cancer patients
Beck Depression Inventory II (BDI-II) [49]	Minimal: <14 Mild: 14 to 19 Moderate: 20 to 28 Severe: >29 Cut scores: 18 (96/89); 22 (92/100) [43]	• 21-item self-report • Assesses behavioural, cognitive, and somatic domains • Preponderance of somatic symptoms

Appendix 3. Psychological Features Distinguishing the Continuum of Depression.

Normal Sadness →	Subthreshold Depression →	Major Depression
• Maintains intimacy and connection • Believes that things will get better • Can enjoy happy memories • Sense of self-worth fluctuates with thoughts of cancer • Looks forward to the future • Retains capacity for pleasure • Maintains will to live	• Shows similar low mood presentation as in major depression but does not meet full criteria for symptom number or duration • Includes persistent depressive disorder if > 2 years duration • Includes episodes lasting < 2 weeks • May include adjustment disorder, which displays marked distress or functional impairment, but is often self-limited, and does not meet other criteria for major depression • Note: the distinction between subthreshold depression and major depression of mild severity may be arbitrary	• Feels isolated • Feeling of permanence • Excessive guilt and regret • Self-critical ruminations/loathing • Constant, pervasive and nonreactive sadness • Sense of hopelessness • Loss of interest in activities • Suicidal thoughts/behaviour

Appendix 4. Psychological Interventions for Depression in Cancer.

The following are selected examples and definitions of psychological interventions frequently used for depression in cancer. Not all modalities are currently supported by a research evidence-base in cancer patients, but their use is extrapolated from the treatment of depression in psychiatric and other medical populations. In practice, various components of different models may be used. For a more complete list, and levels of evidence for the interventions, refer to sources: NICE CP91 [4] and Canadian Network for Mood and Anxiety (CANMAT) clinical guidelines for management of depressive disorder in adults [50].

- **Group-based peer support (self-help) programs** [51-53] for patients with cancer and mild to moderate depression, and for patients with subthreshold depressive symptoms that complicate cancer care should:
    - be delivered to groups of patients with a common cancer type;
    - focus on sharing experiences and feelings associated with having cancer;
    - be supported by practitioners who should facilitate attendance at the meetings, have knowledge of the patients' cancer and its relationship to depression, and review the outcomes of the intervention with the individual patients; and
    - consist typically of one session per week delivered over a period of eight to 12 weeks.

- **Structured group physical activity programs** [53-56] for patients with mild to moderate depression and cancer, and for patients with subthreshold depressive symptoms that complicate care of the cancer, should:
    - be modified (in terms of duration of the program, and frequency and length of the sessions) for different levels of physical ability as a result of the cancer in liaison with the team providing care for the cancer;
    - be delivered in groups with support from a competent practitioner;
    - consist typically of two or three sessions per week of moderate duration (45 minutes to one hour) over 10 to 14 weeks (average 12 weeks); and
    - Be coordinated or integrated with any rehabilitation program for the cancer.

- **Mindfulness Based Stress Reduction and Mindfulness Based Cognitive Therapy** [57,58]: Mindfulness has roots in Buddhist meditation and is based on adopting a moment-to-moment, nonjudgmental awareness. Thoughts, feelings and behaviours are observed with gentle curiosity, rather than analysis. Mindfulness Based Stress Reduction combines stress reduction with mindfulness meditation techniques. Mindfulness Based Cognitive Therapy combines mindfulness meditation with cognitive therapy techniques.

- **Cognitive Behavioural Therapy (CBT)** [59] **:** CBT is a discrete, time-limited, structured psychological intervention, derived from the cognitive behavioural model of affective disorders and in which the patient:

- works collaboratively with the therapist to identify the types and effects of thoughts, beliefs, and interpretations on current symptoms, feeling states and/or problem areas;
- develops skills to identify, monitor and then counteract problematic thoughts, beliefs, and interpretations related to the target symptoms/problems; and
- learns a repertoire of coping skills appropriate to the target thoughts, beliefs and/or problem areas (i.e., cognitive restructuring and behavioural exposure).

- **Behavioural activation therapy (BAT)** [60]: BAT is based on the premise that depression is a consequence of compromised environmental sources of positive reinforcement. Treatment involves increasing patient activity and access to rewarding experiences, evaluating the consequences of depressive versus nondepressive behaviours, and de-emphasizing particular cognitions or mood states as necessary for re-engaging with one's environment.

- **Problem solving therapy (PST)** [61]: PST is a discrete, time-limited, structured psychological intervention, which focuses on learning to cope with specific problem areas and in which therapist and patient work collaboratively to identify and prioritize key problem areas, to break problems down into specific, manageable tasks, to problem-solve, and to develop appropriate coping behaviours.

- **Interpersonal therapy (IPT)** [62]: IPT is a discrete, time-limited, structured psychological intervention, derived from the interpersonal model of affective disorders that focuses on interpersonal issues and in which the therapist and patient:
  - work collaboratively to identify the effects of key problematic areas related to interpersonal conflicts, role transitions, grief and loss, and social skills, and their effects on current symptoms, feeling states and/or problems;
  - seek to reduce symptoms by learning to cope with or resolve these interpersonal problem areas.

- **Behavioural couples' therapy:** Consider for patients with a regular partner when the relationship may contribute to the depression. Therapy is based on behavioural principles, and an adequate course should be 15 to 20 sessions over five to six months. Therapy is based on a model of interactional processes in relationships where:
  - the intervention aims to help participants understand the effects of their interactions on each other as factors in the development and/or maintenance of symptoms and problems
  - the aim is to change the nature of the interactions so that the participants may develop more supportive and less conflictual relationships.

- **Supportive-expressive therapy** [63]: Supportive-expressive therapy in the context of oncology patients involves the creation of a supportive environment in which participants are encouraged to confront their problems, strengthen their relationships, and find enhanced meaning in their lives. Emotionally expressive, rather than didactic, discussion regarding shared experiences is facilitated around themes such as fears of dying and death, reordering life priorities, improving support from and communication with family and friends, integrating a changing self and body image, and improving communication with physicians. Coping strategies and psychoeducation are provided in a nondidactic manner.

- **Core conflictual relationship theme (CCRT)** [64]: CCRT is a 16-week structured short-term psychodynamic psychotherapy focusing on a central pattern of intrapsychic and interpersonal conflicts. The initial phase identifies a recurrent maladaptive wish, the expected response of the other, and the response of the self in relationships (the CCRT). Middle sessions focus on exploring the CCRT in current relationships and the relationship to the therapist, with a termination phase focusing on separation. Booster sessions are included to consolidate treatment progress.
    - CCRT has been adapted specifically for depression in cancer populations by Zwerenz et al [65].

- **Dignity Therapy** [66]: An individual, legacy project intervention for palliative patients using a tape recorded interview and based on a nine-question interview protocol. The dignity interview focuses on issues that matter most to the patient or that the patient would most want remembered. Edited transcripts of the interview are given to patients to share with family.

- **Meaning-Centred Psychotherapy** [67,68]: A brief intervention focusing on historical, attitudinal, creative, and experiential sources of meaning developed for patients with advanced cancer. Developed as either an eight-week group or seven-week individual intervention.

- **Managing Cancer and Living Meaningfully (CALM)** [69]**:** A brief, manualized, semi-structured individual and couple-based psychotherapy designed to alleviate distress in patients with advanced cancer. CALM consists of three to eight sessions delivered over six months that address four broad domains: symptom management and communication with health care providers, changes in self and relations with close others, sense of meaning and purpose, and thoughts about the future and mortality. It has been shown to alleviate depression and anxiety about death, and to improve the patient's sense of meaning and peace (spiritual well-being).

Appendix 5. Practical Tools for Clinicians Prescribing an Antidepressant.

Selecting an Antidepressant

- Past psychiatric history (e.g., past positive treatment responses to an antidepressant)
- Family psychiatric history (e.g., past positive treatment responses to an antidepressant)
- Concurrent medications (e.g., potential drug-drug interactions)
- Somatic symptom profile (e.g., sedating antidepressant for those with prominent insomnia; weight gaining antidepressant for cachectic patients)
- Potential for dual benefit (e.g., duloxetine and TCAs for neuropathic pain, venlafaxine for hot flashes)
- Type of cancer (e.g., avoid bupropion in those with central nervous system cancers)
- Comorbidities (e.g., avoid psychostimulants or TCAs in cardiac disease)
- Cancer prognosis (e.g., consider psychostimulants if very short life expectancy)

Initiating an Antidepressant

- Screen for possible medical contributors to presenting conditions (e.g., TSH, vitamin B_{12}), as well as substance use
- Start on lowest dose to minimize detrimental side effects and titrate up to therapeutic dose after first week
- Discuss potential detrimental side effects (particularly initial gastrointestinal (GI) upset, headache, or anxiety) which should resolve within the first week
- Explain that detrimental side effects occur before therapeutic benefit, which can take four to six weeks to reach full beneficial effect
- Advise of need to take medications daily and continue even after remission of depressive symptoms
- Counsel about potential discontinuation symptoms if medications are stopped abruptly
- Reassure patients that dependence or tolerance does not occur
- Discuss concerns related to antidepressants and potential increased suicidality

Managing Risk of Suicide

- Advise risk of increased suicidality from antidepressants is small, most often associated with adolescents, and occurs early in the course of treatment
- Explain that increased risk may arise from improved motivational activation, occurring before improvement in the depressed mood which underlies the suicidal thoughts
- Provide guidance on how to seek help

- Note that suicidal thoughts can be common, but completed suicide accounts for <0.02% of cancer deaths (this is 1.5 times the general population's risk), and overall suicide risk is decreased by treatment of depression
- Inquire separately about suicidal ideation, intent, and plan
- Distinguish suicidal ideation from rational thoughts of death, and desire for hastened death
- Reassess adherence and mood after one week if suicidal ideation is present
- Refer to mental health specialist if considerable imminent risk

Maintaining an Antidepressant

- Provide support in first week when risk of nonadherence is greatest; follow up every two to four weeks until remission
- Monitor agitation, increased anxiety, and insomnia. Consider short-term benzodiazepine for initial symptoms, if required
- Assess response after three to four weeks at a therapeutic dose; increase dose if no response; switch medication if no response after six weeks
- Regularly monitor for changes in medical status and cancer treatments and adjust accordingly
- Continue at effective dose for at least six months after full remission
- Patients with a history of recurrent depression should be advised to continue maintenance treatment for at least two years or indefinitely

Discontinuing an Antidepressant

- Be aware that discontinuation syndromes (malaise, dizziness, agitation, headache, nausea, paresthesia) may occur with abrupt termination or missed doses at high dosage levels
- Understand that discontinuation syndromes are more common with antidepressants with a shorter half-life (i.e., venlafaxine, paroxetine); they do not occur with fluoxetine
- Taper gradually over four weeks to minimize discontinuation syndromes; symptoms may be more prominent toward the end of the taper
- Advise that symptoms are usually mild and self-limiting over approximately one week
- If symptoms are severe, taper more slowly or consider switching to longer half-life SSRIs such as fluoxetine and then stopping
- Monitor for possible depression relapse over the next few months

Appendix 6. Antidepressant Classes Used for Patients with Cancer [70,71].

Drugs	Common Side Effects	Cautions
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Citalopram, Escitalopram, Fluoxetine, Sertraline, Paroxetine, Fluvoxamine	• GI upset, headache, dizziness, anxiety on initiation • Sweating, sexual dysfunction, tremor, bruxism	• Citalopram/escitalopram corrected QT interval (QTc) prolongation at high doses • Paroxetine/Fluoxetine/ Fluvoxamine drug interactions • Paroxetine discontinuation syndrome • Risk of GI bleeding, hyponatremia
Mixed Action Reuptake Inhibitors (RIs) - serotonin (S), noradrenaline (N), dopamine (D)		
Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran (SNRI)	• GI upset, headache, dizziness, anxiety on initiation • Sweating, sexual dysfunction, constipation	• Venlafaxine discontinuation syndrome and hypertension risk • Duloxetine dose-dependent hepatotoxicity
Bupropion (norepinephrine-dopamine reuptake inhibitor [NDRI])	• Agitation	• Seizure risk at high doses
Reboxetine (norepinephrine reuptake inhibitor [NRI])	• Insomnia, sweating, dizziness, tachycardia	• Caution in comorbid cardiac disease
"Atypical" Antidepressants		
Mirtazapine (noradrenergic and specific serotonergic antidepressant [NaSSA])	• Sedation, weight gain, dry mouth, constipation	• Rarely, reversible neutropenia

Drugs	Common Side Effects	Cautions
Agomelatine	• Nausea, dizziness, headache, somnolence	• Contraindicated in renal or hepatic impairment
Tricyclic Antidepressants (TCAs)		
3^0 amines - Amitriptyline, Imipramine 2^0 amines - Nortriptyline, Desipramine	• Sedation, constipation, anticholinergic, orthostatic hypotension, tachycardia	• High toxicity in overdose, *do not prescribe Dosulepin* • Poor tolerability, especially with 3^0 amines • Risk of QTc prolongation
Psychostimulants		
Methylphenidate, Dexamphetamine, Modafinil	• Insomnia, agitation, tremor, anxiety, hypertension, tachycardia, arrhythmia	• Contraindicated in significant cardiovascular disease • Risk of dependence
"Atypical" Antipsychotics (as Adjuncts)		
Quetiapine, Olanzapine, Risperidone, Aripiprazole Lurasidone Asenapine	• Sedation, weight gain, metabolic syndrome • Olanzapine and quetiapine may be helpful for insomnia, anorexia and nausea • Aripiprazole may be less sedating	• Risk of QTc prolongation • Caution with Risperidone, Lurasidone and Olanzapine in breast cancer due to risk of increase in prolactin levels. Asenapine and aripiprazole are preferred due to a minimal effect on prolactin levels • Anticholinergic and sexual side-effects
Alternative Therapies		
St. John's Wort, Omega-3, S-adenosylmethionine (SAM-e)	• Recommended in CANMAT guidelines for mild to moderate depression • May be preferred by patients with cancer who are reluctant to consider pharmaceutical antidepressants • Lack of standardization in formulation and dose in most countries and limited knowledge of drug interactions	

Appendix 7. Antidepressant-Oncology Drug Interactions.

Refer to Miguel and Albuquerque (2011) [72] and NICE CG 91 Appendix 16 [4] for further information.

Oncology drug	Antidepressants	Comments
All cytotoxic agents	Avoid mianserin	Risk of bone marrow suppression
Protein kinase inhibitors (PKIs) (e.g., imatinib, nilotinib, sorafenib, sunitinib, trastuzumab)	Avoid TCAs due to QTc prolongation	Nilotinib inhibits cytochromes P450 (CYPs) 3A4 and 2D6; caution with all antidepressants
Cyclophosphamide, procarbazine, dacarbazine	Caution with paroxetine, fluoxetine, sertraline, fluvoxamine, bupropion	Effectiveness reduced by CYP 2B6, 2C19, and 1A inhibitors
Alkylating agents (ifosfamide, thiotepa)	Caution with fluoxetine, sertraline, paroxetine, fluvoxamine	Effectiveness reduced by CYP 3A4 inhibitors
Corticosteroids, etoposide, PKIs, antimicrotubules (paclitaxel, docetaxel, vinblastine, vincristine)	Caution with fluoxetine, sertraline, paroxetine, fluvoxamine	Increased levels and toxicity by CYP 3A4 inhibitors
Irinotecan	Avoid SSRIs	Risk of rhabdomyolysis and severe diarrhea
Common antidepressants with the least impact on CYP enzymes are generally the safest options with antineoplastic agents:		
Citalopram or escitalopram	Venlafaxine/desvenlafaxine	Mirtazapine
Common antineoplastic agents for which there are no significant pharmacokinetic drug interactions with antidepressants:		
Temozolomide 5-fluorouracil Gemcitabine Cisplatin Carboplatin Oxaliplatin	Doxorubicin Duanorubicin Epirubicin Vorinostat Melphalan Chlorambucil	Busulfan Estramustine Mechlorethamine Mercaptopurine Thioguanine

Abbreviations: QTc = corrected QT interval, TCA = tricyclic antidepressant

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Guideline # 19-4: Section 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Management of Depression in Patients with Cancer: Systematic Review

M. Li, E.B. Kennedy, N. Byrne, C. Gerin-Lajoie, E. Green, M. R. Katz, H. Keshavarz, S. M. Sellick, and the Management of Depression in Patients with Cancer Expert Panel

Report Date: May 11, 2015

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]. Management of this depressive continuum, ranging from nonpathological sadness, adjustment disorders, and subthreshold depressions, to major depression has been the subject of numerous systematic and narrative reviews [2-4]. Relatively few high-quality studies have been conducted in this field and, in fact, there have been more evidence-based reviews published in this field than primary research studies to support such reviews. Practice guidelines on the management of depression in cancer have therefore either been based on extrapolation from evidence on the treatment of depression in populations without cancer, or limited to general statements on the overall effectiveness of antidepressants and psychological therapies for depression in patients with cancer, with few specific recommendations to guide practice.

Depressive disorders in the context of cancer have clinically relevant impacts on health outcomes. Depression has been associated with more prolonged hospital stays, increased physical distress [5], poorer treatment compliance [6], lower quality of life [7], and increased desire for hastened death [8]. More severe depression in cancer has also been shown to be a risk factor for death, independent of medical variables [9,10]. However, as with other medical illnesses, the mediating mechanisms are unknown and evidence that treatment of depression improves survival rates is lacking [11]. Improving the efficacy of the treatment of depression in patients with cancer will be required to further such research.

Major depression refers to a syndrome characterized by at least five symptoms, one of which is depressed mood or loss of interest in nearly all activities for at least two weeks. The other symptoms include appetite or sleep disturbance, psychomotor agitation or retardation, decreased energy, feelings of worthlessness or excessive guilt, difficulty thinking or concentrating, and recurrent thoughts of death or suicidal ideation. Major depression can manifest in mild, moderate, or severe forms depending on the intensity of the symptoms and functional impairment. Subthreshold depression refers to depressive symptoms that cause significant distress or impairment, but do not meet diagnostic criteria for major depression in terms of either symptom number or duration. The Diagnostic and Statistical Manual of Mental

Disorders, 5th Edition [12] categorizes subthreshold depressions as either "depressive episode with insufficient symptoms" or "persistent depressive disorder". Toward the milder end of the depressive continuum lie adjustment disorder and normative sadness.

Confounding the literature on treating depression in cancer is the diagnostic complexity across the severity continuum, where 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 due to 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 prior to or concurrently with depressive symptoms. Clinicians must also consider potential detrimental pharmacotherapy side effects, adverse drug interactions, and treatment compliance issues unique to the cancer context.

This update to the previous Cancer Care Ontario Program in Evidence-Based Care (PEBC) guideline [13] will systematically review the literature on pharmacological and psychological treatments for depression in patients with cancer since 2005. This literature review will be extended to include collaborative care (CC) interventions, and the recommendations (Section 1) will integrate practical management tools to assist clinicians in selecting appropriate specific treatments for depression in patients with cancer.

BACKGROUND

The previous version of this systematic review [14] evaluated the efficacy of pharmacological and psychological treatments for patients with cancer who had been diagnosed with major depression, dysthymia, adjustment disorder, or minor depression through a structured diagnostic interview, or with depressive symptoms scoring beyond a determined cut point on a validated assessment scale. The evidence-base, which was current to 2005, included seven randomized controlled trials (RCTs) of pharmacological agents and four of psychological interventions for treatment of depression in patients with cancer. The authors concluded that there was limited evidence of the effectiveness the interventions and no evidence of the superiority of one treatment over another. Recommendations advised that antidepressant medications should be considered for the treatment of moderate to severe depression in patients with cancer, with the choice of antidepressant informed by individual medication and patient factors, including detrimental side effects, tolerability, response to prior treatment, and patient preference. Combining pharmacological treatment with psychological or psychosocial treatments, including those that provide information and support and any combination of emotional, cognitive, and behavioural factors, was also recommended. An update of that work was undertaken because of a perceived need to offer clinicians who work in the cancer field practical tools to guide them in the management of depression in patients with cancer.

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RESEARCH QUESTION

What is the efficacy of treatment (pharmacological and/or psychological) for depression in the adult cancer population?

TARGET POPULATION

Adult patients with cancer who are diagnosed with a major depressive disorder based on a structured diagnostic interview, or who have a suspected depressive disorder based on meeting a threshold on a validated depression rating scale.

INTERVENTIONS

Pharmacological and/or psychological or psychosocial or collaborative care interventions for depression.

COMPARISONS

Observation (usual care), placebo, or another treatment intervention.

OUTCOMES OF INTEREST

Outcomes of interest include:

- Depression severity (reduction in severity according to a validated depression rating scale).
- Cases of depression (reduction in cases measured by structured diagnostic interview).
- Depression response (50% reduction in score from baseline on a validated depression rating scale).
- Depression remission (score after treatment is below a predetermined significant threshold on a validated depression rating scale).

METHODS

A Working Group was formed that included members with expertise in psychiatry, psychology, psychosocial oncology, and health research methodology, with the goal of updating the previous 2007 PEBC systematic review [14] and guideline [13]. The members of the Working Group began by searching for existing practice guidelines as a potential source of recommendations that could be adapted or endorsed. Guidelines were eligible to be used for this purpose if they were based on a systematic review of the literature that was more current than the previous version of this guideline, or on a methodologically sound formal or informal consensus process. If no such guidelines were found, or if gaps remained, the members of the Working Group agreed to consider adopting an evidence base from one or more appropriate systematic reviews. Finally, if no systematic reviews were found that addressed the research questions of interest or were sufficiently up to date, then the members of the Working Group planned to draw on evidence from RCTs and conduct an original meta-analysis, if feasible. For the sake of efficiency, the search for guidelines, systematic reviews, and primary studies was conducted simultaneously.

Selection of Clinical Practice Guidelines, Systematic Reviews, and Randomized Controlled Trials

The electronic databases MEDLINE, EMBASE, PsycINFO, and the Cochrane Library were searched for guidelines, systematic reviews, and RCTs that were published after the final search date of the previous version of this systematic review (June 2005) and before January 2015, using the search terms listed in Section 2, Appendix 1. In addition, files of the Working Group members were searched. Websites of international guideline developers, Canadian provincial and national cancer agencies, and CancerViewCanada (http://www.cancerguidelines.ca) were searched for existing evidence-based practice guidelines using the word "depression." See Section 2, Appendix 2 for a complete list of databases and associations that were searched. Shortly before the guideline was completed, an additional search from March 2013 to January 2015 was conducted to ensure the currency of the evidence base.

Documents were screened by the project research methodologist. Full-text guidelines and/or systematic reviews that appeared to meet the selection criteria were retrieved, and the full set of selection criteria, including whether the population, intervention, comparisons, and outcomes of interest were appropriate was applied independently by the methodologist and by the lead author of the Working Group. In cases of disagreement, consensus was achieved through discussion.

Inclusion Criteria for Randomized Controlled Trials

Primary studies were eligible if they were full publications (not abstracts), included a randomized comparison (either blinded or nonblinded) with a treatment group compared with another treatment group or a placebo/usual care control group. Nonrandomized or single-arm trials, narrative reviews, retrospective observational studies, case-control studies, case series, before-and-after studies, letters, and editorials were excluded. Non-English-language publications were excluded because full-text translation resources for these items were not available.

Trials were only included if all individuals in the study population met a cut-off for diagnosis of depression on a validated depression rating scale or structured clinical interview. Therefore, depression prevention trials were excluded. This also meant that studies for which depression was not an inclusion criterion were not eligible, as was the case with most studies in which depression was not the primary outcome. However, studies where analyses were conducted on a subgroup of patients that met the criteria for depression were considered eligible. There was no minimum number of patients defined for study eligibility.

Data Extraction and Quality Assessment

After an initial screen to ensure that guidelines met the basic inclusion criteria, a quality assessment was conducted by one methodologist and one or two members of the Working Group independently, using version II of the Appraisal of Guidelines for Research and Evaluation (AGREE II) tool [15]. Systematic reviews that met the basic inclusion criteria were assessed for quality using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [16].

The Cochrane Risk of Bias Tool was used to assess the quality of randomized controlled trials [17]. Other study characteristics such as measurement scales used and outcome measures were extracted. Data extraction was verified by a project research assistant. All authors reviewed and discussed a draft of the evidence summary. Strengths and weaknesses were evaluated with the aim of characterizing the quality of the evidence base as a whole, without the use of a scoring system or cut-offs.

Statistical Analysis

Meta-analyses of response and remission outcome measures were conducted with Review Manager software (RevMan version 5.3, Cochrane Collaboration [18]). Random effects models were used for all analyses, with the underlying assumption that different studies estimate different, yet related intervention effects. Analyses were conducted by time period from the start of treatment in order to compare the short- and long-term effectiveness of interventions. Definitions of short-term and long-term were arrived at by consensus of the members of the Working Group based on the time frames used in the individual studies. Results from intent-to-treat analyses were combined with completer analyses, because a previous analysis of studies of depression in physically ill populations showed that this did not affect the results [19].

Where available, estimates that had been adjusted for potential confounding variables were used in the meta-analyses. A probability level for the chi-square statistic of ≤10% ($p \leq 0.10$) and/or an I^2 of greater than 50% were considered indicative of statistical heterogeneity between

studies. In the meta-analyses, effect sizes are expressed as odds ratios (ORs) for dichotomous variables and standardized mean differences for continuous variables, with 95% confidence intervals (CIs) around the estimates. Where standard deviation was not available it was calculated using the standard error estimates that were reported in the study results.

For the pharmacological interventions, all classes of antidepressants were combined, because a previous subgroup analysis according to antidepressant class conducted on 51 studies of individuals with a physical illness suggested that selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and mianserin/mirtazapine were effective in the treatment of depression in the physically ill compared with placebo [19], and the Working Group's members did not have reason to believe that this conclusion would not apply to the specific population of physically ill patients addressed in this review.

RESULTS

Search for Existing Guidelines

Of the 1376 potentially relevant citations that were identified, 56 citations were excluded because of duplication and 1248 citations were excluded after title and abstract screening. The full texts of the remaining 72 publications were retrieved. Two of these guidelines (Table 1) met the inclusion criteria and were evaluated using the AGREE II instrument [15]. The members of the Working Group concluded, largely based on high scores for rigour of development, that the development methods for these guidelines were of high quality (Section 2, Appendix 3) and that they were based on a systematic review of evidence. See Section 2, Appendix 4 for a list of excluded guidelines and reasons for their exclusion.

An examination of the specific studies included in the evidence base for these two guidelines revealed that very little new information on interventions for depression in patients with cancer had been published since Cancer Care Ontario's previous guideline [13]. The Working Group agreed that it is reasonable to assume that depression is similar in different physical diseases, and that the two guidelines listed in Table 1, which are not specific to patients with cancer, should be retained for possible endorsement or adaptation. As a next step, the Working Group undertook additional searching to ensure the currency of the evidence base in the oncology-specific patient population.

Table 1. Guidelines meeting inclusion criteria.

Organization	Guideline	Scope	Final Search Date
National Institute for Health and Care Excellence (NICE) [20]	Depression in adults with a chronic physical health problem.	Psychological and psychosocial recommendations based on expert consensus and pharmacological recommendations based on a systematic review. Also includes recommendations for a stepped care model.	March 2008
European Palliative Care Research Collaborative (EPCRC) [21]	The management of depression in palliative care	Most current systematic review for recommendations regarding antidepressants. Also includes consensus-based psychological and psychosocial recommendations.	December 2009

Systematic Reviews and Randomized Controlled Trials

To improve the currency of the evidence-base, members of the Working Group undertook a search for systematic reviews published after the National Institute for Health and Care Excellence (NICE) [20] and European Palliative Care Research Collaborative (EPCRC) [19] final search dates (Table 1). Four additional systematic reviews were located that met the inclusion criteria [3,22-24]. The members of the Working Group compared these systematic reviews and Rodin et al [14], and found considerable duplication regarding included studies (Table 2, Table 3); therefore, it was decided that rather than present the results of each systematic review, the reviews would be used as a source of primary studies. Because the latest search date for these reviews was December 2010 for pharmacological interventions [3] and October 2011 for psychological or psychosocial interventions [22], a final search for more recent primary studies (individual RCTs) in the oncology-specific patient population was conducted, with the goal of creating an evidence base that would include all RCTs that had been published on the topic of management of depression in patients with cancer. More detail on the search for RCTs is presented subsequently.

Table 2. Pharmacological intervention studies found in eligible systematic reviews.

Study, year (reference)	Rodin et al, 2007 [14]	NICE, 2009 [20]	Rayner et al, 2010 [19]	Laoutidis and Mathiak, 2013 [3]	Ng et al, 2011[23]	Hart et al, 2012 [22]	Current evidence base (2015)
Costa et al 1985 [25]	✓	✓	✓	✓	✓	✓	✓
Holland et al, 1991 [26]	✓	X	--	--	✓	--	X
Razavi et al, 1996 [27]	✓	✓	✓	✓	✓	✓	✓
Van Heeringen and Zivkov 1996 [28]	✓	✓	✓	✓	✓	✓	✓
Holland et al, 1998 [29]	✓	✓	--	✓	✓	--	✓
Cankurtaran et al 1998 [30]	--	X	--	✓	--	--	X
Pezella et al, 2001 [31]	✓	✓	--	✓	✓	--	✓
Morrow et al, 2003 [32]	--	✓	X	X	X	--	X
Fisch et al, 2003 [33]	✓	✓	X	✓	✓	✓	✓
Musselman et al, 2006 [34]	NP	✓	✓	✓	✓	✓	✓
Navari et al, 2008 [35]	NP	--	--	✓	--	X	X
Ng et al 2014 [36]	NP	NP	NP	NP	NP	NP	✓

NICE = National Institute for Health and Care Excellence, NP = study not published at time of review, -- = study not mentioned, ✓ = included, X = excluded. See Section 2, Appendix 5 for reasons for study exclusions.

Table 3. Psychological interventions included in eligible systematic reviews.

Study, year (reference)	Rodin et al, 2007 [14]	NICE, 2009 [20]	Van Straten et al, 2010 [24]	Hart et al, 2012 [22]	Current evidence base (2015)
Speer 1987 [37]	--	--	✓	--	X
Greer et al, 1992 [38]	✓	X	--	--	X
Moorey et al 1994 [39]	✓	--	--	--	X
Evans and Connis 1995 [40]	--	✓	✓	✓	✓
McQuellon et al, 1998 [41]	✓	--	--	--	X
Kissane et al, 2003 [42]	✓	--	--	--	X
Nezu et al, 2003 [43]	--	--	✓	✓	✓
Sharpe et al, 2004 [44]	✓	--	--	--	X
Savard et al, 2006 [45]	NP	✓	✓	✓	✓
Courneya et al, 2007 [46]	NP	✓	--	--	X
Kissane et al, 2007 [47]	NP	✓	--	--	X
Manne et al, 2007 [48]	NP	✓	--	--	X
Goerling et al, 2011 [49]	NP	NP	NP	X	✓
Hopko et al, 2011 [50]	NP	NP	NP	--	✓
Rodriquez Vega et al, 2011 [51]	NP	NP	NP	--	✓
Kangas et al, 2013 [52]	NP	NP	NP	NP	✓
Qiu et al, 2013 [53]	NP	NP	NP	NP	✓
Beutel et al, 2014 [54]	NP	NP	NP	NP	✓

NICE = National Institute for Health and Care Excellence, NP = study unpublished at time of review, -- = study not mentioned, ✓ = included, X = excluded. See Section 2, Appendix 5 for reasons for study exclusions.

Randomized Controlled Trials

Methodological Quality and Other Study Characteristics (Table 5, Table 6)

Pharmacological Interventions

Six pharmacological trials [25,27-29,31,33] from the previous version of this guideline met current inclusion criteria. These studies had several limitations, including lack of detail regarding description of randomization method, which made risk of bias unclear. The sample sizes were generally smaller, ranging from 38 [29] to 128 [31] patients, reducing the likelihood of sufficient power to detect differences between treatment and control groups.

One additional study [34] was a double-blind three-arm trial of paroxetine compared with desipramine or a placebo control. It included an intention-to-treat analysis (ITT) and completer analysis with a follow-up time of six months, carried out with industry support. It did not achieve the required sample size to detect differences among groups with the desired power of 85%. The risk of bias in this trial was unclear because details on the methods used to randomize subjects were not described. In addition, a double-blind study of methylphenidate as an add-on therapy to mirtazapine compared with mirtazapine plus placebo, in patients with any type of cancer under palliative care included assessment of outcomes at time periods ranging from three to 28 days [36].

Psychological Interventions

None of the psychological intervention studies included in the previous version of this guideline [13] met the inclusion criteria for this review, either because they did not have a randomized study design, or because the baseline depression scores were well below a threshold for diagnosis of depression.

Nine eligible RCTs that assessed a variety of psychological interventions, including cognitive behavioural therapy (CBT) [40,45,52,53], social support [40], problem-solving therapy (PST) [43], behavioural activation treatment (BAT) [50], "low-threshold" psycho-oncological support [49], narrative therapy [51], and psychodynamic psychotherapy [54], compared with other pharmacological or nonpharmacological treatments, or a waiting list or a usual-care control group were located.

Five of the studies provided a power calculation [50-54], and a randomization method including allocation concealment was adequately described in three studies [45,53,54]. Attrition ranged from 35% of patients responding to assessment at 12 months [49] to 92% completing follow-up assessments [40]. Blinding of participants and clinicians was for the most part not possible due to the nature of the interventions. However, in six cases, the initial and/or follow-up examiners were blinded [45,50-54]. Outcomes were assessed using the initial randomized study population as the denominator (ITT analysis) in six studies [49-54].

Collaborative Care Interventions

The systematic review identified a novel category of intervention, namely collaborative care interventions, which are comprehensive strategies characterized by active collaboration between specialist and primary care providers, usually assisted by a care manager, and typically including measurement-based care. The strategies may incorporate increases in the level or intensity of intervention as needed according to the principles of stepped care. Very few of these trials were included in the articles located as part of the Working Group's search for systematic reviews (Table 4).

Table 4. Collaborative care RCTs included in eligible systematic reviews.

Study, year (reference)	Rodin, 2007 [14]	NICE, 2009 [20]	Van Straten, 2010 [24]	Hart, 2012 [22]	Current evidence base (2014)
Dwight-Johnson et al, 2005 [55], Ell et al, 2008 [56], Ell et al, 2011 [124]	NP	✓	--	✓	✓
Strong et al, 2008 [57]	NP	✓	--	✓	✓
Fann et al, 2009 [58]	NP	NP	NP	--	✓
Kroenke et al, 2010 [59]	NP	NP	NP	--	✓
Sharpe et al, 2014 [60]	NP	NP	NP	NP	✓
Walker et al, 2014 [61]	NP	NP	NP	NP	✓

NICE = National Institute for Health and Care Excellence, NP = study unpublished at time of review, -- study not mentioned, ✓ = included.

Four RCTs assessed collaborative care interventions. One of these was a subgroup analysis of the oncology patients included in a larger study of a collaborative care intervention for late-life depression in a primary care setting [58]. Another study assessed the same model (IMPACT), in a lower income, visible minority population [56]. Results of an intervention called depression care for people with cancer were identified [60,61]. Finally, Kroenke et al assessed a telephone-based intervention [59].

In general, the collaborative care studies had larger sample sizes that allowed for more power to detect differences between intervention and control groups (sample size range: 200

to 500 patients). In four cases, the sample size needed to generate adequate power was calculated [57,59-61], and in two cases, an adequate sample size was accrued [59,60].

Attrition rates ranged from 2% at three months [57], to only 55% of those randomized remaining at 12 months [56]. In five studies, the randomization method was adequately described [56,58-61] and in four of these, allocation was sufficiently concealed [56,58,60,61]. In all studies, patients and clinicians were not blinded, but initial and/or outcome assessors were blinded. Analysis was according to ITT in most of the studies [56,59-61].

Collaborative care interventions were delivered by nurses supervised by psychiatrists or, in one case, a primary care physician, and medications were prescribed by psychiatrists, oncologists, or primary care physicians. The interventions included one-on-one sessions of psychological therapy (e.g., PST), usually carried out on a weekly basis, that lasted from six to 12 weeks (Table 6). Structured algorithms for medication decision-making or for all decisions about treatments were used in three studies [56,58,59]. Maintenance and follow-up assessment were provided for all patients. Details regarding the components of the interventions and rates of antidepressant use in the treatment and control groups are included in Section 2, Appendix 6.

Two trials used a structured diagnostic interview to determine diagnosis, whereas the other two used a self-report measure to determine eligibility and did not include a structured interview. The depression care for patients with cancer intervention used a screening service to identify patients. Maintenance and monitoring for outcomes lasted for a maximum of 24 months.

Table 5. Quality assessment of included RCTs.

Study, year (reference) Country	Comparison groups	Sample size	Power calculation described	Adequate sample for specified power?	Loss to follow-up	Randomization method/sequence generation (SG)/allocation concealment (AC)	Blinding of patients, personnel, outcome assessors	ITT	Comments
Pharmacological									
Musselman et al, 2006 [34] USA	Paroxetine vs. desipramine vs. placebo	35	Yes	No	60% remained at week 6	Not described	Double-blind	Yes	Baseline differences in cancer stage, prior treatment and performance status
Ng et al, 2014 [36] Malaysia	Methylphenidate and mirtazapine vs. placebo and mirtazapine	88	Yes	No	44% completed intervention	Computer-generated table of random numbers (block of 8)/AC not described	Double-blind	Modified ITT	
Psychological									
Evans and Connis, 1995 [40] USA	CBT vs. SS vs. no treatment	78	No	NA (study likely insufficiently powered)	92% completed follow-up assessments	Not described	No	No	Seriously ill underrepresented as they were more likely to drop out.
Nezu et al, 2003 [43] USA	PST vs. PST-SO vs. WLC	150	No	NA	88% provided baseline and post-treatment data	Random numbers table/AC not described	No	No	
Savard et al, 2006 [45] Canada	CBT vs. WLC	45	No	Authors speculate that this study was under-powered	82% were analyzed	Computer-generated random numbers table/sealed envelopes used for allocation	Initial and follow-up assessors blinded	No	Projected sample size not obtained (major challenge recruiting pts with

Study, year (reference) Country	Comparison groups	Sample size	Power calculation described	Adequate sample for specified power?	Loss to follow-up	Randomization method/sequence generation (SG)/allocation concealment (AC)	Blinding of patients, personnel, outcome assessors	ITT	Comments
									metastatic breast cancer)
Goerling et al, 2011 [49] Germany	"low-threshold" psycho-oncological support vs. observation	101 (high risk group)	No	NA	35% of low and high risk patients at 12 months	No	Unclear	No; but all pts present at first assess-ment	Pilot trial
Hopko et al, 2011 [50] USA	BATD vs. PST	80	Yes	Yes	81% completed	Allocation based on a "pre-established randomization chart"/AC not mentioned	Initial examiners blinded	Yes	
Rodriguez Vega et al, 2011 [51] Spain	NT and escitalopram vs. UC and escitalopram	72	Yes	Yes	94% completed wk 12 and 78% completed wk 24	Centralized randomization by a table of random numbers/AC not described	Outcome assessors blinded	Yes	Approximately one-half of the potential candidates refused to participate before randomization
Kangas et al, 2013 [52] Australia	Brief, early CBT vs. nondirective supportive counselling	43	Yes	Yes	74% remaining at 1 month, 66% at 6 months, 51% at 12 months	Not described	Assessors blinded	Yes	
Qiu et al, 2013 [53] China	Group CBT vs. wait list control	62	Yes	Yes	87% assessed at 6 months	Computerized randomization sequence/ independent AC	Raters and statistician blinded	Yes	
Beutel et al, 2014 [54] Germany	STPP vs. UC	157	Yes	Yes	In final analysis: Intervention: 66% Control: 68%	Computer-generated sets of numbers with random length by trial-independent research staff/AC	Follow-up assessors blinded	Yes	Time period between randomization and follow-up assessment was an average of 4

Study, year (reference) Country	Comparison groups	Sample size	Power calculation described	Adequate sample for specified power?	Loss to follow-up	Randomization method/sequence generation (SG)/allocation concealment (AC)	Blinding of patients, personnel, outcome assessors	ITT	Comments
									months longer in STPP.
Collaborative care									
Dwight-Johnson et al, 2005 [55] USA	CC vs. UC	55	No	NA	65% completed assessment at 4 or 8 months.	Computed generated random assignment/sealed envelope	Assessors blinded	Yes	Pilot study – validation provided in Ell 2008; some imbalances at baseline
Ell et al, 2008 [56], 2011 [62] USA	CC vs. EUC	472	No	NA	67% remained at 6 months, 55% at 12 months, 44% at 24 months	Computed generated random assignment/sealed envelope	Assessors blinded	Yes	Larger study based on Dwight-Johnson pilot. Lower-income visible minority study population.
Strong et al, 2008 Scotland UK [57]	CC vs. OUC	200	Yes	No (197 pts analyzed)	98% remaining at 3 months	Not described	Initial assessors blinded	No	An initial proof of concept trial of a collaborative care system
Fann et al, 2009 [58] USA	CC vs. UC	215	Calculated for entire IMPACT study [63] but not for this subgroup of pts with cancer	NA	96% analyzed at 6 months, 91% at 12 months, 88% at 18 months, 85% at 24 months	Computer generated random assignment/sealed envelope [63]	Initial and follow-up assessors blinded [63]	No	Subgroup analysis of pts with cancer who participated in the IMPACT collaborative care management program for late-life depression [63]. Pts at

Study, year (reference) Country	Comparison groups	Sample size	Power calculation described	Adequate sample for specified power?	Loss to follow-up	Randomization method/sequence generation (SG)/allocation concealment (AC)	Blinding of patients, personnel, outcome assessors	ITT	Comments
									least 60 years of age.
Kroenke et al, 2010 [59] USA	Telephone-based CC with automated symptom monitoring vs. UC	405	Yes	Yes	88% participation at 1 month, 85% at 3 months, 84% at 6 months, 84% at 12 months	Computer-generated randomization/AC not mentioned	Assessors blinded	Yes	
Sharpe et al, 2014 [60] Scotland	CC vs. UC	500	Yes	Yes	Range: 95% at 12 weeks, 89% at 48 weeks	Randomization by software algorithm/allocation concealed	Outcome assessors and statisticians blinded	Yes	Effectiveness trial based on Strong 2008 [57]
Walker et al, 2014 [61] Scotland	CC vs. UC	142	Yes	No (150 was target sample)	Range: 87% at 4 weeks, 65% at 32 weeks	Randomization by software algorithm/allocation concealed	Outcome assessors and statisticians blinded	Yes	Effectiveness trial based on Strong 2008 (lung cancer patients only)

BATD = Behavioural Activation Treatment for Depression, CBT = cognitive behavioural therapy, CC = collaborative care, EUC = enhanced usual care, IMPACT = Improving Mood-Promoting Access to Collaborative Treatment, ITT = intent-to-treat, MDD = major depressive disorder, NA = not applicable, NT = narrative therapy, OUC = optimized usual care, PST = problem-solving therapy, PST-SO = problem-solving therapy with significant other, pts = patients, SS = social support, STPP = short-term psychodynamic psychotherapy, UC = usual care, vs. = versus, wk = week(s), WLC = wait list control.

Table 6. Characteristics of included studies.

Study, year (reference) Country	Patients enrolled, n	Disease site/stage	Screen for eligibility	Structured interview to determine diagnosis?	Duration of intervention	Covariates adjusted for	Primary Outcome, Assessment timeframe
Pharmacological							
Musselman et al, 2006 [34] USA	35	Breast, stage I-IV	HRSD score ≥14 (mild) on the first 17 items of the 21-item HRSD.	DSM-3-R criteria for MDD duration ≥1 month, adjustment disorder with depressed mood for at least 2 months	6 weekly sessions	None	12-item HRSD mean score. At least 50% from baseline HRSD score Remission at 6 weeks
Ng et al, 2014 [36] Malaysia	88	Any site, palliative stage	Patients approached for participation if they had been referred to psychiatric services with a diagnosis of MDD as defined in the DSM-4 (confirmed by Mini International Neuropsychiatric Inventory)		28-day period of twice-daily methylphenidate (5 mg), and daily mirtazapine (30 mg)	Baseline MADRS, gender	Change in depression score measured by the MADRS.
Psychological							
Evans and Connis, 1995 [40] USA	78	Mixed type, stage II, receiving radiation therapy	CES-D ≥16 indicating probable depression (mild)	No	"Brief" 8 weekly one-hour therapy sessions	Preintervention scores	CES-D mean scores at 8 weeks and 6 months
Nezu et al, 2003 [43] USA	150	Mixed, early stage, active treatment	Verbal report of significant emotional distress. GSI ≥63 ≥14 on the HRSD (mild)	Intake included a semi-structured clinical interview including HRSD.	10 1.5 hour weekly sessions	None	Psychological distress measured by mean scores on the HRSD, BSI and POMS post-treatment (12-13 weeks)

Study, year (reference) Country	Patients enrolled, n	Disease site/stage	Screen for eligibility	Structured interview to determine diagnosis?	Duration of intervention	Covariates adjusted for	Primary Outcome, Assessment timeframe
Savard et al, 2006 [45] Canada	45	Metastatic breast cancer, stage IV, nonterminal	HADS-D ≥7 or BDI ≥15 (at least borderline to mild)	SCI-DSM-4 followed HADS-D	8 weekly sessions of CT plus 3 booster sessions at 3-week intervals	Lifetime use of hormone therapy, oxazepam, pamidronate, systemic therapy side effects, appetite loss, pain level, alcohol use, tobacco use, activity level, perceived impact of life events	HADS-D, HRSD, and BDI mean scores at 8 weeks
Goerling et al, 2011 [49] Germany	101 (high-risk subgroup)	Mixed disease site, stage NR	Total HADS score ≥12	No	"Short-term intervention"; talks average 4 sessions of 41 min. Median length of inpatient care: 13 days	None	HADS-D mean score at hospital discharge and 12 months after discharge
Hopko et al, 2011[50] USA	80	Breast cancer, mixed stage	HANDS score ≥9	diagnosis of MDD with ADIS-IV followed HANDS	"brief" therapy; 8 weekly sessions of BATD or PST	No	HRSD and BDI-II response (at least 50% reduction from baseline). Remission (scores ≤7 on HRSD and ≤10 on BDI-II). Follow-up assessments at 3, 6, 9, and 12 months
Rodriguez Vega et al, 2011 [51] Spain	72	Non-metastatic breast, lung and colon	HADS-D ≥8	SCI DSM-4-TR MDD single episode or recurrent, adjustment disorder	Pharmacological treatment time 6 months. Narrative therapy 12 weekly sessions.	Time as repeated effect covariate; baseline scores included in mixed linear regression model	HADS-D mean score at 24 weeks
Kangas et al, 2013	43	Head and neck cancer, mixed stage	BDI-II ≥14	SCI-DSM-4 assessment for MDD	"Brief early intervention"; six weekly	PTCI Self-blame score	BDI-II mean scores at 1, 6, and 12 months

Study, year (reference) Country	Patients enrolled, n	Disease site/stage	Screen for eligibility	Structured interview to determine diagnosis?	Duration of intervention	Covariates adjusted for	Primary Outcome, Assessment timeframe
[52] Australia					sessions for either intervention CBT or SC		
Qiu et al 2013 [53] China	62	Breast cancer selected 6 to 36 months after surgery/ stages 0-IV	17-HAMD	DSM-4 used for diagnosis but SCI not mentioned; HAMD score of at least 17 also required	10 2-hour weekly sessions plus a booster session one month after end of intervention	Age, education, marriage status, time after surgery, past psychiatric history, state of tumour-node-metastasis, chemotherapy, radiotherapy, recurrence	HRSD score at completion of study and 6 months later
Beutel et al, 2014 [54] Germany	157	Breast cancer, stages T0-4, N0-1, MO	HADS-D ≥8 (mild)	SCID criteria for MDD, dysthymia, adjustment disorder	20 weekly psychotherapy sessions	Treatment centre, baseline scores and follow-up time	Remission: no depression according to SCID and a decrease in depression of ≥2 HADS-D points at treatment termination (56 weeks after initiation of treatment for STPP and 37 weeks for TAU)
Collaborative Care							
Dwight-Johnson et al, 2005 [55] Pilot test	55	Breast or cervical, mixed stage	MDD, dysthymia, or persistent depressive symptoms, adjustment disorder excluded. Mean PHQ-9 scores (mild)	No	PST delivered weekly for eight weeks	No	Rate of response (50% reduction from baseline in PHQ-9 score) at 4 months or 8 months

Study, year (reference) Country	Patients enrolled, n	Disease site/stage	Screen for eligibility	Structured interview to determine diagnosis?	Duration of intervention	Covariates adjusted for	Primary Outcome, Assessment timeframe
Ell et al 2008 [56], [64] USA	472	Mixed type and stage	One of the two cardinal depression symptoms >half of days to nearly every day, and PHQ-9 score ≥10, and/or two questions from the SCI-DSM-4 indicating dysthymia.	No	PST delivered weekly for 6-12 weeks. Telephone maintenance/relapse prevention and outcomes monitoring continued for 12 months.	Yes; baseline depression severity, anxiety, dysthymia, cancer stage, cancer type, treatment status, sex, race, years in USA	Rate of response (>50% reduction from baseline in PHQ-9 score), also a 5-point reduction in PHQ-9 score was considered clinically meaningful. Assessments at 6, 12, 18 and 24 months.
Strong et al, 2008 [57] Scotland, UK	200	Mixed type and stage	HADS-D ≥15 Eligible if had MDD defined by SCL-20 ≥1.75. Adjustment disorder not included.	SCI DSM-4 for MDD	Intervention: max of 10 one-to-one therapy sessions over 3 months	3 month scores adjusted for baseline score, sex, age, diagnosis, extent of disease. 6 and 12 month scores unadjusted.	SCL-20 mean scores at 3 months after assignment. Outcomes also reported at 6 and 12 months.
Fann et al, 2009 [58] USA	215	Mixed disease site and stage	Some pts identified through referral from primary care. Others recruited using a two-question screen adapted from the PRIME- MD study	SCI DSM-4 to diagnose major depression or dysthymia	Intervention for up to 12 months (PST offered for 6 to 8 sessions). UC participants followed for additional year after initial 12 months.	No	SCL-20 (depression items from the SCL-90) mean score. Remission defined as SCL-20 score less than 0.5. Response (50% reduction from baseline in SCL-20) Reported for 3, 6, 12, 18, and 24 months
Kroenke et al, 2010 [59] USA	405	Mixed type and stage	At least moderately severe depression (PHQ-9 score ≥10) and endorsement of depressed mood and/or anhedonia	No	Phone calls at weeks 1, 4, and 12. Calls also triggered by automatic symptom monitoring.	p-value not adjusted for multiple comparisons (does not affect primary outcome). Baseline value of the outcome variable and time	SCL-20 mean scores at 1, 3, 6, and 12 months

Study, year (reference) Country	Patients enrolled, n	Disease site/stage	Screen for eligibility	Structured interview to determine diagnosis?	Duration of intervention	Covariates adjusted for	Primary Outcome, Assessment timeframe
Sharpe et al, 2014 [60] Scotland	500	Breast, gyne, GU, GI, "good prognosis"	Conducted by an NHS screening service	SCI DSM-4 to diagnose probable major depression	10 sessions over 4 months	Trial centre, age, primary cancer, sex, baseline score	At least 50% reduction in SCL-20 at 24 weeks.
Walker et al 2014 [61] Scotland	142	Lung cancer, "poor prognosis"	Conducted by an NHS screening service	SCI DSM-4 to diagnose probable major depression	Up to 32 weeks	Trial centre, age sex, cancer type, baseline score	Depression severity (using SCL-20) over time in trial (up to 32 weeks)

ADIS-IV = Anxiety Disorders Interview Schedule, fourth edition, BATD = Behavioral Activation Treatment for Depression, BDI = Beck Depression Inventory, BDI-II = Beck Depression Inventory-II, BSI = Brief Symptom Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, CT = cognitive therapy, DSM-3-R = Diagnostic and Statistical Manual of Mental Disorders Third Edition Revised, DSM-4 = Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, GI = gastrointestinal, GSI = Global Severity Index, GU = genitourinary, HADS = Hospital Anxiety and Depression Scale, HADS-D = Hospital Anxiety and Depression Scale depression subscale, HANDS = Harvard Department of Psychiatry/NDSD scale, HRSD = Hamilton Rating Scale for Depression, MADRS = Montgomery–Åsberg Depression Rating Scale, MDD = major depressive disorder, NHS = United Kingdom National Health Service, NR = not reported, PHQ-9 = Patient Health Questionnaire 9, POMS = Profile of Mood States, PRIME-MD = Primary Care Evaluation of Mental Disorders, PST = problem-solving therapy, PTCI = Posttraumatic Cognitions Inventory, pts = patients, SCI-DSM-4 = Structured Clinical Interview for DSM-4 Axis I Disorders, SC = supportive counseling, SCI-DSM-4-TR = Structured Clinical Interview for DSM-4-TR Axis I Disorders, SCID = Structured Clinical Interview for DSM Disorders, SCL-20 = Hopkins Symptom Checklist, SCL-90 = Symptom Checklist-90, STPP = short-term psychodynamic psychotherapy, TAU = treatment as usual, UC = usual care.

Study Outcomes

Pharmacological Interventions

Of eight pharmacological studies meeting the inclusion criteria, two studies of mianserin compared with placebo control group [25,28], and one study of methylphenidate plus mirtazapine compared with placebo plus mirtazapine [36] found significant differences between groups (Table 7).

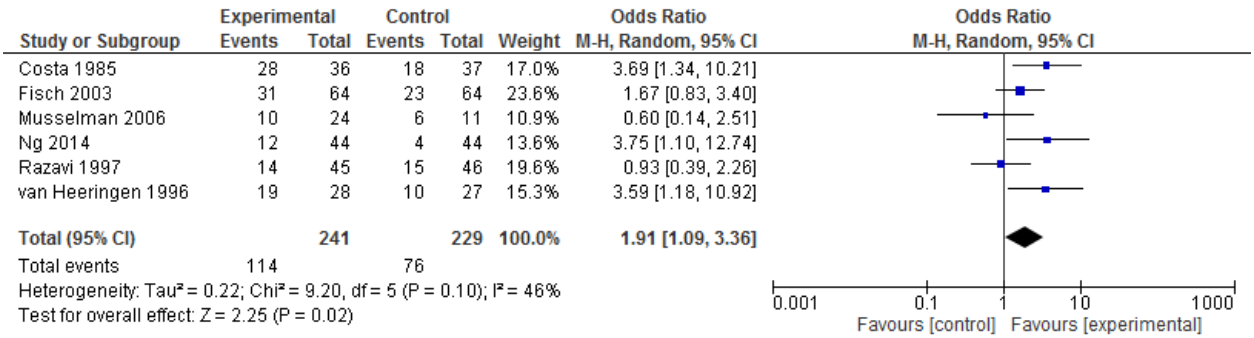
Table 7. Odds ratios for short-term response to pharmacological therapy.

Study, year (reference)	Comparison groups	Sample size	Effect sizes expressed as odds ratios (95% confidence interval) for short-term response (range 3 to 8 weeks)
Costa et al, 1985 [25]	Mianserin vs. placebo	73	**3.69 (1.34, 10.21)**
Razavi et al, 1996 [27]	Fluoxetine vs. placebo	91	0.93 (0.39, 2.26)
Van Heeringen et al, 1996 [28]	Mianserin vs. placebo	55	**3.59 (1.18, 10.92)**
Holland et al, 1998 [29]	Fluoxetine vs. desipramine	38	no significant differences post-treatment ($p>0.05$) (mean scores not reported)
Pezzella et al, 2001[31]	Paroxetine vs. amitriptyline	175	1.27 (0.69, 2.33)
Fisch et al, 2003 [33]	Fluoxetine vs. placebo	128	1.67 (0.83, 3.40)
Musselman et al, 2006 [34]	Paroxetine vs. desipramine vs. placebo	35	0.32 (0.07, 1.48)
Ng et al, 2014 [36]	Methylphenidate+mirtazapine vs. placebo+mirtazapine	88	**3.75 (1.10-12.74)**

Values in bold indicate significantly better outcomes for the treatment group compared with the placebo group. Odds ratios are for response to the administration of treatment or placebo, as measured by a validated depression rating scale. vs. = versus.

The two new pharmacological studies that met the study inclusion criteria [34,36] were added to the relevant RCTs from the previous version of this guideline to provide an estimate of the beneficial effect of this type of therapy on patients with concurrent cancer and depression (Figure 1). The overall effect when all studies were combined was an OR of 1.91 (95% CI, 1.09 to 3.36) (Figure 1). Of the studies that found no difference, at least one did not have a large enough sample size to achieve the specified power to detect a treatment effect [34]. There was a moderate level of statistical heterogeneity among studies in this analysis (I^2 = 46%). A sensitivity analysis (not shown) that removed each study in turn from the analysis did not result in a reduction in heterogeneity; therefore, all studies were retained in the analysis, and the Working Group advises that the results be interpreted with caution.

Figure 1. Estimate of overall efficacy of pharmacological therapy (short-term response over three to eight weeks).



Psychological

Intervention effects were assessed immediately after treatment (13 days [49] to 56 weeks [54]), and some studies provided data for follow-up assessments, at time periods that ranged from 24 weeks to 12 months [49]. Four studies found a significant improvement in mean depression scores or odds of remission post-treatment for interventions including CBT [40,53] social support [40], problem solving therapy with or without a significant other [43], brief psycho-oncological support [49], and short-term psychodynamic psychotherapy [54] (Table 8). The significant differences found post-treatment did not persist at follow-up assessments in all but one study [53].

Table 8. Results of trials of psychological interventions.

Study Year [reference] Country	Comparison groups	Sample size	Effect size expressed as SMD (95% confidence interval) post-treatment (2-56 weeks)	Effect size expressed as SMD (95% confidence interval) at follow-up (24 weeks to 12 months)
Evans et al, 1995 [40] USA	CBT vs. no treatment SS vs. no treatment	78	**-0.65 (-1.21, -0.08)** **-0.96 (-1.58, -0.34)**	0.14 (-0.41, 0.69) -0.56 (-1.16, 0.04)
Nezu et al, 2003 [43] USA	PST vs. WLC PST-SO vs. WLC	150	**-3.79 (-4.49, -3.08)** **-4.33 (-5.11, -3.55)**	NR
Savard et al, 2006 [45] Canada	CBT vs. WLC	45	-0.23 (-0.88, 0.42)	NR
Goerling et al, 2011 [49] Germany	"low-threshold" psycho-oncological support vs. observation	101	**-0.79 (-1.19, -0.38)**	-0.10 (-0.72, 0.52)
Hopko et al, 2011 [50] USA	BAT vs. PST	80	BDI-II: 0.14 (-0.30, 0.58) HRSD: -0.16 (-0.60, 0.28)	BDI-II: -0.12 (-0.56, 0.32) HRSD: -0.07 (-0.51, 0.36)
Rodriguez Vega et al, 2011 [51] Spain	NT and escitalopram vs. UC and escitalopram	72	-0.31 (-0.77, 0.16)	-0.40 (-0.87, 0.07)
Kangas et al, 2013 [52] Australia	Brief, early CBT vs. nondirective supportive counselling	35	0.14 (-0.53, 0.82)	-0.39 (-1.07, 0.29)
Qiu et al, 2013 [53] China	Group CBT vs. wait list control	62	**-2.17 (-2.80, -1.53)**	**-1.49 (-2.06, -0.93)**
Beutel et al, 2014 [54] Germany	STPP vs. UC	157	**OR for HADS-D reduction of at least 2 points or remission as measured by SCID: 7.6 (2.3-25.1)**	NR

BAT = behavioural activation treatment, BDI-II = Beck Depression Inventory-II, CBT = cognitive behavioural therapy, CI = confidence interval, HADS-D = Hospital Anxiety and Depression Scale depression subscale, HRSD = Hamilton Rating Scale for Depression, NR = not reported, NT = narrative therapy, OR = odds ratio, PST = problem-solving therapy, PST-SO = problem-solving therapy with significant other, SCID = Structured Clinical Interview for DSM Disorders, SMD = standardized mean difference, SS = social support, STPP = short-term psychodynamic psychotherapy, UC = usual care, vs. = versus, WLC = wait list control.
Values in bold indicate significantly better outcomes for the treatment group compared with the control or usual care group.
Where usual care is compared with a treatment group, negative SMD values indicate lower (better) scores in the treatment group.

The studies that compared treatment groups with a usual care/no treatment control group were included in meta-analyses of shorter- and longer-term effects (Figure 2 and Figure 3, respectively). Where more than one intervention was compared with a control group in a study, the intervention groups were collapsed to avoid multiple comparisons with the same control group [40]. The level of heterogeneity was considerable in the analysis of short-term efficacy (I^2=96%); therefore, a sensitivity analysis was conducted to determine its source. The elimination of two studies [43,53] that reported the largest effect sizes (Table 8) reduced the level of heterogeneity to an acceptable level (17%). The members of the Working Group could

not determine the reason for the additional heterogeneity introduced by these two studies; therefore, they were retained in the analyses and the members of the Working Group advise that the results be interpreted with caution. The results significantly favoured the experimental groups both when the highly heterogeneous studies were included (standardized mean difference [SMD], -1.40 [95% CI, -2.50 to -0.29]) (Figure 2) and when they were omitted from the analysis (SMD, -0.55 [95% CI, -0.81 to -0.28]).

The significant difference between experimental and control groups did not persist at follow-up in the four studies that provided longer-term data (SMD, -0.55 [95% CI, -1.14 to 0.04]) (Figure 3).

Figure 2. Response to psychological interventions: mean difference post-treatment (2 to 13 weeks)[1,2]

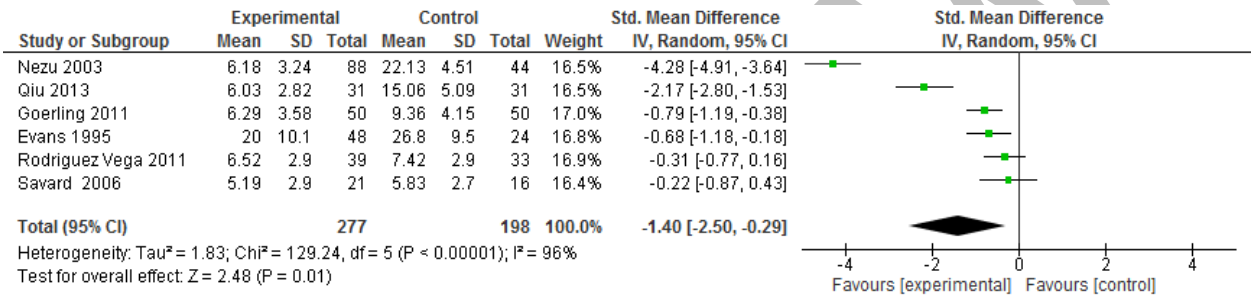
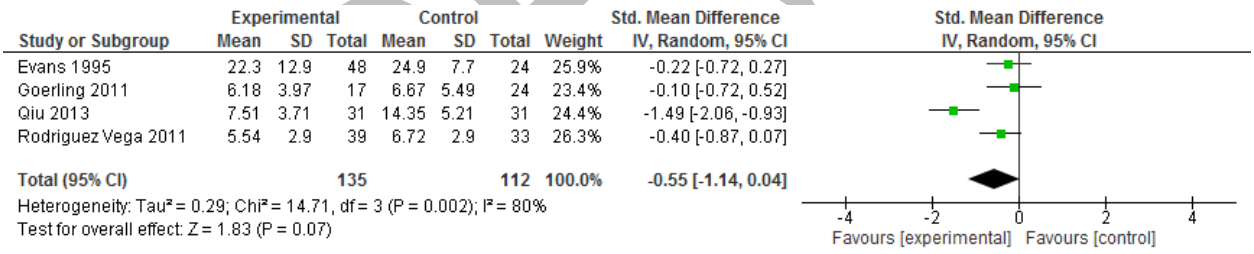


Figure 3. Response to psychological interventions: mean difference at follow-up (24 weeks to 12 months)



Collaborative care

Two measures of effect size are reported in Table 9 for the collaborative care interventions included in this review: the SMD between groups post-treatment and the OR for 50% reduction in score on a validated depression rating scale. In all studies significant beneficial effects of treatment, as measured by SMD and/or OR, were observed at various time periods,

[1] Outcomes for the two treatment groups in Evans and Connis [104] and Nezu et al [107] were combined to produce an overall treatment group effect size by dividing the difference in means by the pooled standard deviation (s_{pooled}), where $s_{pooled} = \sqrt{\frac{s_1^2(n_1-1)+s_2^2(n_2-1)}{n_1+n_2-2}}$.

[2] Where the standard deviation (s) was not provided, it was calculated using standard error (SE) according to the formula s=SE(√[n-1]).

including three, six, 12, 18, and 24 months following initiation of a collaborative care intervention. Significant results are presented in bold in Table 9.

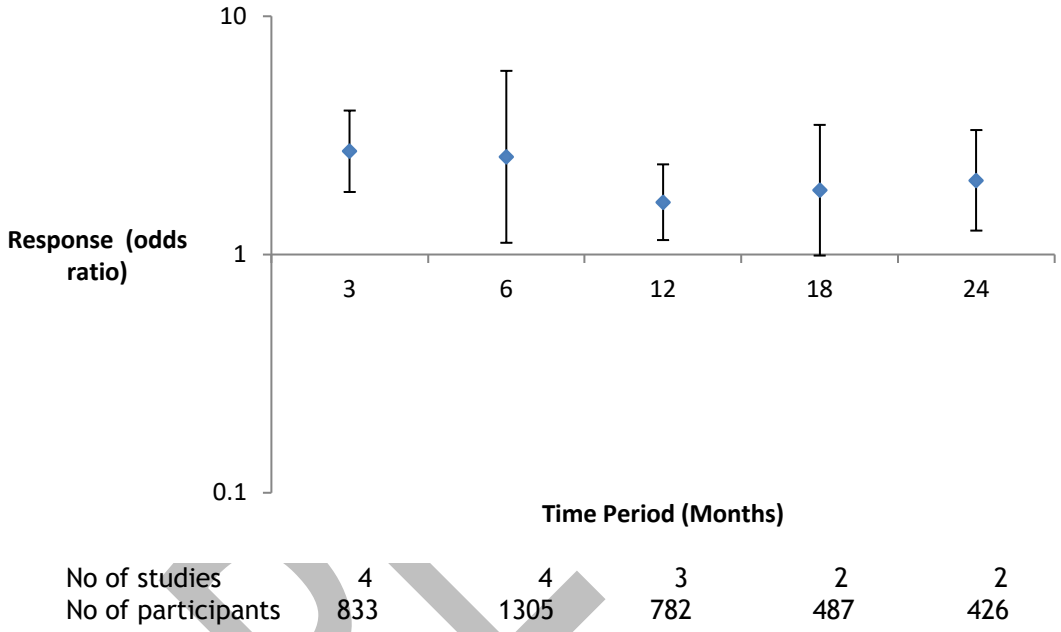
Table 9. Effect sizes for response to collaborative care interventions versus usual care.

Study, year (reference)	pts, n	Effect size (95% CI) according to time period from treatment (months)							
		3		6		12		18†	24†
		SMD (95% CI)	OR (95% CI)	SMD (95% CI)	OR (95% CI)	SMD (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Ell et al, 2008 [56]	472	NR	NR	-0.19 (-0.41, 0.03)	1.36 (0.88, 2.12)	-0.23 (-0.47, 0.02)	**1.72 (1.04, 2.83)**	NR	NR
Ell et al, 2011 [124]	472	NR	NR	NR	NR	NR	NR	1.45 (0.87, 2.41)	**2.09 (1.13, 3.86)**
Strong et al, 2008 [57]	200	**-0.38 (-0.66, -0.09)**	**2.12 (1.19,3.77)**	**-0.60 (-0.88, -0.31)**	NR	**-0.34 (-0.62, -0.06)**	NR	NR	NR
Fann et al, 2009 [58]	215	**-0.45 (-0.72, -0.18)**	**3.01 (1.54, 5.90)**	**-0.35 (-0.62, -0.08)**	**2.26 (1.30, 3.93)**	**-0.47 (-0.74, -0.20)**	**2.36 (1.26, 4.44)**	**2.79 (1.44, 5.41)**	**1.99 (1.01, 3.92)**
Kroenke et al, 2010 [59]	405	NR	**2.15 (1.24, 3.73)**	**-0.45 (-0.68, -0.22)**	**1.78 (1.03, 3.07)**	**-0.35 (-0.57, -0.12)**	1.18 (0.68, 2.07)	NR	NR
Sharpe et al, 2014 [60]	500	**-0.87 (-1.06, -0.69)**	NR	**-1.03 (-1.22, -0.85)**	**2.57 (1.12, 5.90)**	**-1.02 (-1.20, -0.83)** ††	NR	NR	NR
Walker et al, 2014 [61]	142	NR	**5.88 (2.42, 14.33)**	NR	NR	NR	NR	NR	NR

CI = confidence interval, NR = not reported, OR = odds ratio for 50% reduction in mean score on a validated depression rating scale, pts = patients, SMD = standardized mean difference in scores between collaborative care intervention group compared with control group.
Values in bold indicate significantly better outcomes for the collaborative care intervention group compared with the control or usual care group.
†No studies reported SMDs at 18 or 24 months. †† Outcome at 48 weeks.

In the studies of collaborative care interventions, the odds of response to treatment, defined as a 50% reduction in score on a validated depression rating scale, were significantly higher in the intervention groups at various time periods following the initiation of the intervention: OR, 2.72 (95% CI, 1.83 to 4.02) at three months; OR, 2.57 (95% CI, 1.12 to 5.90) at six months; OR, 1.66 (95% CI, 1.15 to 2.39) at 12 months; OR, 1.87 (95% CI, 0.99 to 3.50) at 18 months; and OR, 2.05 (95% CI, 1.26 to 3.33) at 24 months (Figure 4). The two studies that assessed outcomes at 24 months retained 44% and 85% of their participants, respectively. Detailed forest plots for the data in Figures 4 to 6 are available in Section 2, Appendix 7.

Figure 4. Odds ratios for 50% decrease in depression mean score after initiation of a collaborative care intervention (intervention group versus control group).

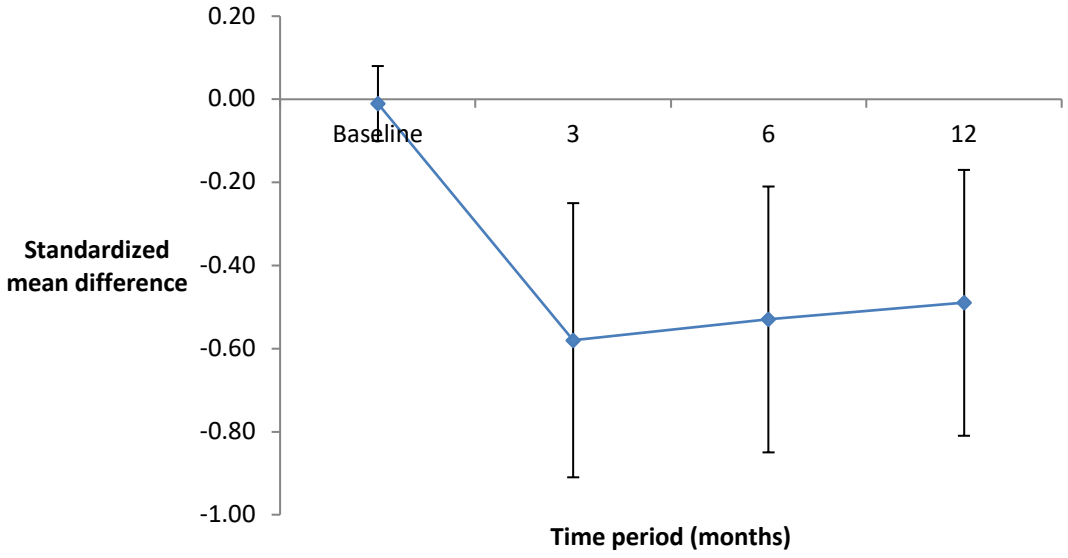


No of studies	4	4	3	2	2
No of participants	833	1305	782	487	426

Error bars represent 95% confidence intervals. Results are presented on a logarithmic scale.

The baseline SMD of -0.01 with a 95% CI of -0.10 to 0.08 indicates that the intervention and control groups did not differ in mean scores prior to the initiation of treatment. After initiation of the collaborative care intervention, the mean scores for those who received the intervention were significantly lower than the mean scores for those who had been randomized to usual care (Figure 5). The greatest difference in means was observed at the three-month assessment (SMD, -0.58 [95% CI, -0.91 to -0.25]), and significant differences were also detected at six months (SMD, -0.53 [95% CI, -0.85 to -0.20]) and 12 months (SMD, -0.49 [95% CI, -0.81 to -0.16]) (Figure 5).

Figure 5. Standardized mean difference in scores on a validated depression rating scale for collaborative care intervention and control groups.

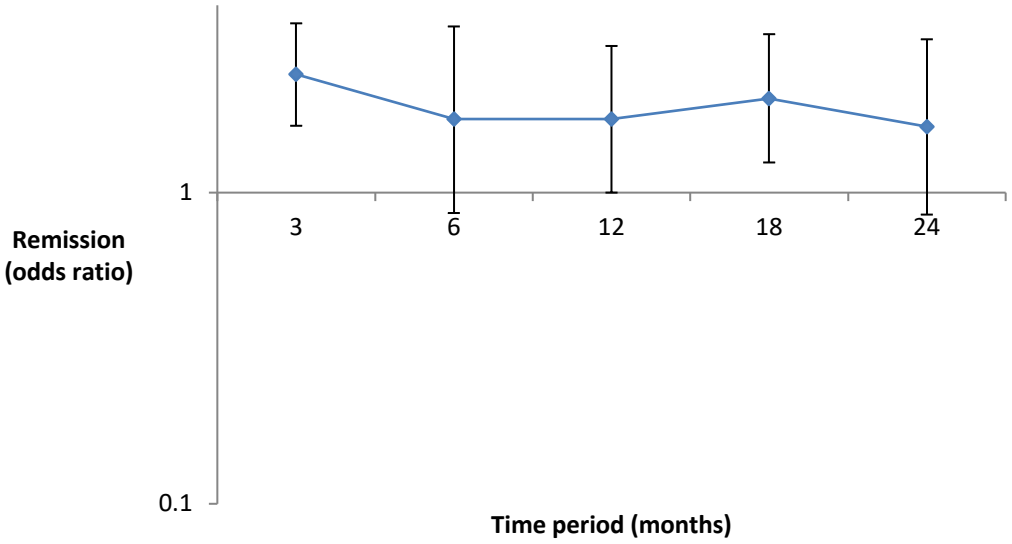


No of studies	6	3	5	5
No of participants	1934	911	1542	1482

Error bars represent 95% confidence intervals.

Remission of depression, defined as a score below an established threshold for diagnosis of depression on a validated depression rating scale, was assessed at three, six, 12, 18, and 24 months (Figure 6). At three months (OR, 2.40 [95% CI, 1.64 to 3.52]), the odds of remission were significantly greater for intervention participants compared with patients assigned to usual care. The odds ratio at 18 months was also significant (OR, 1.72 [95% CI, 0.86 to 3.42]). In general, fewer studies and participants included in the analyses of remission rates resulted in less power to detect statistically significant differences (Figures 4 and 5), compared with the analyses of response rates.

Figure 6. The odds ratios for remission in the collaborative care intervention groups compared with control groups at 3-, 6-, 12-, 18- and 24-month time periods as measured by a validated depression rating scale.



No of studies	3	2	3	2	2
No of participants	601	535	661	535	535

Error bars represent 95% confidence intervals. Results are presented on a logarithmic scale.

Adverse Events

Overall adverse effects were more common with mianserin compared with placebo (p>0.05) [25]. Emesis was more common with fluoxetine compared with placebo (p=0.01) [33], and dry mouth was more likely with fluoxetine compared with desipramine (p=0.008) [29].The new pharmacological intervention report identified in this systematic review [34] found that 15% of the paroxetine group, 9% of the desipramine group, and 18% of the placebo group left the study early due to adverse events, the nature of which were consistent with the safety profiles for SSRIs and TCAs. Adverse events data were not captured for the studies of psychological interventions.

DISCUSSION

Pharmacological and Psychological Interventions

Strikingly, only five placebo-controlled RCTs of pharmacological interventions in cancer populations in which threshold depression was an entry criteria have been published to date, to our knowledge [25,27,28,33,34]. Similarly, there have only been six wait list or usual care controlled psychological intervention studies for patients with cancer and threshold depression [40,43,45,49,53,54]. The few additional studies comparing active pharmacological [29,31] or psychosocial [50-52] interventions have failed to show group differences.

In pharmacotherapy, there is rigorous evidence of effectiveness only for mianserin [25,28], which is no longer available in North America, and is not ideal due to risk of bone marrow suppression. Three trials of fluoxetine [27,29,33] and two trials each of paroxetine [31,34] and desipramine [29,34], failed to demonstrate separation from placebo. Paroxetine and desipramine are also not recommended as first-line treatments in patients with cancer due to significant drug interactions and detrimental side effects. In the seven years since the previous version of this guideline, there have been only two new RCTs of pharmacological treatments for threshold depression in patients with cancer [34,36], and the first of these two was underpowered to detect differences.

In psychotherapy, there has been considerable controversy [65,66] over the effectiveness of psychosocial interventions in reducing depression, largely due to the preponderance of group-as-a-whole studies which fail to take into account floor effects from enrolling patients with cancer and without major depression as an entry criterion [67]. No studies from the previous version of this guideline met the inclusion criteria for the updated systematic review, mostly because depression was not an inclusion criterion in those studies. Since then, eight qualifying RCTs have been published, and these demonstrate short-term superiority of intervention over controls (Figures 2 and 3), but there remains insufficient evidence to support the superiority of one modality over another.

Cuijpers et al suggested that combined pharmacological and psychological treatments are more effective than either approach alone in primary depression [68], but this has not been adequately tested in cancer populations. Only a single RCT combining narrative therapy with escitalopram detected no added benefit over escitalopram alone in patients with nonmetastatic breast, lung, and colon cancer [36]. Such combined treatments, however are often included as components of the emerging collaborative care models of treatment in patients with cancer.

Collaborative Care Interventions

While there is a paucity of new literature to inform recommendations for single interventions, new RCTs of collaborative care interventions in the population of interest have been identified in this review. Collaborative care interventions are based on the Chronic Care Model, which has six essential elements, including:

- The community,
- The health system,
- Self-management support,
- Delivery system design,
- Decision support, and
- Clinical information systems [69] .

Collaborative care interventions included in this review were characterized by active collaboration between specialist and primary care providers, usually assisted by a care manager, typically including measurement-based care. In many cases, a stepped care approach to interventions was used, with low-intensity interventions being considered first, and

intervention intensity tailored to depression severity. Collaborative care interventions were evaluated as first-line treatments in groups of patients with major depressive disorder.

This meta-analysis found that these interventions resulted in significantly better depression scores compared with usual care at three months or longer after initiation. The finding that these beneficial effects were maintained up to 24 months is encouraging. Because these interventions include several components, it is difficult to determine the contribution of each component to the overall effect, or to determine which single component made the greatest contribution.

Limitations of the Evidence Base

The literature on managing depression in patients with cancer presents many challenges. As mentioned, the literature includes many studies of depression interventions in patients with subthreshold levels of depression in which it is difficult to observe an effect of treatment due to floor effects. Therefore, we chose to limit the eligibility of studies to those in which patients met validated thresholds for major depression or a depressive disorder. Many systematic reviews were found that had overlapping scope and slight variations in inclusion criteria, so we decided to use RCTs as our evidence base, rather than trying to resolve the results of many similar systematic reviews. Trials that are underpowered to detect differences between treatment and control groups are a major issue. Some studies reported difficulties accruing sufficient sample sizes to achieve adequate power [34], a problem that is also reflected in the relative absence of new placebo-controlled studies. The strong placebo effects in depression intervention studies result in positive findings for most interventions, making effect size measured as the SMD compared with placebo the gold standard for the effectiveness of an intervention. One of two pharmacological studies published since the last version of this guideline was underpowered to detect differences due to recruitment challenges [34], and placebo effects in psychological intervention studies are arguably even more powerful and difficult to control. Placebo effects are a well-recognized confounding variable in depression treatment studies, accounting for almost 40% of symptom reduction in control groups, compared with the average 50 to 60% symptom reduction with antidepressants or psychotherapy [70].

Other methodological issues were the inconsistency with respect to study populations, with some studies including patients with adjustment disorder, and multiple comparisons using several different assessment scales. A further confounding variable is the use of only depression rating scale scores for study entry due to the uncertainty regarding appropriate cut-off thresholds for depression in patients with cancer, whose scores may be elevated by cancer-related symptoms. Validated screening and case-finding cut-offs used in psychiatric populations are generally too low to represent, with specificity, major depression in patients with cancer [71].

FUTURE RESEARCH

Future research priorities include studies with significantly larger sample sizes, designed and powered to detect placebo-controlled differences for moderate/severe major depression, and stratified to study effectiveness in subthreshold/mild depression. Such studies would be facilitated by research better characterizing the phenomenology of depressive symptoms in patients with cancer in terms of diagnostic thresholds, qualitatively distinguishing depressive symptoms from cancer-related symptoms, and elucidating the nosology of subthreshold and mild depressive symptoms in the context of cancer.

Studies are urgently needed that can identify effective strategies for patients with cancer who are resistant to treatment of depression or for whom first–line treatment is not successful. Methodological barriers to the conduct of such studies, including exploration of

factors associated with low patient recruitment, and the ethical challenge of conducting placebo-controlled studies in patients with cancer and depression, will first need to be overcome. Future CC trials in patients with cancer should explore the relative effectiveness of the individual components in the model.

Specific areas of need regarding pharmacological research include the use of stimulant medication, particularly in patients with a limited lifespan. Longer-acting stimulants such as lisdextroamphetamine or OROS-methylphenidate, either alone or in combination with a traditional antidepressant agent, have not been studied in patients with cancer. Similarly, atypical antipsychotics such as aripiprazole, olanzapine, or quetiapine, which have been shown to possess efficacy particularly as augmentation agents in treatment-resistant major depression, should also be a focus of future cancer research. These agents can affect prolactin levels to varying degrees and this may have relevance to patients with breast cancer who have prolactin-sensitive tumours [72]. Vortioxetine, a novel multimodal antidepressant, has demonstrated efficacy for depression and cognitive outcomes in non-medically ill populations, and may be of interest to study in depressed cancer patients with chemotherapy induced cognitive dysfunction [73].

Emerging psychological therapies that may contribute to recommendations for future versions of this guideline include Meaning Centred-Therapy [74,75], Dignity Therapy [76], Managing Cancer and Living Meaningfully (CALM) [77] and Mindfulness-Based Stress Reduction or Mindfulness-Based Cognitive Therapy (briefly described in Appendix 5). These modalities have shown promise in reducing emotional distress in patients with cancer, but have yet to demonstrate effectiveness for depression outcomes. There is a need for research to focus on the tailoring of psychological therapies to address unique needs or patient characteristics that may enhance the efficacy of specific interventions for individual patients. For example, demographic, disease, or personality factors may lead to a preference for individual versus group therapy formats. Finally, there should be a focus on conducting high-quality research to establish an evidence base for the management of subthreshold/mild depression, which is the most common presentation of depression in patients with cancer.

CONCLUSIONS

This systematic review found limited evidence for the effectiveness of antidepressants in patients with cancer, which is largely attributable to the paucity of the evidence base. Therefore, recommendations around the management of depression in patients with cancer have been extrapolated from existing guidelines on the general management of depression in psychiatric and other medical populations. Supportive evidence for the effectiveness of psychological interventions for patients with cancer who are experiencing clinically significant depression was identified, and the NICE stepped care model for management of depression in patients with chronic physical health problems was endorsed for low- and high-intensity psychological interventions due to limited evidence (in cancer populations) for recommending one type of intervention over another.

In this review, the most effective interventions were based on collaborative care models, which allow for combined psychological and antidepressant treatment tailored to depression severity. In addition to efficacy, collaborative care interventions have also been shown to be associated with modest additional costs [60]. Implementation of collaborative care in Ontario for patients with cancer who are experiencing depression implies a reorganization of care delivery that may be a significant challenge. Another consideration is that optimal interventions may not be easily accessible or accessible in a timely way.

This updated systematic review did not find any new evidence to alter the conclusions of the previous version of this guideline regarding individual pharmacological or psychological therapies for patients with cancer and depression. Patients with cancer who are diagnosed with

major depression may benefit from pharmacological or psychological interventions either alone or in combination, without evidence for the superiority of any specific treatment over another. A renewed research agenda is urgently needed to re-invigorate interventional research for depression in cancer, with the ultimate goal of improving quality of life and health outcomes for all patients with cancer.

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A complete list of the members of the Management of Depression in Patients with Cancer Expert Panel and the Working Group, with their affiliations and conflict of interest information, is provided in Section 3, Appendix 1.

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Appendix 1. Literature Search Strategy

1. dysthm*.tw.
2. (subclinical adj2 depressi*).tw.
3. (subsyndromal adj2 depressi*).tw.
4. (subthreshold adj2 depressi*).tw.
5. (subdiagnostic adj2 depressi*).tw.
6. Depression/
7. depressive disorder/ or depressive disorder, major/ or dysthymic disorder/
8. depressive disorder.mp. or exp depressive disorder /
9. exp depressive disorder / or exp dysthymic disorder/
10. major depression.mp.
11. dysthymic disorder.mp. or exp dysthymic disorder/
12. or/1-11
13. meta-analysis.pt,ti,ab,sh.
14. (meta anal$ or mataanal$).ti,ab,sh.
15. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
16. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.
17. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
18. (medline or embase or cochrane).ti,ab.
19. review.pt,sh.
20. or/13-19
21. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
22. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
23. random allocation/ or double blind method/ or single blind method/
24. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
25. or/21-24
26. cancer.mp.
27. (tumour: or tumor: or neoplas:).mp.
28. cancer.tw.
29. (tumour: or tumor: or neoplas:).tw.
30. exp neoplasms/
31. or/26-30
32. 12 and 30 and (19 or 24)
33. (comment or editorial).pt.
34. 32 not 33
35. limit 34 to english language
36. limit 35 to yr=2013-2014
37. exp practice guidelines/
38. guideline?.tw,pt,sh.
39. consensus.sh,tw,pt.
40. or/37-39
41. 40 not 33
42. limit 41 to english language
43. limit 42 to yr="2005-2013"
44. 43 and 12 and 30
45. remove duplicates from 44

46. remove duplicates from 36
47. 45 or 46

Appendix 2. Websites included in environmental scan and search for guidelines.

Database/Source (Website)
Standards and Guidelines Evidence (SAGE) http://www.cancerguidelines.ca
National Institute for Health and Clinical Excellence (NICE) (UK) http://www.nice.org.uk/
Canadian Medical Association (CMAJ) http://www.cma.ca
Scottish Intercollegiate Guidelines Network (SIGN) (UK) http://www.sign.ac.uk/guidelines/index.html
ASCO (USA) http://www.instituteforquality.org/practice-guidelines
National Health and Medical Research Council (Australia) http://www.nhmrc.gov.au/publications/subjects/cancer.htm
New Zealand Guidelines Group http://www.health.govt.nz/
EPHA http://ec.europa.eu/
Canadian Network for Mood and Anxiety Treatments (CANMAT) http://www.canmat.org/
Canadian Association of Psychosocial Oncology (CAPO) http://www.capo.ca
Province of British Columbia http://www.BCGuidelines.ca
Vancouver Island Health Authority (VIHA) http://www.viha.ca/

Appendix 3. Results of AGREE II quality rating of evidence-based guidelines. (1 = strongly disagree, 7 = strongly agree).

AGREE II Domain Scores (average scores for three reviewers for items measured on a seven-point scale)						
Guideline	Scope and Purpose (3 items)	Stakeholder Involvement (2 items)	Rigour of Development (8 items)	Clarity of Presentation (3 items)	Applicability (4 items)	Editorial Independence (2 items)
NICE [20]	6.6	6.6	6.9	7	4.1	6.6
EPCRC [21]	6.2	5.9	5.8	6.1	2.2	6.4

Appendix 4. Excluded guidelines.

Organization	Guideline	Include?	Reason for exclusion/inclusion
European Organization for Research and Treatment of Cancer (EORTC) [78]	The management of depression in palliative cancer care	No	Treatment recommendations are based on the same systematic reviews as EPCRC [21] and recommendations are the same.
Canadian Network for Mood and Anxiety Treatments [79]	The CANMAT task force recommendations for the management of patients with mood disorders and select comorbid medical conditions	No	Narrative (not systematic) review
American College of Physicians[80]	Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians	No	Search date too old; based on evidence published prior to previous PEBC guideline (29).
Canadian Association of Psychosocial Oncology [81]	A Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer,	No	Limited overlap in scope; this guideline mostly addresses screening, secondary assessment, and its treatment algorithm addresses distress rather than mild/major depression.

Appendix 5. References to studies excluded after full text review.

Study, year (reference)	Reason for exclusion
Amodeo et al, 2012 [82]	Dosing study
Bjorneklett et al, 2012 [83]	Overall low baseline depression scores
Boele et al, 2013 [84]	Trial of modafinil
Brown et al 2010	Secondary cross-sectional analysis
Cankurtaran et al, 2008 [30]	Outcomes not reported separately for the group of patients with depression
Courneya et al, 2007 [46]	Depression not an inclusion criteria
Dobkin et al, 2008 [85]	Not an RCT (no comparison group)
Duffy et al, 2006 [86]	Low baseline depression scores
Feng et al 2011 [87]	Not a comparison of a psychological or pharmacological intervention
Greer et al, 1992 [38]	Study of patients with subthreshold depression
Holland et al, 1991 [26]	Assessment of alprazolam; not an antidepressant medication.
Jean-Pierre et al, 2010	Depression not an inclusion criterion
Johns et al, 2011 [88]	Depression outcomes of interest not reported
Khan et al, 2012 [89]	Depression not an inclusion criterion
Kim et al, 2013 [90]	Both treatment and control groups mean baseline depression scores were subthreshold
Kissane et al, 2003 [42]	Study of patients with subthreshold depression
Leydon et al, 2012 [91]	Not an RCT (feasibility study)
Manne et al, 2007 [92]	Depression not a study inclusion criterion
McQuellon et al, 1998 [41]	Depression not an inclusion criterion. Low % depressed at baseline (treatment: 37%, control: 32%)
Moorey et al, 1994 [39]	Update of Greer et al 1992 [38]. Study of patients with subthreshold depression
Navari et al, 2008 [35]	Prevention trial; patients with clinical depression excluded from eligibility
Perna et al 2010[93]	Depression not an inclusion criterion.
Roscoe et al, 2005 [94]	Primarily a study of reduction of fatigue. Depression not an inclusion criterion
Sharpe et al, 2004 [44]	Comparison of two separate cohorts. Not an RCT
Speer et al 2007 [37]	Thesis. Not available for analysis
Steel et al 2011[95]	Depression outcomes not reported
White et al 2012[96]	Depression not an inclusion criterion
Zwerenz et al, 2012 [97]	Not an RCT (study protocol)
Kissane et al, 2007 [47]	Low rates of depression in treatment and control groups

Appendix 6. Details of collaborative care interventions.

Study, year (reference)	Individual primarily responsible for delivery of intervention	Interventions provided	Algorithm-based care management	Supervision of person responsible for delivery of intervention	Medication prescription	Frequency of maintenance an follow-up	% receiving treatment
Ell et al, 2008 [56] El et al, 2011 [64] (Alleviating Depression Among Patients With Cancer (ADAPt-C), adapted from the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) model)	Cancer depression clinical specialist (social worker with master's degree)	Psychotherapy, community services navigation personalized treatment plan included AM or PST (weekly for 6-12 weeks);	Structured algorithm for stepped care management (to ensure patients received care that was consistent with their clinical presentation) and protocol for PST	Psychiatrist	Psychiatrist	CDCS telephone maintenance/relapse prevention and outcomes monitoring over 12 months.	At six-month assessment, of 166 patients analyzed in intervention group: AM: 4% PST: 43% AM and PST:31% None: 22%
Strong et al, 2008 [57] [60,61] Depression Care for People with Cancer (DCPC)	Nurses with no previous experience in psychiatry trained to deliver intervention	Maximum of 10 one-to-one 45 minute sessions over three months, in-person, by telephone or at home. Sessions included education about depression and its treatment, (including AM); PST	Not mentioned	Progress reviewed by psychiatrist	Primary care physician	A further three-month monitoring of treatment with monthly phone calls using PHQ-9 One to two additional sessions as needed	At three months: 69% of intervention group and 42% of control group taking a therapeutic dose of antidepressants. 11% of total patients saw a mental health specialist (psychiatrist, psychologist, or psychiatric nurse) during the first six months of the trial
Fann et al, 2009 [58] (IMPACT)	Depression care manager (DCM), nurse, or clinical	Psychosocial history, education, behavioural activation, helping patients	Stepped care pharmacotherapy algorithm	DCM met weekly with supervising psychiatrist and expert primary care	Primary care physicians	Contact occurred about every two weeks during acute-phase treatment and monthly contact during continuation and maintenance phases.	At six months, antidepressant use in previous three months was 64% for intervention group

Study, year (reference)	Individual primarily responsible for delivery of intervention	Interventions provided	Algorithm-based care management	Supervision of person responsible for delivery of intervention	Medication prescription	Frequency of maintenance an follow-up	% receiving treatment
	psychologist in primary care clinic	identify treatment preferences. Treatment options: AM and six to eight sessions of "PST in primary care"		physician to monitor progress and adjust treatment		Follow-up to 12 months after initial 12 month treatment	and 48% for usual care group
Kroenke et al, 2010 [59] (Indiana Cancer Pain and Depression (INCPAD) trial	Nurse care manager	"Telephonic care management" Nurses assessed symptom response, medication adherence, provided pain and depression education, treatment adjustments. Calls at baseline, 1, 4, and 12 weeks or triggered by inadequate symptom improvement, nonadherence to medication etc. Patients who preferred not to take antidepressants were encourage to consider psychotherapy	Stepped-care model used for prescription of medication	Weekly case review with pain-psychiatrist specialist or between meetings as needed	Oncologist	Automated symptom monitoring via phone or web up to 12 months, frequency as needed. (PHQ-9)	Of patients with depression in the intervention group, 58% were taking an antidepressant for three or more months.

Appendix 7. Results of meta-analyses of collaborative care interventions.

<u>Figures 1 to 5 show collaborative care response expressed as 50% reduction in score at three, six, 12, 18, and 24 months, and at baseline.</u>

Fig. 1. Collaborative care response (50% reduction in score) at three months.

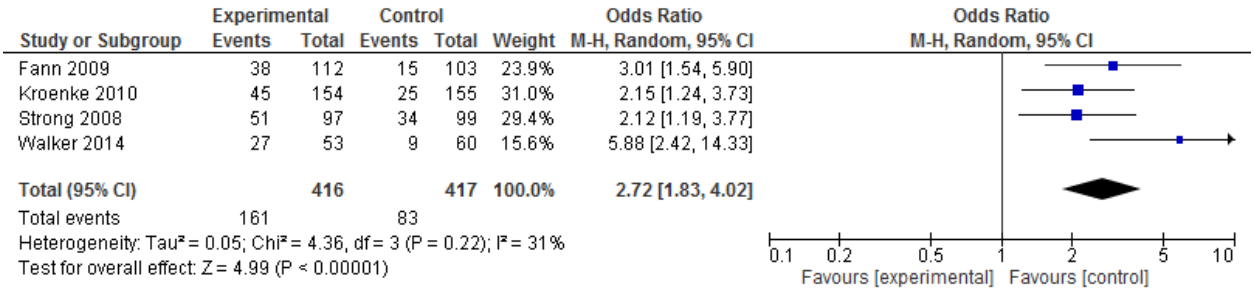


Fig. 2. Collaborative care response (50% reduction in score) at six months.

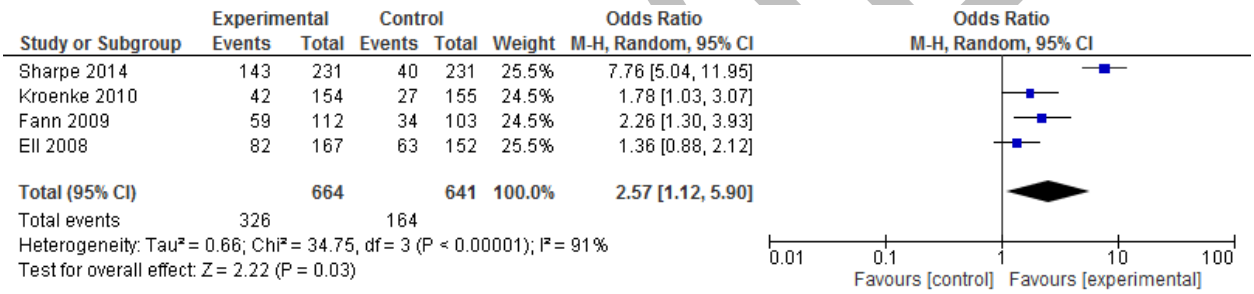


Fig. 3. Collaborative care response (50% reduction in score) at 12 months.

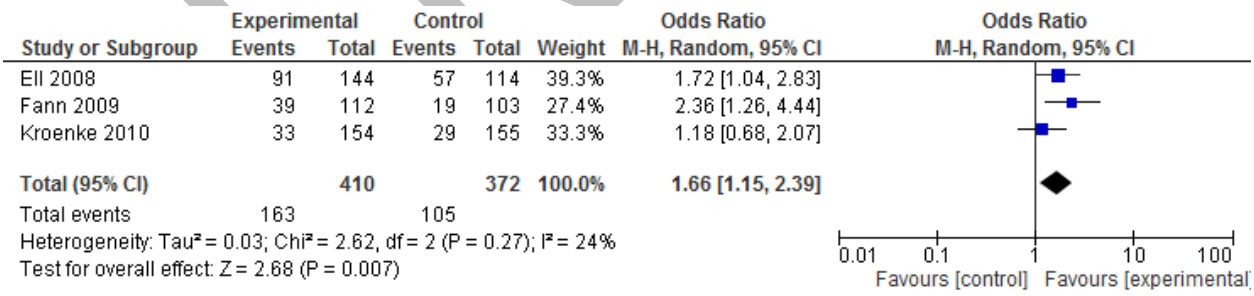


Fig. 4. Collaborative care response (50% reduction in score) at 18 months.

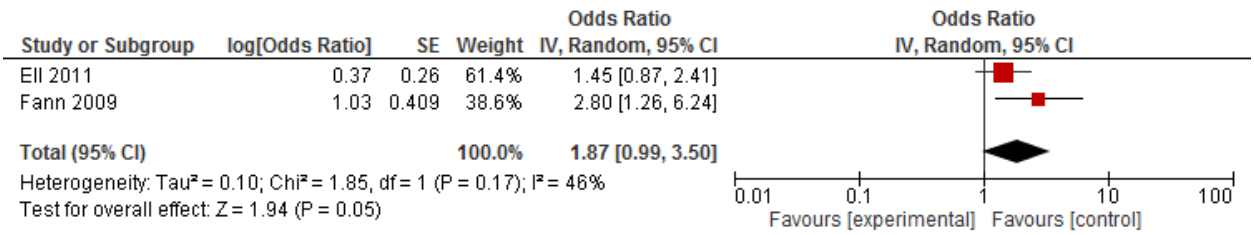
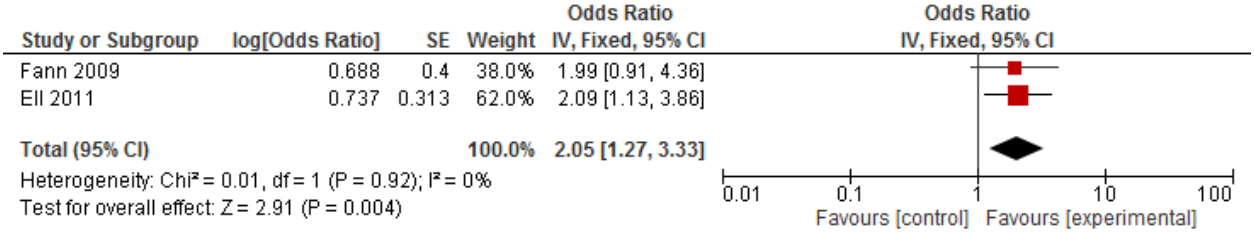


Fig. 5. Collaborative care response (50% reduction in score) at 24 months.



Figures 6 to 9 show the collaborative care response expressed as the difference in mean scores at baseline, at three, six, and 12 months.

Fig. 6. Collaborative care response (difference in mean scores) at baseline.

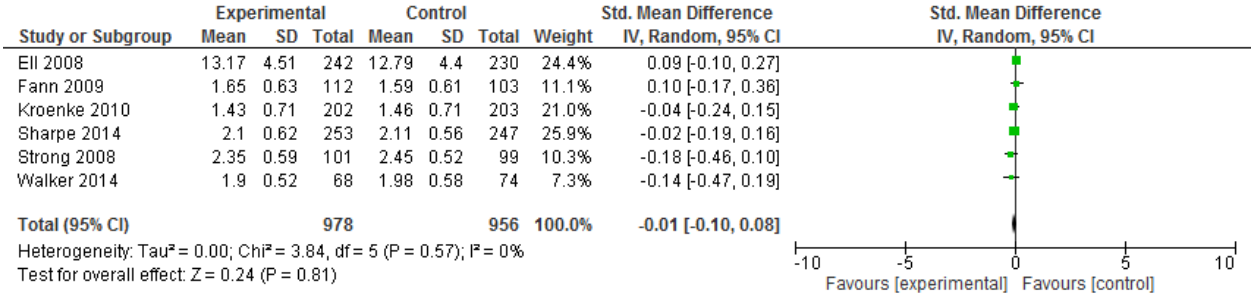


Fig. 7. Collaborative care response (difference in mean scores) at three months.

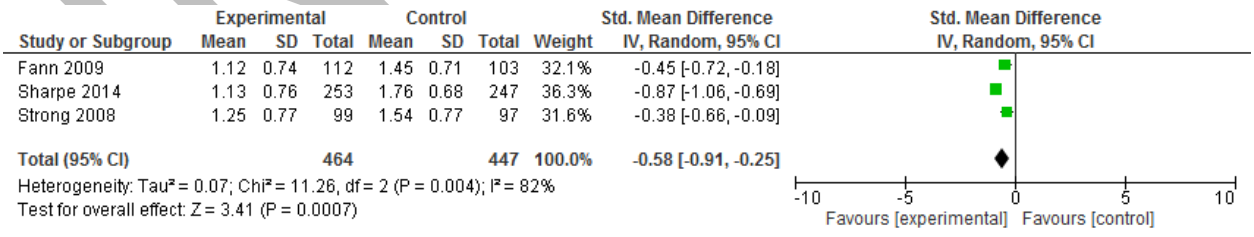


Fig. 8. Collaborative care response (difference in mean scores) at six months.

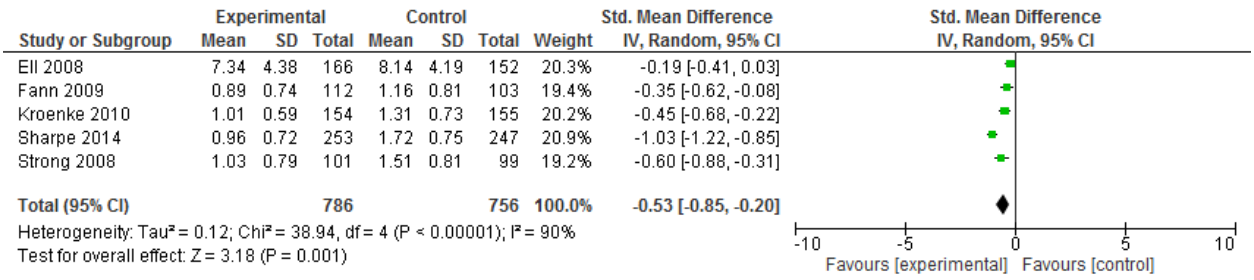
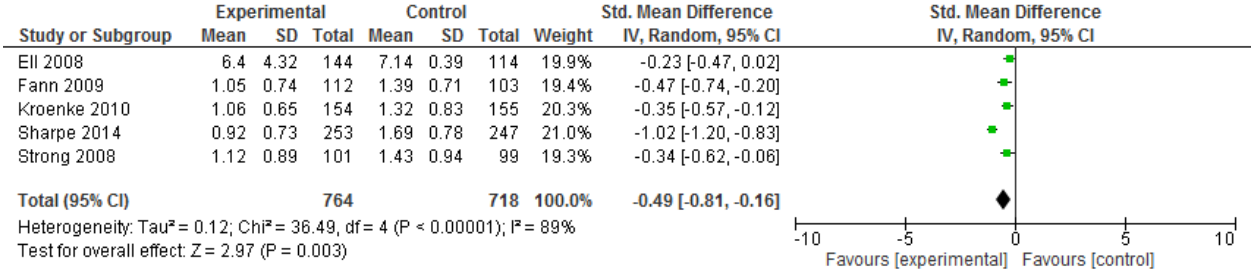


Fig. 9. Collaborative care response (difference in mean scores) at 12 months.



Figures 10 to 14 show the collaborative care remission rates at three, six, 12, 18, and 24 months.

Fig. 10. Collaborative care remission at three months.

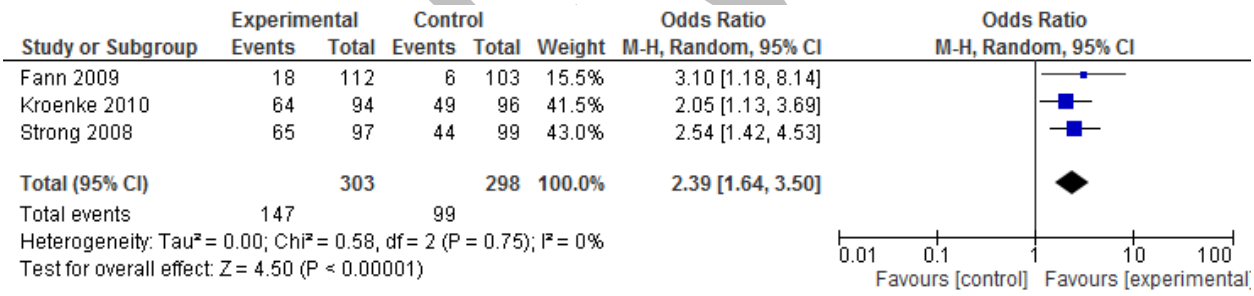


Fig. 11. Collaborative care remission at six months.

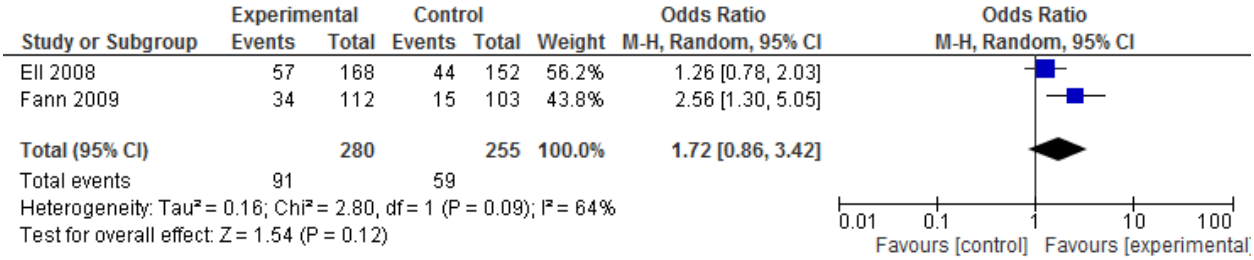


Fig. 12. Collaborative care remission at 12 months.

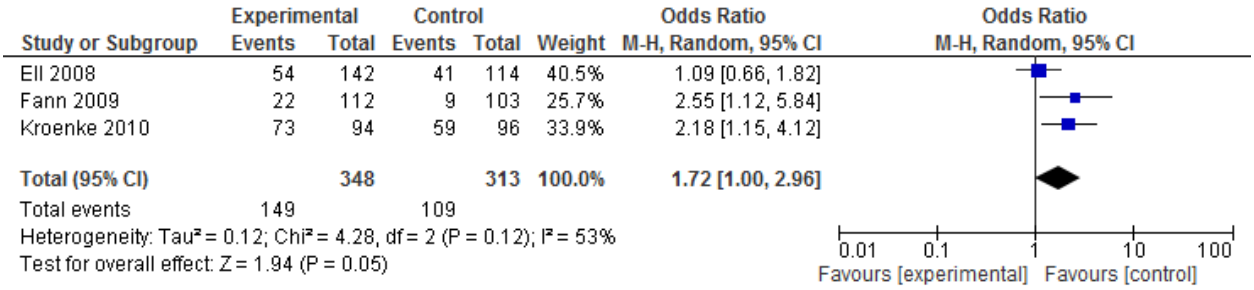


Fig. 13. Collaborative care remission at 18 months.

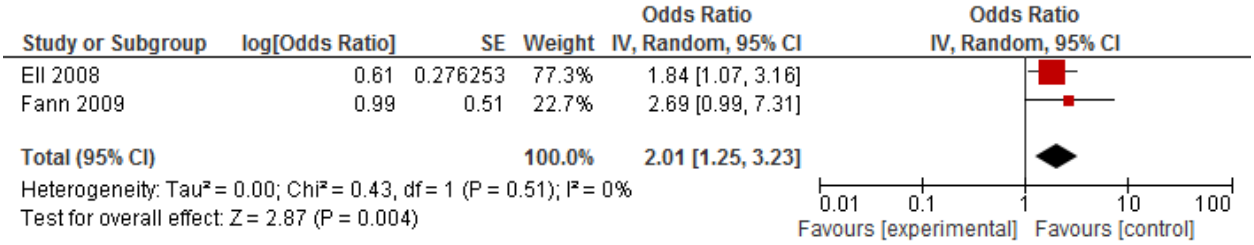
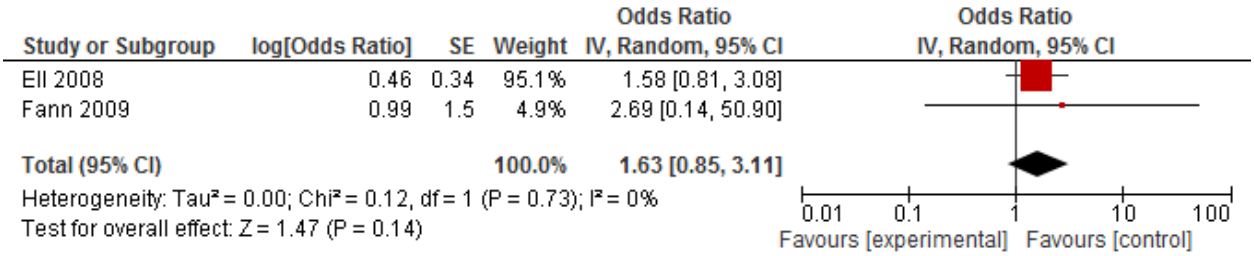


Fig. 14. Collaborative care remission at 24 months.



Guideline #19-4: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Management of Depression in Patients with Cancer: Guideline Development and External Review – Methods and Results

M. Li, E.B. Kennedy, N. Byrne, C. Gerin-Lajoie, E. Green, M. R. Katz, H. Keshavarz, S. M. Sellick, and the Management of Depression in Patients with Cancer Expert Panel

Report Date: May 11, 2015

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidelines using the methods of the Practice Guidelines Development Cycle [1]. The report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This report is comprised of the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved, and a formalized external review in Ontario by review participants.
- *Section 2: Systematic Review*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

- *Section 3: Development Methods, Recommendations Development, and External Review Process.* Summarizes the development process, the recommendations development process and the results of the formal external review of the draft version.

FORMATION OF WORKING GROUP

Cancer Care Ontario's Psychosocial Oncology Program asked the PEBC to develop a guideline on the management of depression in patients with cancer. A Working Group was identified, consisted of members with expertise in psychiatry, psychology, nursing, and health research methodology.

OBJECTIVES

The Working Group developed the following objective for this guideline, consistent with the previous version of the guideline:

- The objective of this guideline is to recommend best practices to improve the quality and consistency of the management of depression in Ontario for patients with cancer.

GUIDELINE REVIEW

Almost all PEBC document projects begin with a search for existing guidelines that may be suitable for adaptation. This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with *de novo* recommendations development.

For this document, a search for guidelines was conducted using the resources listed in Section 2, Appendix 2. Only guidelines published after 2005 were considered. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the Appraisal of Guidelines for Research and Evaluation AGREE II instrument.

EVIDENTIARY BASE DEVELOPMENT and INITIAL RECOMMENDATIONS

Using the objective described above, a search for existing systematic reviews and a systematic review of the primary literature were conducted, as described in Section 2 of this report. The Working Group began with the recommendations from the original version of this guideline, and then considered the new evidence and determined that new recommendations were required.

INTERNAL REVIEW

PEBC documents undergo internal review by an Expert Panel and the Report Approval Panel (RAP). The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels approved the document before it was sent to External Review.

Expert Panel Review and Approval

The Expert Panel for this document consisted of members with expertise in aspects of psychosocial oncology. The members of this group were required to submit conflict of interest declarations prior to reviewing the document. These declarations are described at the end of this section. For the document to be approved, 75% of the Expert Panel must cast a vote or abstain, and of those that voted, 75% must approve the document. At the time of the voting, panel members could suggest changes to the document, and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be submitted for approval again. The

nine-person Expert Panel was asked to review the document from October 15, 2014 to November 21, 2014. Responses were received from seven Expert Panel members, all of whom approved the document. Suggestions for changes were made, as outlined in Table 1:

Table 1. Expert Panel comments and Working Group response.

No.	Comment	Location in Document	Guideline Development Group Response
1	Many of the high-intensity interventions may be ideal, but are not easily accessed or not easily accessed in a timely way.	General comment	This was added as an implementation consideration in the discussion of Section 2.
2	The title refers to "Cancer Patients". Some advocacy groups would prefer "Patients with Cancer" to provide less identification of the person with the disease.	Title	This change has been made to the title and elsewhere to use the label "patients with cancer".
3	There is a note that the patient should be told that depression is "a medical illness requiring treatment". This implies that a medical disease model is the generally accepted view of depression, whereas in reality this continues to be a matter of some debate. No one would argue, however, that depression is "a serious problem" requiring treatment; "medical illness", however, would raise eyebrows in some quarters.	Page 7	We removed the term medical illness, and instead will use "serious problem" and refer specifically to clinical depression.
4	PHQ-9 1. A cut-off score of 8 on the PHQ-9 is pretty low, and hinges largely on one study that I doubt will stand the test of time. The reference below maybe of some use. http://www.ncbi.nlm.nih.gov/pubmed/22184363 2. (for PHQ-9) Although not as sensitive as cut-off score method: eg http://www.ghpjournal.com/article/S0163-8343(14)00254-0/pdf	Page 17	The Working Group disagrees with this comment. The table is showing cut-scores for which there is validation in cancer. There is only 1 publication. The algorithm method has not been validated in cancer and has poor sensitivity. Other meta-analysis shows range which includes 8, but it is not based in cancer.
5	Should there be mention made of the importance of supporting caregivers and of the frequent dyadic and family therapy that is done with cancer patients	Section 1 - Appendix 4	Agree. NICE guidelines include "behavioural couples' therapy" in high intensity interventions; therefore it has been added as an option in Appendix 5. Also added under general management principles that it's important to mobilize supportive caregivers (social support) and to more generally encourage family members to be brought in, provide education etc. resolve or encourage communication re prognosis and problems in the support network
6	Should there not be mention made that these therapies would be cancer focused; for example, it is very rare that pure CBT is used as first line	General comment	The Working Group intends for this appendix to be an outline of potential therapies that will be applied in the context of patients with cancer.

7	Each cancer centre in Ontario is mandated to screen for distress/symptom management. Would it be possible to make a statement about the use of this guideline with symptom management screening. Also how would you encourage the use of the guideline with the CAPO guideline for Depression. I believe this would provide clarity for the front line clinician using the various tools in Ontario	Page 7	In response, we added a reference to the Symptom Management Guidelines (SMG) in recommendation 1 – including mention that our guidelines apply to care pathways 2 and 3 of the SMG.
8	Could you provide a definition about collaborative care interventions to the recommendations?	Rec #5	Definition has been added to Recommendation #5.
9	(re Supportive-expressive therapy) This description doesn't seem accurate. The intervention is much more emotion-focused in application to cancer.	Appendix 4	Agree. Revise description to match SEGT (Segal).
10	on left hand side, LOW Intensity Intervention-box, there is another box below with arrow that links to Pharmacotherapy box, I would also have an arrow go to High Intensity Interventions under Moderate Depression, so arrow going up linking to that box and pharmacotherapy box. Some patients may not do well in a group or for other reasons, need the individual CBT or couple therapy etc. The diagram as is does not reflect this.	Fig 1	Agree. The algorithm was revised to include the stepped care diagram, which was previously presented as a separate appendix.
11	Should there not be mention of collateral from or assessment with the family in figure 1?	Fig 1	The working group addressed this comment under rec #2, general management principles.
12	The box **Assess Suicidal Ideation and Intent** – given that it may be the oncology teams doing this, it might be better to be very explicit and state suicidal ideation, plan and intent. Also from experience, this is a highly contentious issue. Skills/comfort level in this realm vary, as do opinions as to whose responsibility it is to complete this assessment.	Fig 1	Added plan to the appropriate box in Figure 1.
13	• …the content on this one page is very relevant but the algorithm itself is somewhat confusing to follow. Also, there are some new terminology used – "stepped care approach" and "collaborative care model" for example, that get lost on this one page, • I would suggest a revision of this quick reference, one (or two) pager, where perhaps it aligns more closely with the format and level of information similar to the symptom management guidelines.	Fig 1	• Provided references within the figure to definition of collaborative care. Stepped care has been added as a component of the algorithm. • This guideline does not exactly align with the SMG. A reference to where our recommendations fit in with SMG has been added to Rec #1 (see following comment).
14	the positioning of **Optimizing Cancer related physical symptoms**. Does that not sometimes have to be done before you can diagnose accurately?, for example we would address pain through their primary oncology team, and then see them again before being sure it was depression or anything else.	Fig 1	This is confusion with the SMG, which starts with screening for depression. Our algorithm starts with a depressed patient. In response, we added a reference to the SMG in recommendation 1 – including mention that our guidelines apply to care pathways 2 and 3 of the SMG.

Report Approval Panel Review and Approval

The purpose of the RAP review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of two clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director for Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

The RAP reviewed this document between October 15, 2014 and November 28, 2014, and approved the document, with changes suggested as outlined in Table 2.

Table 2. Report Approval Panel comments and Working Group response.

No.	Comment	Location in Document	Guideline Development Group Response
1	please list potential antidepressant discontinuation symptoms	Section 1, Appendix 5,	These symptoms are listed in the last table in Section 1, Appendix 5.
2	The objective is very succinct – "to improve the quality and consistency of the management of depression in cancer patients in Ontario." It might be enhanced by referring to whom the guideline is targeted (not clear) and to indicate that the document is a summary of the best available evidence to guide the management of depression in the cancer patient. It might also be explicit about the degree of depressive symptoms that it is intended to address.	Guideline Objective	Added that this is a summary of the best available evidence to the preamble. Target population and intended users are detailed already under separate headings. We have explicitly stated that we are referring to individuals who have had a diagnosis of major depression on a validated depression rating scale.
3	This guideline does not use the approach of defining and answering a question(s) in Section 1 but a research question is posed in Section 2. I think it would be helpful if it were inserted into Section 1	Research Question	The research question was added to Section 1.
4	It might be helpful to also include in table 2 some of the key information about drug interactions, particularly those used commonly in cancer patients. I would also suggest not including any discussion of drugs that are not available as it only adds confusion.	Table 2	For information on drug interactions, we will refer patients to Section 1 - Appendix 7.
5	Algorithm: It would also be helpful to explain IPT and name the drugs that are SSRIs that are considered to be the first-line therapy for pharmacotherapy cancer patients. Finally the figure might be made more useful by including the recommended examples for a "validated depression	Fig 1	Response: • Spelled out IPT • First line drugs named are citalopram/escitalopram. • Reference to appropriate appendix added for validated depression rating scales.

No.	Comment	Location in Document	Guideline Development Group Response
	rating scale" in the fifth box of the algorithm.		
6	I thought that some of the information in the introduction of Section 2, particularly about the diagnostic complexity of making a diagnosis of depression in the cancer patient was quite useful and wondered if some of it might be included in the preamble in section 1. In addition, the challenges of conducting pharmacologic and non-pharmacologic interventions in cancer patients with depression might also be presented briefly in section 1's preamble.	Intro, Section 2/ Preamble Section 1	Information on the complexity of making a diagnosis was added to the preamble. Challenge of conducting research in this area was included in the Section 1 Discussion.
7	Are there any "adverse effect" consideration for non-pharmacological therapies? Quality of the collaborative approach, non-pharmacological therapies maybe beyond the scope of the guideline, but probably important in terms of efficacy. Worth a statement or two?	General Comment	The Working Group considered this comment and concluded that this is not an area that has been well-studied; therefore it is not possible to report on adverse events.
8	Since the guideline addresses patients with a diagnosis of major depressive disorder, should the title reflect this?	Title	No, because patients may not necessarily have major depression; all those above threshold are included.
9	Is providing practical tools for the management of depression in cancer worth stating upfront? This is stated on page 23 as to why the guideline update was undertaken. A summary/listing of the practical tools in the text maybe worth considering	Appendices	A table of contents listing the Appendices containing practical tools has been added and a mention has been added to the preamble to Section 1.
10	when prior studies have not systematically linked depression screening to the clinical practice change required for depression intervention and follow up Can this phrase be re-written… I read it several times and am still a bit unsure what it means, or is necessary.	Rec 1 Qualifying statement	This sentence has been re-written. It now reads as follows: "Review of this literature is beyond the scope of this guideline; however, it is the opinion of the Working Group that lack of evidence is not equivalent to lack of effectiveness."
11	Since this is an important part of the recommendation, a definition (e.g. the statements on pg 30) of what collaborative care intervention is would be helpful. (or reference the reader to section 2)	Rec #5	Definition has been added to Recommendation #5.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified

content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners. Refer to the PEBC Handbook (https://www.cancercareontario.ca/sites/ccocancercare/files/PEBCHandbook.pdf) for additional detail.

Targeted Peer Review: Eight targeted peer reviewers from Ontario, other Canadian provinces, the United States and Europe who are considered to be clinical and/or methodological experts on the topic were identified by the members of the working group. Three of these individuals provided peer review of the document between January 29, 2015 and March 6, 2015. Their affiliations and conflict of interest declarations are in Section 3, Appendix 1. Key results of the feedback survey are summarized in Table 3. The main written comments from targeted peer reviewers and the Working Group's modifications/actions/responses are summarized in Table 4.

Table 3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					3
2. Rate the guideline presentation.			1		2
3. Rate the guideline recommendations.				1	2
4. Rate the completeness of reporting.				1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	2
6. Rate the overall quality of the guideline report.				1	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	2
8. I would recommend this guideline for use in practice.				1	2
9. What are the barriers or enablers to the implementation of this guideline report?	One review provided feedback on potential barriers or enablers: For successful implementation, it will be necessary to have the full support of oncology management and practice leaders. As well, clinical sites will need to commit resources to enable staff to be trained to use the guideline. As well, in some cases, organizational system restructuring may be necessary to allow staff to implement the processes for management of depression that are outlined in this guideline. For example, all staff responsible for brief screening of depression will need to, according to Figure 1, be trained in DSM so they can follow-up the screen with an application of the DSM diagnostic criteria for depression and adjustment disorder.				

Table 4. Modifications/actions/responses regarding main written comments from targeted peer reviewers.

Main written comments	Modifications, actions, or responses
1. Not clear the reason for headings: Recommendation; summary of key evidence and qualifying statements. This is also not always consistent (ex Recommendation 6 there is no qualifying statement).	Each recommendation is accompanied by a summary of key evidence which supports the recommendation. Qualifying statements are provided only where additional information is required to interpret or act upon the recommendation.
2. I am struggling with Figure 1, and the prominence of ascertaining the DSM diagnosis prior to administration of depression measures to find out the severity of the depression. The Figure suggests that confirmation of a DSM diagnosis must follow any initial screen that suggests depression. However, in most jurisdictions only registered psychologists and psychiatrists are professionally approved to make DSM diagnoses. Even if other classes of clinical specialty can now formally or informally use DSM, these individuals would all have to be trained in the DSM system. Further, in Figure 1 I think it would be useful to make a distinction between DSM major depression and DSM adjustment disorder. The Figure suggests ruling out depression caused by other medical factors, but in many cases there are cancer patients for whom major depression can be ruled out given not other medical conditions but the cancer itself (and there are other patients for whom the cancer diagnosis may trigger a true depressive episode). For these patients whose depressive symptoms are caused by a reaction to the cancer itself, adjustment disorder is the appropriate diagnosis, not depression. I would like to see this issue addressed in the guideline	These guidelines apply to the target population of patients with cancer who either have a DMS-5 diagnosis of major depressive disorder or a suspected diagnosis based on a validated depression rating scale. In other words, following a screen for depression, a diagnosis of depression is required to guide intervention in the stepped care model. Diagnosis of depression is complex in cancer patients and the appendices are intended to provide practical tools to facilitate this. Adjustment disorder is a distinct diagnosis from depression, and technically beyond the scope of the current guidelines. However, it is referenced in Appendix 1 under "subthreshold depression".
3. Good report. Well done. Perhaps make it somewhat clearer the recommendations for different levels of depression.	A paragraph clarifying depression taxonomy and the recommendations for different levels of depression has been added.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals and other stakeholders who are the intended users of the guideline. Nurse practitioners, nurses, primary care physicians, psychologists and psychiatrists as well as those with an interest in palliative care in the PEBC database were contacted by email to inform them of the survey. The survey was also emailed to professional organizations, including the Canadian Association of Psychosocial Oncology, Canadian Partnership Against Cancer, deSouza Institute for Oncology Nursing and the Ontario Psychological Association. All participants were from Ontario, with the exception of one individual each from the provinces of Manitoba and Quebec. Forty-eight responses were received between February 3, 2015 and March 2, 2015. The key results of the feedback survey are summarized in Table 5. The main comments from the professional consultation and the Working Group's modifications/actions/responses are summarized in Table 6.

Table 5. Responses to four items on the professional consultation survey.

	Number (%)

General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	5 (10)	28 (58)	15 (31)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	2 (4)	2 (4)	7 (15)	17 (35)	20 (42)
3. I would recommend this guideline for use in practice.	0	2 (4)	7 (15)	16 (33)	23 (48)

4. What are the barriers to the implementation of this guideline report?	The main barriers to implementation reported by the respondents to the professional consultation fell into the following categories: • Implementation issues related to lack of resources or limited access Turn-around time Depression severity assessment • Document length (too long) • Need for implementation tools (e.g. reference guide) for awareness, uptake and dissemination Training Communication • Treatment complexity • Lack of evidence • Continuity of care
5. What are the enablers?	• Very well organized easy to understand • Very comprehensive report. • Algorithm is an enabler • Drug interaction profiles very helpful • Charts in the guidelines were useful but were likely not all-inclusive.
6. Other comments	• In my work in psychosocial palliative care over the past 20 years I have found that the following issues contribute greatly to depressive symptomatology - ongoing progressive loss and anticipatory grief - encultured psychological isolation (inability of others to offer healthy engaged support around grief and dying), - loss of perceived control of life, - living our vulnerability, neediness and dependency in a culture that overvalues self-sufficiency and autonomy - living with uncertainty - the issue of destigmatization is useful on a personal level but can often be quite isolating when family/friends still buy into prevailing cultural attitudes towards avoiding vulnerability and not talking about death - cancer fatigue and valuing 'being' as much as 'doing' in the world

Table 6. Modifications/actions/responses regarding main written comments from professional consultation.

Main written comments	Modifications, actions, or responses
appendix 5 pharmaceutical treatment selection should also be based on the life expectancy of Pts. with cancer as in palliative care Pts. with life expectancy of < 3 months, we usually start with stimulant and antidepressant and taper the former slowly as most antidepressant takes a few week to be fully effective. appendix 6 quetiapine (Seroquel) is indicated as adjunctive therapy for major depression and I have good experience with it for depressions refractory to the conventional antidepressants.	The use of methylphenidate with or without an antidepressant at end of life varies with personal practice and is not an evidence based standard. Atypical antipsychotics have been added to Appendix 6.
the appendix lists 5 of the common tools, and the text in the recommendation lists 3 (with PHQ-9 listed first). To optimize usefulness of the guide, is it possible to assess which scale is best validated as a screen for depression in the cancer patient. PHQ-9 common in primary care, and in the appendix scores well with concordance with DSM-5.	There is insufficient evidence on which to base recommendation of any specific depression rating scale. The reference to specific scales has been removed from Recommendation 2.
Could use "yes"/"no" arrows for the suicide assessment box.	This has been added.
An explanation for why one wouldn't consider pharmacotherapy for mild depression may be helpful for primary care providers.	It is stated in the qualifying statement for Recommendation 3 that antidepressants are more effective for more severe depression, implying that they are less effective for mild depression. "due to the higher risk-benefit ratio at this level of depression severity" has been added to Recommendation 8.
Some readers may be put off by the use of the negative definition "non-pharmacological" to refer to trials of psychological, psychosocial, or psychotherapeutic interventions. These should be consistently labelled positively according to what they are, rather than what they are not.	This suggestion has been incorporated; we are using the term "psychological."
It seems pretty clear that the collaborative care model has the strongest body of supporting research. This model also seems practical, efficient, and consistent with the stepped care philosophy. Therefore, the final recommendation seems rather weak. Rather than merely noting that "details regarding implementation are beyond the scope of the document," should a stronger advocacy position be taken with regard to collaborative care? Similarly, given the game-changing publication by Sharpe et al. (2014) in the Lancet, it is not really accurate to conclude, as on pg. 33, that "despite the decades-long history of psychosocial oncology research, little has changed over the last decade and high quality studies on the treatment of depression in patients with cancer are still lacking."	The recommendation for collaborative care has been strengthened, and the conclusion regarding the lack of progress in depression research in cancer has been modified to reflect specifically individual pharmacotherapies and psychotherapies.
Please add Nurse Practitioners to the intended users!!	Nurse practitioners have been added.
I see some confusion around psychosocial intervention vs psychological treatment. Depression is a psychological impairment an d should be treated by psychologists or psychiatrists, and not psychosocial providers.	The language has been modified to be more consistently state "psychological treatment"
More detail on the psychological and collaborative approaches would be helpful.	The description of collaborative care interventions has been modified to include more detail. We have added cancer-specific references to the table of psychological therapy options.

I would suggest changing the order of the sections as presented ie Section 2 first which gives a thorough overview and leads into the guideline recommendations. This order also presents a balances presentation of medical and psychological approaches.	We are using the standard PEBC template for this guideline and systematic review.
At a minimum should include a standardized scored depression screening sheet eg Ham D or PHQ-9 and a standardized pt self assessment questionnaire like QIDS.	We are not endorsing any particular measure and many measures are copyrighted, precluding inclusion of a copy with this guideline.
You may want to reconsider use of the DSM-IV given its questionable validity and reliability.	Much of the evidence-based literature is based on SCID for DSM-IV
… in my practice it is helpful in identifying those depressed and persuading therapy. For me it would be helpful to have a discussion about how to assess the degree to which depression, especially mild to moderate depression, might be influencing a patients decision to seek medically assisted death, and how to approach assessing mood in this setting.	Appendix 5 on Managing Risk of Suicide mentions the need to consider this important and valuable clinical point. Details of how to do this are beyond the scope of this guideline.
Add celexa geriatric doing considerations – 20 mg max in seniors	There are many specialized dosing precautions (age, liver and renal impairment, etc.). The reference tables are convenient tools which are not intended to replace consulting more comprehensive prescribing resources.
Please link to Ocfp for distribution and KT.	Noted
In selecting an antidepressant (Appendix 5), there should be a checklist of contraindications – in particular with citalopram, new FDA recommendations to avoid in patients with long Q-T interval on EKG and reduced dose >60 yo.	Risk of QTc prolongation is noted in Appendix 5. The reference tables are convenient tools which are not intended to replace consulting more comprehensive prescribing resources.
• Page 5: Figure 1: should mention screening tools (easiest validated and guideline based tool is PHQ-9) • Page 6: step 4: why SSRI when CANMAT guidelines gives us a variety of options (ie SSRI, SNRI, Bupropion, etc) • Recommendations 3-7: good • Recommendation 8: Don't really agree with this and certainly not guideline based Desvenlafaxine has few to any drug interactions In clinical practice, a selective serotonin reuptake inhibitor (SSRI) such as citalopram/escitalopram should be the first resort due to best tolerability and the least potential for drug interactions. • Table 1 is very good, but disagree with qualifying statement above	• We are not endorsing any specific depression screening tools • SSRI as first line is an evidence-based recommendation from the NICE guidelines • SSRI are recommended as first line, SNRIs are indicated as optimal with tamoxifen because of their stronger evidence for hot flashes
The Qualifying Statement for Recommendation 8 on tamoxifen and CYP2D6 inhibitors was useful. How will the recommendation 'after discussion with treating oncologist and informed consent" be disseminated, as primary care is often the first line prescriber of antidepressants. Bringing this information to the CCO-Primary Care-Survivorship group would be useful.	Noted
while the questionnaires are useful, in practice they are rarely used in family practice but may be a good tool if monitored outside. 5. Need summary version- basically of which drugs interact with chemo drugs and which are recommended anti-depressants.	Provided in Appendix 7 and Table 1
Recommendation 4 on page 8 states "interventions for persistent subthreshold and mild to moderate depression, followed by progression to higher intensity interventions for non-responsive or moderate to severe depression (Figure 1)." Did they mean this to refer to Figure 2?	Corrected.

• In Figure 2, it would be helpful to better operationalize what is meant by "mild", "moderate" and "severe" depression. The reader may think that severe depression is a severe major depressive disorder (DSM), as defined later in the document.	Operationalized in Appendix 3
• in boxes related to steps 3 and 4, I would specify that high-intensity interventions are psychological in nature. –	Definitions of low and high intensity interventions are included in Recommendation 4
• On p. 7, it is suggested to communicate to patients that depression reduces cancer survival rates. I would delete that. The role of depression on cancer survival is still controversial and there is no point in scaring people about this. If they feel guiltier because their depression could affect their prognosis, we are not helping them feeling better.	This is an evidence-based statement. It is up to the practitioner to deliver this information in a way that motivates patient to seek treatment for depression, rather than scaring them
Perhaps it would be better to suggest using the BDI fast screen version which was developed to be used in patients with a medical condition and contains no somatic item which can be confounded with cancer symptoms. I also think that this issue regarding the inclusion of somatic items in the assessment and diagnosis (DSM) of depression should be discussed in more depth. The readers should be warned that their inclusion may lead to depression overdiagnosis.	This guideline is not endorsing the use of any specific screening tool. Mention of somatic symptoms falsely elevating scores has been included in Appendix 2 under the HADS
On p. 10, I totally disagree with the suggested factor for guiding the selection of CBT. This is very simplistic to say that this form of therapy is relevant for patients wanting a symptom-based approach. Patients generally don't know what intervention could be useful for them anyway. Here it would be important to emphasize that this is the type of psychotherapy of which efficacy has been the most supported by research in the general population.	Agree patients may not know what intervention would be most useful for them. The "Patient factors guiding selection" qualifying statement is intended to provide guidance to clinicians in recommending psychological interventions as tailoring of psychological therapies to address unique needs or patient characteristics may enhance the efficacy of specific interventions for individual patients
In Appendix 1, the authors suggest a continuum going from normal sadness to major depression. However, descriptions related to adjustment disorder and subthreshold depression are very similar and difficult to distinguish. Perhaps these two categories should be lumped together.	The table reflects the categories in the DSM-IV. The arbitrary distinction between adjustment and subthreshold depression is indicated in the table, where "transient and self-limited" is the main distinction
In Appendix 2, again I suggest listing the BDI fast screen version (scores have been proposed to distinguish different levels of severity for that version as well).	Appendix 2 lists depression rating scales useful for monitoring treatment response and includes the BDI-II. The BDI fast screen is an abbreviated version useful for depression screening. This guideline is not recommending any specific depression screening tools.
In Appendix 4, a long list of different psychological interventions is proposed. I think it would be important to describe, for each, the various level of evidence available to support their efficacy both in cancer patients and in the general population. In this guideline, several recommendations for pharmacotherapy are based on the literature available in the general population because of a lack of specific evidence in cancer patients.	A sentence has been added to these tables indicating not all treatments are currently supported by a research evidence-base in cancer patients, but their use is extrapolated from the treatment of depression in psychiatric and other medical populations
The same approach should be used for psychological interventions.	

In Appendix 5, it would be relevant to describe recent epidemiological data showing that the risk for suicide is significantly increased in the first year following cancer diagnosis (particularly in the first month; Johnson et al., 2012).	None of the material in Appendix 5 is specifically referenced and suicide risk needs to be assessed at all time points.
On p. 46, please indicate that our study (reference #106; Savard et al.) used a follow-up and found a significant effect at post-treatment that was maintained at the follow-up evaluation.	We only included treatment differences between groups in the results and not differences that were significant pre to post-treatment in the intervention group.
On p. 55, it is said that the most effective interventions were based on collaborative care models. I didn't see the evidence supporting that assertion. Have comparative studies really been done on this research question?	A meta-analysis of the four key randomized controlled trials on collaborative care interventions has been included.
The guideline is a good update. It would be nice to have comments on any studies related to patient experience. Promising research section could be enhanced as well as alternative therapies, and collaborative care. Thank-you to all those involved.	Patient experience is an important topic, but beyond the scope of this depression management systematic review and guideline.

CONCLUSION

This Guideline report reflects the integration of feedback obtained through the external review process with final approval given by the Management of Depression in Patients with Cancer Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol, which can be obtained by contacting the PEBC offices at ccopgi.mcmaster.ca.

Appendix 1. Members of the Management of Depression in Patients with Cancer Working Group, Expert Panel, PEBC Report Approval Panel and Targeted Peer Reviewers and their declarations of conflict of interest.

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- **Dr. Homa Keshavarz,** PhD Health Research Methodologist, Cancer Care Ontario Program in Evidence-based Care and McMaster University Department of Oncology (to Dec. 2013)
- **Dr. Nelson Byrne,** PhD, Clinical Psychologist, CBT Associates of Toronto
- **Ms. Esther Green**, RN, Provincial Head of Nursing and Psychosocial Oncology, Cancer Care Ontario
- **Dr. Caroline Gerin-Lajoie**, MD, Psychiatrist, Medical Lead, Psychosocial Oncology Program, Ottawa Hospital Cancer Centre, Ottawa, Ontario
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- **Dr. Cheryl Harris**, PhD, Psychologist, The Ottawa Hospital, Ottawa, Ontario
- **Dr. Janet Ellis**, MD, Psychiatrist, Sunnybrook Health Sciences Centre, Toronto, Ontario
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Targeted Peer Reviewers

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Conflict of Interest

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Management of Depression in Patients with Cancer Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

NB reports partnership in a private practice that provides psychological intervention for cancer patients and others for which income exceeds $10,000 annually.

NB is also a member of the Board of Directors of the Canadian Association of Psychosocial Oncology. CGL reports a completing a book review for the *Canadian Journal of Psychiatry* on "Depression and Cancer" by David Kissane, published 2011. ML reports authorship on a narrative review on this topic published in the *Journal of Clinical Oncology*, as well as creating an International Psycho-Oncology Society webcast and providing DeSouza content expertise on this topic. MK reports receiving consulting income from Lundbeck, Pfizer, Sunovian, Lilly, Janssen, Shire, and Bristol Myers Squibb within the past five years. The other guideline authors do not report any relevant conflicts of interest.

The declared conflicts did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca

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