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**Guideline #19-4**

## 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**



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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 3-5 | Severe |

**Figure 1. Quick reference management algorithm.**

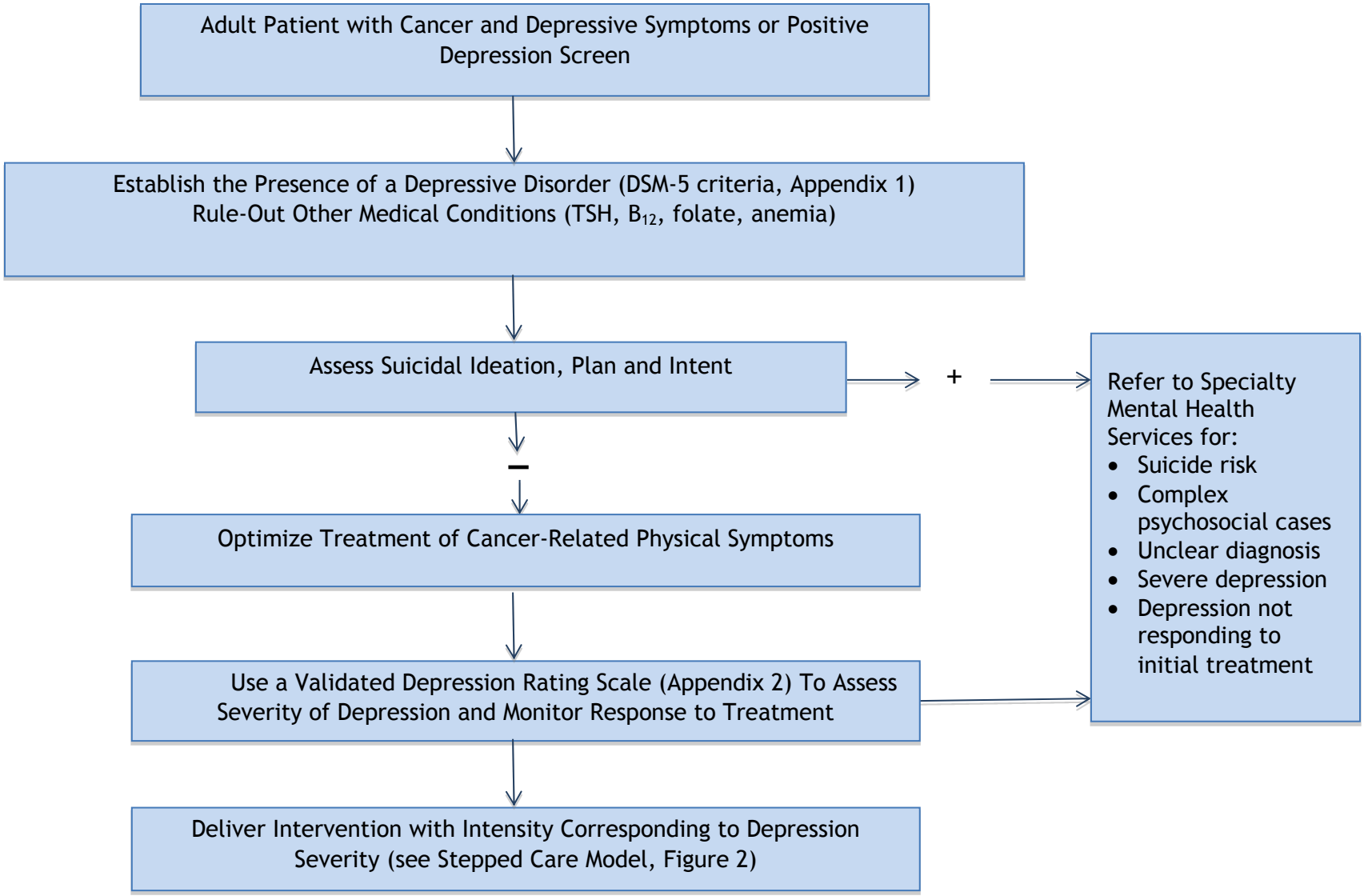
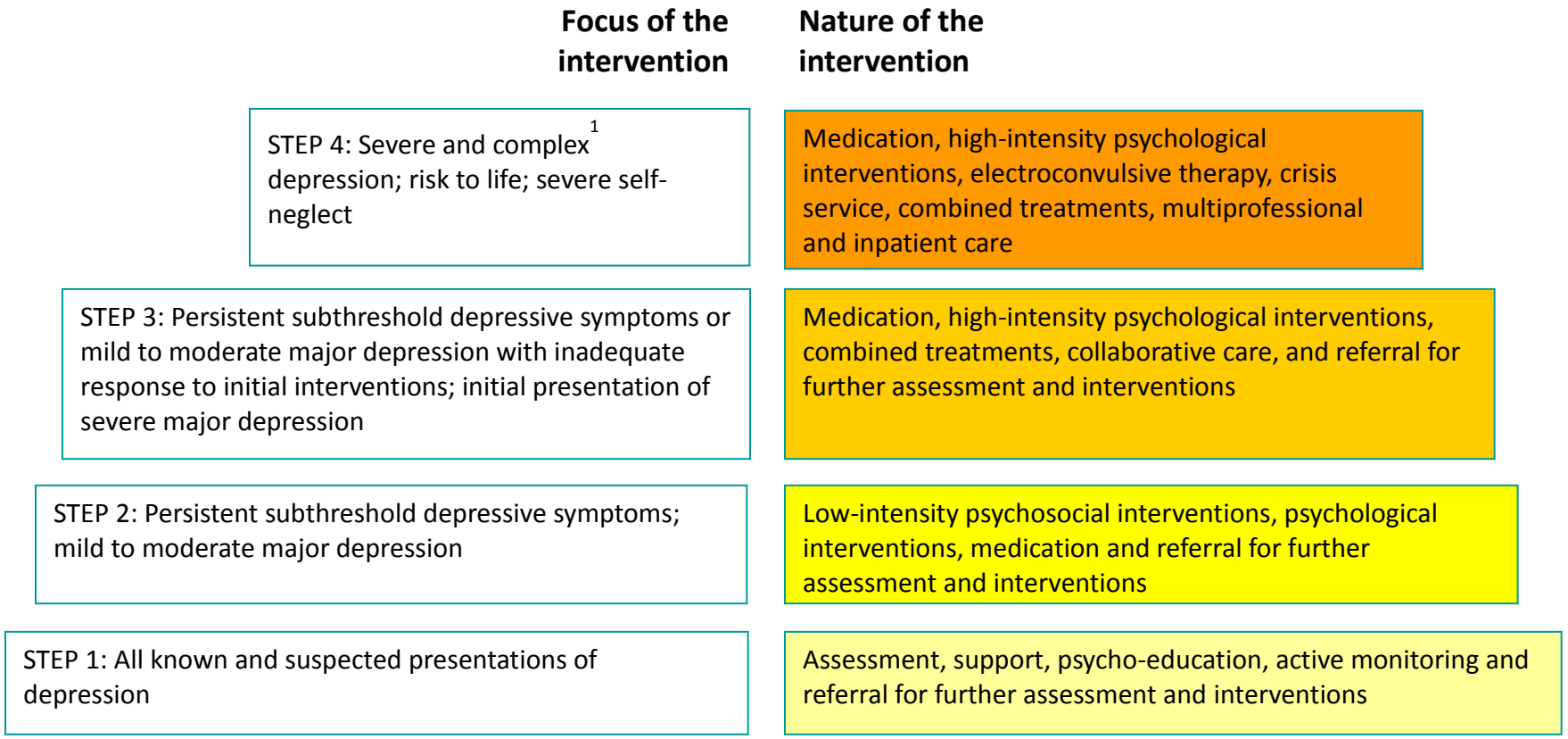


**Figure 2. Delivery of intervention corresponding to the Stepped Care Model.**




[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])<br>Goal: 20 to 40 mg / (10 to 20 mg)<br>Max: 40 mg od / (20 mg qhs) | • May help with hot flashes<br>• 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)<br>Goal: 75 to 225 mg / (50 to 100 mg)<br>Max: 300 mg qam / (100 mg) | • Optimal choice for patients on tamoxifen (see qualifying statement below)<br>• Consider for prominent hot flashes |
| Bupropion XL | Start: 150 mg qam<br>Goal: 150 to 300 mg<br>Max: 450 mg qam | • Consider for prominent fatigue<br>• Aids sexual function<br>• Smoking cessation aid<br>• Weight neutral |
| Duloxetine | Start: 30 mg qam<br>Goal: 30 to 60 mg<br>Max: 120 mg qam | • Separate indications for neuropathic and chronic pain |
| Mirtazapine | Start: 7.5 to 15 mg orally (po) qhs<br>Goal: 15 to 45 mg<br>Max: 60 mg po qhs | • Consider for prominent insomnia, anorexia/cachexia, anxiety, nausea, diarrhea, pruritus<br>• 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.<br>**1.** Depressed mood most of the day<br>**2.** Markedly diminished interest or pleasure in almost all activities most of the day<br>**3.** Significant weight loss or gain (change of >5% in a month), or decrease or increase in appetite<br>**4.** Insomnia or hypersomnia<br>**5.** Psychomotor agitation or retardation<br>**6.** Fatigue or loss of energy<br>**7.** Feelings of worthlessness or excessive or inappropriate guilt<br>**8.** Diminished ability to think or concentrate, or indecisiveness<br>**9.** Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation, or a suicide attempt or plan<br>**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<br>Moderate: 18 to 24<br>Severe: >25<br><br>Cut score: 10 (100/67) [43] | • 24-item measure, 17 items scored<br>• Clinician-rated<br>• 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<br><br>Cut score: 16 (100/67) [43] | • 20-item self-report<br>• Measures negative affect, well-being, somatic and interpersonal symptoms<br>• Not congruent with DSM-5 |
| Patient Health Questionnaire 9 (PHQ-9) [45] | Mild: >5<br>Moderate: >10<br>Moderately Severe: >15<br>Severe: >20<br><br>Cut score: 8 (93/81) [46] | • Nine-item self-report<br>• 100% concordant with DSM-5 diagnostic criteria<br>• Includes diagnostic algorithm |
| Hospital Anxiety and Depression Scale (HADS) [47] | Normal: 0 to 7<br>Mild: 8 to 10<br>Moderate: 11 to 14<br>Severe: 15 to 21<br><br>Cut score on depression subscale: 7 (86/81) [48] | • 14-item self-report<br>• Separate anxiety and depression subscales<br>• Separate scoring ranges for total HADS<br>• Excludes somatic symptoms which may falsely elevate scores in cancer patients |
| Beck Depression Inventory II (BDI-II) [49] | Minimal: <14<br>Mild: 14 to 19<br>Moderate: 20 to 28<br>Severe: >29<br><br>Cut scores: 18 (96/89); 22 (92/100) [43] | • 21-item self-report<br>• Assesses behavioural, cognitive, and somatic domains<br>• Preponderance of somatic symptoms |

**Appendix 3. Psychological Features Distinguishing the Continuum of Depression.**

| Normal Sadness → | Subthreshold Depression → | Major Depression |
|---|---|---|
| • Maintains intimacy and connection<br>• Believes that things will get better<br>• Can enjoy happy memories<br>• Sense of self-worth fluctuates with thoughts of cancer<br>• Looks forward to the future<br>• Retains capacity for pleasure<br>• Maintains will to live | • Shows similar low mood presentation as in major depression but does not meet full criteria for symptom number or duration<br>• Includes persistent depressive disorder if > 2 years duration<br>• Includes episodes lasting < 2 weeks<br>• 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<br>• Note: the distinction between subthreshold depression and major depression of mild severity may be arbitrary | • Feels isolated<br>• Feeling of permanence<br>• Excessive guilt and regret<br>• Self-critical ruminations/loathing<br>• Constant, pervasive and nonreactive sadness<br>• Sense of hopelessness<br>• Loss of interest in activities<br>• 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<br>• Sweating, sexual dysfunction, tremor, bruxism | • Citalopram/escitalopram corrected QT interval (QTc) prolongation at high doses<br>• Paroxetine/Fluoxetine/ Fluvoxamine drug interactions<br>• Paroxetine discontinuation syndrome<br>• 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<br>• Sweating, sexual dysfunction, constipation | • Venlafaxine discontinuation syndrome and hypertension risk<br>• 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 |
| Agomelatine | • Nausea, dizziness, headache, somnolence | • Contraindicated in renal or hepatic impairment |

| Drugs | Common Side Effects | Cautions |
|---|---|---|
| **Tricyclic Antidepressants (TCAs)** | | |
| $3^0$ amines - Amitriptyline, Imipramine<br>$2^0$ amines - Nortriptyline, Desipramine | • Sedation, constipation, anticholinergic, orthostatic hypotension, tachycardia | • High toxicity in overdose, *do not prescribe Dosulepin*<br>• Poor tolerability, especially with $3^0$ amines<br>• Risk of QTc prolongation |
| **Psychostimulants** | | |
| Methylphenidate, Dexamphetamine, Modafinil | • Insomnia, agitation, tremor, anxiety, hypertension, tachycardia, arrhythmia | • Contraindicated in significant cardiovascular disease<br>• Risk of dependence |
| **"Atypical" Antipsychotics (as Adjuncts)** | | |
| Quetiapine, Olanzapine, Risperidone, Aripiprazole Lurasidone Asenapine | • Sedation, weight gain, metabolic syndrome<br>• Olanzapine and quetiapine may be helpful for insomnia, anorexia and nausea<br>• Aripiprazole may be less sedating | • Risk of QTc prolongation<br>• 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<br>• 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<br>• May be preferred by patients with cancer who are reluctant to consider pharmaceutical antidepressants<br>• 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<br>5-fluorouracil<br>Gemcitabine<br>Cisplatin<br>Carboplatin<br>Oxaliplatin | Doxorubicin<br>Duanorubicin<br>Epirubicin<br>Vorinostat<br>Melphalan<br>Chlorambucil | Busulfan<br>Estramustine<br>Mechlorethamine<br>Mercaptopurine<br>Thioguanine |

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

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*Updating*

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at: https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=122178



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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**

**A systematic review manuscript based on this EBS has been submitted to a peer-reviewed journal. The full EBS will be posted on the CCO Web site once the publication process is completed.**

**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<br>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.<br>http://www.ncbi.nlm.nih.gov/pubmed/22184363<br>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 | Page 7 | In response, we added a reference to the Symptom Management Guidelines (SMG) |

| | | | |
|---|---|---|---|
| | 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 | | 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)<br>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,<br>• 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.<br>• 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 rating scale" in the fifth box of the algorithm. | Fig 1 | Response:<br>• Spelled out IPT<br>• First line drugs named are citalopram/escitalopram.<br>• Reference to appropriate appendix added for validated depression rating scales. |
| 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 | 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. |

| No. | Comment | Location in Document | Guideline Development Group Response |
|---|---|---|---|
| | 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. | | |
| 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.<br>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<br><br>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.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=10144) 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 | 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, |

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| 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 | 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.<br><br>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 | 2 (4) | 2 (4) | 7 (15) | 17 | 20 (42) |

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| of this guideline in my professional decisions. | | | | (35) | |
| 3. I would recommend this guideline for use in practice. | 0 | 2 (4) | 7 (15) | 16 (33) | 23 (48) |

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| 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:<br>• Implementation issues related to lack of resources or limited access Turn-around time Depression severity assessment<br>• Document length (too long)<br>• Need for implementation tools (e.g. reference guide) for awareness, uptake and dissemination Training Communication<br>• Treatment complexity<br>• Lack of evidence<br>• Continuity of care |
| 5. What are the enablers? | • Very well organized easy to understand<br>• Very comprehensive report.<br>• Algorithm is an enabler<br>• Drug interaction profiles very helpful<br>• 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.<br>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.<br><br>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. |

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| 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.<br>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)<br>• Page 6: step 4: why SSRI when CANMAT guidelines gives us a variety of options (ie SSRI, SNRI, Bupropion, etc)<br>• Recommendations 3-7: good<br>• 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.<br>• Table 1 is very good, but disagree with qualifying statement above | • We are not endorsing any specific depression screening tools<br>• SSRI as first line is an evidence-based recommendation from the NICE guidelines<br>• 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. |

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| • 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. | |

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| 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.

**Working Group**

- **Dr. Madeline Li,** MD (chair), Psychiatrist, Princess Margaret Hospital, Toronto, Ontario
- **Ms. Erin Kennedy,** Health Research Methodologist, Cancer Care Ontario Program in Evidence-based Care and McMaster University Department of Oncology
- **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
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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.

Among the review authors, Dr. Mark Katz has served on the speakers' bureau and received honoraria from Lundbeck, Pfizer, Eli Lilly, Sunovion, Astra Zeneca, Janssen and

Shire, although this work does not endorse any specific pharmacotherapeutic agent. No conflicts were declared by any other review author, Expert Panel members or Targeted Peer Reviewers.

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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