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Guideline #19-4 IN REVIEW

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

The Management of Depression in Patients with Cancer

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

Report Date: May 11, 2015

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

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

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

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Guideline #19-4: Section 1

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

The Management of Depression in Patients with Cancer: Guideline Recommendations

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

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GUIDELINE OBJECTIVE

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

TARGET POPULATION

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

INTENDED USERS

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

RESEARCH QUESTION

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

INTRODUCTION

Knowing of the significant prevalence of depressive disorders in patients with cancer and of the clinical relevance of depression to health outcomes, the Program in Evidence-based Care (PEBC) developed an initial guideline for the management of depression in patients with cancer, which was published in 2007 [1]. The recommendations contained in this section are an update of the 2007 recommendations, based on the results of an updated systematic review (Section 2) and the consensus opinion of the members of the project Working Group. While this guideline summarizes the best available evidence to guide the management of depression in patients with cancer, members of the Working Group acknowledge the challenge of conducting research in an area of diagnostic complexity across the depression severity continuum. Clinicians must distinguish physical symptoms of cancer from neurovegetative symptoms of depression, functional impairment from decreased activities due to anhedonia, and rational thoughts of death from suicidality. Treatment complexity is further compounded by medical and psychosocial factors, such as pain or inadequate social supports, that contribute to

depression and often need to be addressed prior to or concurrently with depressive symptoms. Clinicians must also consider potential detrimental pharmacotherapy side effects, drug interactions, and treatment compliance issues unique to the cancer context.

The eight recommendations developed in this guideline have been synthesized into a quick reference guide for the initial management of depression in patients with cancer (Figure 1). This management algorithm provides a general approach and practical guidance tool for health care providers treating patients with cancer who present with a depressive disorder. Most of the steps in the tool are described in more detail within the recommendations. Recommendations and Practical Tools can be found at the following locations within Section 1:

TAXONOMY

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

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

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

Figure 1. Quick reference management algorithm.

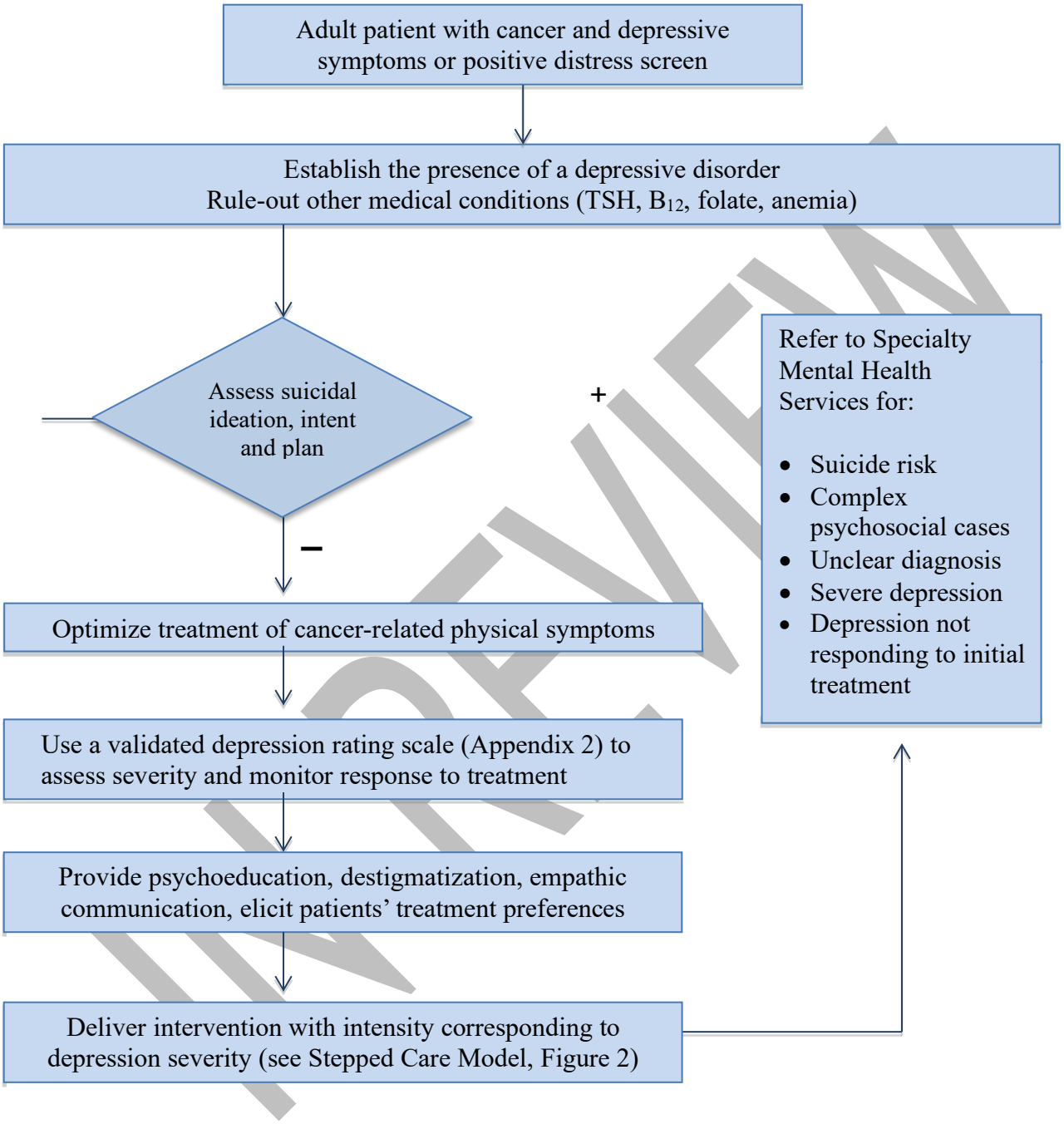
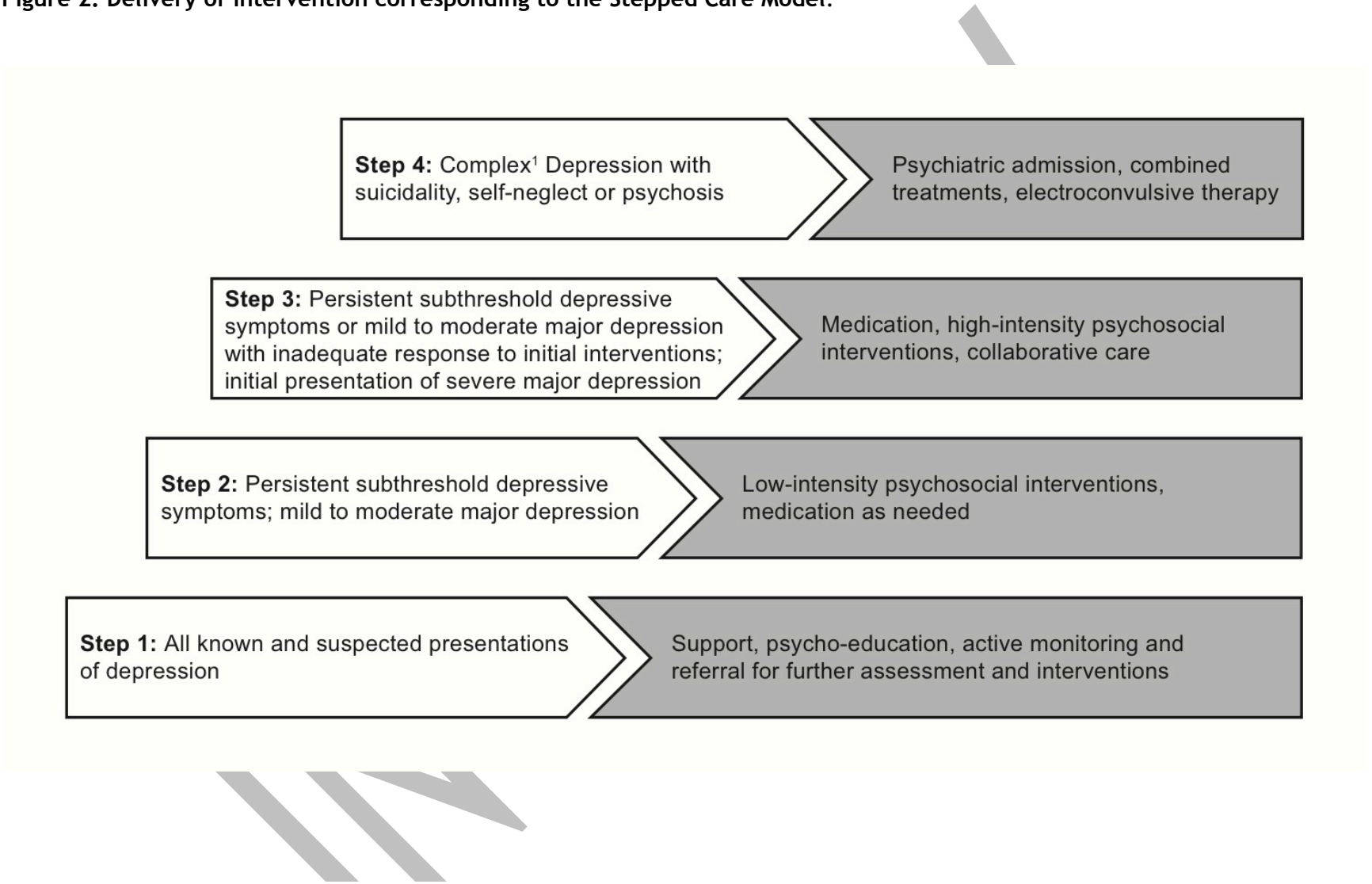


Figure 2. Delivery of intervention corresponding to the Stepped Care Model.



[1]Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors. Stepped care algorithm adapted from NICE CG91, p.110 [1].

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1. Screening of patients with cancer for distress or depression

Patients with cancer should be screened for depression. Many cancer programs incorporate depression screening into Screening for Distress programs. A clear diagnosis of depression is required to guide treatment. See Appendix 3 for psychological features that distinguish the continuum of depressive symptoms. To improve health outcomes, screening must be linked to effective interventions [6].

Summary of Key Evidence for Recommendation 1

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

Qualifying Statements for Recommendation 1

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

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

Recommendation 2. General management principles

The following general management principles are recommended:

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

Summary of Key Evidence for Recommendation 2

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

Recommendation 3. Pharmacological or psychological/psychosocial interventions

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

Summary of Key Evidence for Recommendation 3

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

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

Qualifying Statements for Recommendation 3

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

Recommendation 4. Depression severity and a stepped care approach

Interventions for depression in patients with cancer should be delivered according to a stepped care model. This involves assessment of the severity of depression for each patient (Appendix 3), provision of support and psychoeducation to all patients, delivery of lower-intensity interventions for persistent subthreshold and mild to moderate depression, followed by progression to higher intensity interventions for nonresponsive or moderate to severe depression (Figure 2). Low-intensity psychosocial interventions include structured group physical activity programs, group-based peer support or self-help programs, and guided self-help programs based on cognitive behavioural therapy (CBT), behavioural activation, or problem-solving techniques. High-intensity psychosocial interventions include individual or group CBT, behavioural couples' therapy, and individual or group supportive-expressive psychotherapies.

Summary of Key Evidence for Recommendation 4

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

Qualifying Statement for Recommendation 4

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

Recommendation 5. Collaborative care interventions

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

Summary of Key Evidence for Recommendation 5

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

Qualifying Statements for Recommendation 5

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

Recommendation 6. Specialist referral

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

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

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

Summary of Key Evidence for Recommendation 6

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

Recommendation 7. Selection of psychological therapies

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

- Among patients with cancer presenting with depressive symptoms, most are mild to moderate. The stepped care model recommends that psychological interventions be considered first for mild to moderate depression [21].
- Psychological therapies should be delivered by health care professionals competent in the modality, but non-mental health specialists can be trained in basic psychosocial interventions.

Summary of Key Evidence for Recommendation 7

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

Qualifying Statements for Recommendation 7

- Delivery of therapy:
    - Empathic communication, psychoeducation, problem-solving, and behavioural activation are therapeutic techniques that may be delivered by trained health care professionals.
    - Supportive-expressive and structured psychotherapies (e.g., CBT, interpersonal therapy, psychodynamic therapy) require specially trained therapists.
- Patient factors guiding selection:
    - CBT may be useful for patients wanting a symptom-based approach.
    - Supportive-expressive therapies may be of value with more psychologically minded patients (i.e. patients with the capacity for self-reflection and introspection, and the ability to gain insight into their motivations and behaviours).
    - Individual therapies may be more practical in patients who are in the palliative phase.

Recommendation 8. Use of antidepressant medication

Do not use antidepressants routinely to treat subthreshold depressive symptoms or mild depression, due to the higher risk-benefit ratio at this level of depression severity. Antidepressant medication should be considered first for severe depression. Table 1 provides practical guidance on selecting commonly used antidepressants for patients with cancer (see Appendix 5, Appendix 6, and Appendix 7 for further guidance on antidepressant prescribing practices, classes of antidepressants for use in cancer patients, and information on antidepressant drug interactions, respectively). In clinical practice, a selective serotonin

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

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

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

Summary of Key Evidence for Recommendation 8

This recommendation is based on the consensus opinion of the members of the Working Group, supported by NICE CG91 [4] and other guidelines and reviews on pharmacotherapy in medical and cancer populations [22]. Despite the limitations of the evidence-base, the members of the Working Group recognize that both antidepressants and antipsychotic agents are widely prescribed for patients with cancer [23,24]; this is most particularly the case for patients with advanced illness [25]. Only case series and open trials have been published for newer antidepressants, such as escitalopram, citalopram, venlafaxine, desvenlafaxine, mirtazapine, bupropion, and duloxetine, which are routinely used in cancer patients. Indications for these agents include not only depression but also anxiety and hot flashes in the case of SSRIs and serotonin-norepinephrine reuptake inhibitors [26,27], neuropathic pain with serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants [28], and nausea, sleep disturbances, and appetite enhancement in the case of mirtazapine and atypical antipsychotics [27].

Qualifying Statement for Recommendation 8

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

and mortality [29,30]. However, meta-analyses have suggested that the reductions in endoxifen do not translate into increased breast cancer recurrence rates or mortality rates, possibly because the therapeutic dosing of tamoxifen fully saturates the estrogen receptor [31,32]. Existing recommendations have been conservative, cautioning avoidance of potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, high-dose sertraline, bupropion) with tamoxifen. Although these antidepressants are not recommended as first-line agents, clinical judgement can be exercised in their use with patients for whom safer alternatives are not an option, after discussion with the treating oncologist has occurred and informed consent been obtained. More potent CYP2D6 inhibitors may be safer to use in postmenopausal women or women with a known extensive metabolizer CYP2D6 genotype [33]. When possible, it is prudent to prefer antidepressants with low CYP2D6 inhibition (e.g., citalopram/escitalopram, venlafaxine/desvenlafaxine, or mirtazapine) as first-line agents.

DISCUSSION

This guideline does not include recommendations for the management of depressive symptoms in the normative or nonpathological range of severity. Studies addressing this level of depression have been highly heterogeneous, group-as-a-whole studies, and were beyond the scope of this systematic review. Such studies have been extensively reviewed in previous publications [34,35], with management recommendations provided in other guidelines [5].

Recommendations for the management of threshold depressive disorders are integrated into the quick reference guide provided in Figure 1. This management algorithm includes steps not fully articulated in these recommendations, because they represent accepted standard of care and have been extensively reviewed elsewhere. For example, assessment for suicidality requires either direct inquiry, or the use of depression rating scales that contain items assessing suicidal ideation (e.g., Patient Health Questionnaire 9, Beck Depression Inventory II). Further guidance on the management of suicidal ideation in patients with cancer is available through the International Psycho-Oncology Society's core curriculum webcast series [36]. Empathic communication by health care providers is an important component of management at all levels of depression severity in patients with cancer. The significance of good patient-provider communication has been extensively reviewed in other guidelines [37] and excellent online training resources for cancer care providers are available [38]. More specific management tools, including strategies for the management of depression in patients who do not respond to initial treatments, are provided in Appendices 1 to 7 accompanying this guideline. These tools were developed by consensus by the members of the Working Group.

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

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

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

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PRACTICAL TOOLS (APPENDICES 1-7)

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

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

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

Appendix 2. Select Validated Depression Screening Scales.

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

Appendix 3. Psychological Features Distinguishing the Continuum of Depression.

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

Appendix 4. Psychological Interventions for Depression in Cancer.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix 5. Practical Tools for Clinicians Prescribing an Antidepressant.

Selecting an Antidepressant

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

Initiating an Antidepressant

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

Managing Risk of Suicide

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

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

Maintaining an Antidepressant

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

Discontinuing an Antidepressant

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

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

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

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

Appendix 7. Antidepressant-Oncology Drug Interactions.

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

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

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

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