SPECIAL ARTICLE

Anxiety and depression in adult cancer patients: ESMO Clinical Practice Guideline[†]

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INTRODUCTION

Anxiety and depression are the most common psychological symptoms in patients with cancer, irrespective of disease stage, primary cancer site and phase of treatment. Symptoms may range from nonpathological states, such as concerns, worry, sense of uncertainty, sadness and increased levels of hopelessness, to specific psychiatric syndromes (i.e. anxiety and depressive disorders). The latter are associated with significant distress and marked disability, poor quality of life (QoL), increased physical symptoms (e.g. pain or nausea), poor adherence to treatment, increased risk of suicide (in people with depression), poorer prognosis and higher mortality.[1-4] It is important for clinicians to understand the difference between nonpathological fluctuations in anxious or depressive states, which are not intense and are short-lived emotional responses to life challenges, and the more specific and impactful psychopathological conditions, such as anxiety and/or depressive disorders. There is a spectrum of highly comorbid syndromes which can be categorised by the criteria of the World Health Organization International Classification of Diseases (ICD), 11th edition (updated chapter on 'Mental, behavioural or neuro-developmental disorders')[5] and the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM), fifth edition-Text Revision (DSM-5-TR).[6]

This clinical practice guideline (CPG) provides an up-to-date, evidence-based approach to assessing and managing anxiety and depression as a spectrum of psychiatric disorders in patients with cancer. In 2013, the DSM reclassified post-traumatic stress disorder (PTSD), which is a further significant problem in patients with cancer, from 'anxiety disorders' to 'stress and stress-related spectrum disorders'. Therefore, this CPG will discuss adjustment disorders with anxious or depressed mood, but PTSD will not be covered. The authors followed the levels of evidence and grades of recommendation as detailed in the 'Methodology' section.

INCIDENCE AND PREVALENCE

Anxiety and depressive disorders are highly prevalent in the general population, with an estimated 264 million people globally (3.6% of the global population) living with depression and 322 million (4.4% of the global population) living with anxiety in 2015.[7] In recent years, the incidence and prevalence of both disorders has rapidly increased, with an estimated additional 53.2 million [95% confidence interval (CI) 44.8-62.9 million] cases of major depressive disorder and 76.2 million (95% CI 64.3-90.6 million) cases of anxiety disorder globally in 2020, compared with pre-coronavirus disease (COVID)-19 pandemic levels.[8] The burden from these diseases is becoming an increasingly important worldwide problem.[9] Major depression, or depression alone, is estimated to be the primary cause of disability, ahead of cardiovascular diseases and cancer

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itself.[10] It is thus evident that the concomitance of depression and cancer is extremely disabling for patients.

Many studies in oncology have examined the prevalence of anxiety and, in particular, depressive spectrum conditions, in different contexts (e.g. cancer outpatient clinics, inpatient settings, palliative care settings) at different stages across the cancer diagnosis and treatment trajectory (e.g. early diagnosis, recurrence, survivorship, advanced stages) and in relation to different cancer sites. In most studies, symptoms have been assessed with validated self-report instruments [e.g. the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI), the Patient Health Questionnaire (PHQ)]. While such measures have been shown to be valuable screening tools for anxiety and depression in patients with cancer, semi-structured diagnostic interviews are the gold standard when seeking a specific diagnosis of depression and different specific forms of anxiety.

There are, however, studies which have explored the accuracy of self-report instruments by comparing them with the results of ICD or DSM interviews (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop. 2023.101155).[11,12] Screening for anxiety and depression in patients with cancer is important, since cases are rarely identified by surgeons or oncologists and are seldom referred to specialist psychiatry or psycho-oncology services.[13,14] If not treated, depression can have serious negative consequences for the recovery of patients and their physical, psychological and social functioning.[15,16] In a study of >20 000 patients with cancer, of those diagnosed as having major depressive disorder ($n = 1538$; 7.5% of the sample), 1130 (73%) did not receive any potentially effective treatment for their depression. Only 370 (24%) received an antidepressant (AD) drug at a minimal effective dose or higher, and only 74 (5%) were seen by a mental health professional.[17]

Anxiety

Anxiety is a normal, potentially adaptive reaction in situations perceived as threatening, but becomes a clinical problem when it is all-pervasive and its severity and duration exceed normal expectations. Several studies have evaluated anxiety in large samples of patients with cancer at various stages of disease using self-report tools [e.g. HADS, Generalised Anxiety Disorder-7 questionnaire (GAD-7), State-Trait Anxiety Inventory (STAI)], reporting prevalences of 12%-25%,[18] with higher prevalence reported in pancreatic and lung cancer, females and younger patients.[19,20]

Meta-analyses of data from 10 071 patients with cancer across 14 countries in onco-haematological settings, and 4007 patients across 7 countries in palliative care settings, showed a rate of anxiety disorders of ∼10%.[21] Similar results were reported in other reviews and meta-analyses (see Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101155). A German study of >2000 patients using the ICD-10 psychiatric interview

reported a 4-week prevalence rate of 11.5%, a 12-month prevalence rate of 15.8% and a lifetime prevalence rate of 24.1% for any anxiety disorders in patients with cancer.[22,23] Data on the time course of specific anxiety disorders in patients with cancer are limited.

Although not a formal psychiatric diagnosis, fear of progression (FoP) in patients with cancer during active treatment and fear of cancer recurrence (FCR) in cancer survivors are further significant cancer-specific anxiety-related clinical conditions. They reflect the fear, worry or concern relating to the possibility that cancer will come back or progress and are among the most common concerns and unmet needs of cancer survivors. Data show that 40%-50% of cancer survivors report moderate to severe levels of FCR.[24] While a certain level of worry may be adaptive, more intense episodes of FCR can compromise psychological functioning and QoL, exacerbate anxiety, cause sleep disturbances and favour the onset of depression.[25]

Death anxiety,[26] which is partially related to FCR, should also be considered a significant clinical condition, particularly in patients at the end of life, but also in survivors.[27] Although this state may be a normal reaction to one's own death, it can become pathological like other forms of anxiety. The difficult challenge for patients at the end of life and receiving palliative care is to balance two conflicting states: remaining engaged and enjoying what remains in life, while being aware of their physical deterioration and imminent death. The proportion of patients with advanced cancer suffering distressing thoughts around death is ∼80%, and if distress is severe (∼25%) it can be associated with demoralisation, dependency, depression, fears of suffering, desire for hastened death and requests for euthanasia or medically assisted death.[28]

Depression

Depression is estimated to affect approximately one in four patients with cancer, who are five times more likely to have depression than the general population.[29] Depression can be observed in any phase of illness, including long-term cancer survivors.[30] Studies assessing depression with self-report instruments have shown a prevalence ranging from 5% to >40%. The previously described German study reported a 4-week total prevalence rate for any mood disorder (i.e. major depression, dysthymia) of 6.5% using the ICD-10 psychiatric interview with an additional 11.1% for adjustment disorders (with anxious or depressed mood). There was a 12-month prevalence rate of 12.5% and a lifetime prevalence rate of 20.5% for any mood disorder.[22,23] Demoralisation, a clinically significant mental health dimension that differs phenomenologically from major depression, is not included as a formal psychiatric diagnosis in the ICD or DSM criteria, but has been shown to exert a highly negative impact on QoL.[31] The prevalence of clinical levels of demoralisation in patients with cancer has been estimated at 25%-30% based on either specific structured interviews (e.g. the Diagnostic Criteria for

Psychosomatic Research measure)[32] or self-report scales (e.g. the Demoralisation Scale).[33,34]

Both anxiety and depression have been shown to interfere with treatment adherence, and depression has also been associated with poorer prognosis and shorter survival in patients with cancer.[35,36]

RISK FACTORS

Anxiety

Many of the risk factors for anxiety in patients with cancer are shared with those for depression, and mixed states of anxiety and depression may actually be more common than isolated states of anxiety or depression.[18] Risk factors for anxiety in cancer populations include the acute phase following the diagnosis of life-threatening cancer, more advanced and longer duration of disease, unemployment, younger age, more physical symptoms, chemotherapy (ChT) treatment, impaired social and cognitive functioning, insecure attachment style and less satisfactory communication with health care providers.[37]

Although a precancer history of anxiety may be a risk factor for cancer-related anxiety, it should be noted that two-thirds of patients with cancer who report symptoms of anxiety have no history of precancer anxiety.[38] FCR is more common in patients who are female, younger, and in those who have received ChT or radiotherapy, or have experienced treatment failure.[39-41] Risk factors for death anxiety include female gender, unemployment, lower income and less preparation for the end of life.[27] Access to health care resources may also play a role in the occurrence of anxiety after the onset of cancer; a systematic review has suggested that the prevalence of anxiety in patients with cancer may be higher in lower- and middle-income countries than in high-income countries.[42]

Depression

Depression in people with cancer typically emerges from a complex interaction of individual, social, disease- and treatment-related risk and protective factors. The cascade effect of these interacting factors has been referred to as a 'final common pathway of distress'.[43] Individual risk factors for depression in cancer include younger age, female gender, a past history of mood disorder, substance abuse or other psychiatric conditions, lack of adequate social support and lower socioeconomic status.[2] Psychological risk factors include the relative lack of attachment security, which refers to internalised expectations of low levels of support and an inability to make use of it, low self-esteem and the lack of a sense of meaning and purpose.[4] Furthermore, depression prevalence is higher in patients with cancer of the pancreas (where depression can pre-date the cancer diagnosis), lung or thyroid, younger patients and those with a history of depression.[44]

Disease- and treatment-related factors may also contribute to the onset and persistence of depression in patients with cancer. Greater physical burden of disease and treatment, more advanced disease and ChT have all been shown to be significant risk factors for depression.[1,2] Furthermore, there is increasing evidence that higher tumour cell burden and treatment-related tissue destruction are associated with increased release of proinflammatory cytokines, which, in turn, may increase the risk of developing depression.

There is a growing body of research on the role of inflammation, hyperactivity of hypothalamic—pituitary—adrenal axis and glutamate excitotoxicity in major depression. The overlapping mechanisms between inflammation, cancer and cancer therapies (e.g. hormone therapy, targeted therapy) with depression allows oncologists to better understand the potential biological mechanisms involved in psychiatric disorders in patients with cancer.[45,46]

CLASSIFICATION AND DIAGNOSIS OF ANXIETY AND DEPRESSIVE DISORDERS

The appropriate criteria for recognising and diagnosing the different forms of depression and anxiety in cancer patients have been extensively debated in recent years. The diagnostic criteria for anxiety and depression are summarised in Tables 1 and 2, respectively.

Anxiety disorders

The common anxiety disorders observed in cancer care are generalised anxiety disorder (GAD), panic disorder and adjustment disorder with anxiety. The ICD-11 and DSM-5-TR share diagnostic criteria but differ in duration requirement and manifestations of anxiety; the ICD-11 also includes sympathetic autonomic overactivity among its criteria.[47] Field studies with ICD-11 support its clinical utility for GAD and panic disorder.[48]

Depressive disorders

The common depressive disorders observed in cancer care include major depression, persistent depression, adjustment disorder with depressive mood and demoralisation. The criteria of the two commonly used nosological systems, ICD-11 and DSM-5-TR, are compared in Table 2.

Diagnosis using DSM-5-TR is based on a set number of symptoms, while the ICD-11 follows a more flexible approach in which the clinician can pattern-fit the symptoms to a diagnosis. Both systems assess severity (mild, moderate or severe intensity of symptoms) and the degree of resulting functional impairment. The inclusion of hopelessness as a symptom of depression in ICD-11 is a noteworthy difference between the two classification systems, with hopelessness being a more powerful driver of diagnosis than the combined outcome of half of the DSM-5-TR criteria. ICD-11 is the first version to introduce diagnostic 'qualifiers' to match the 'specifiers' for depression in DSM-5-TR; both are included due to the perceived utility of these in guiding management.

Both DSM-5-TR and ICD-11 recognise depressive disorders after bereavement as distinct from the sadness of grief. This distinction is also relevant regarding grief following a

Table 1. Diagnostic criteria for anxiety disorders met in cancer care

Diagnosis	DSM-5-TR criteria[6]			ICD-11 criteria[5]		
	Symptoms	Timeline and threshold for symptoms	Specifiers	Symptoms	Timeline and threshold for symptoms	Qualifiers
GAD	1. Worry, fear 2. Restless, edgy 3. Fatigued 4. Loss of concentration, mind going blank 5. Irritable 6. Muscle tension 7. Insomnia	• ≥6 months' duration • More days than not • Difficult to control • Focus on a number of events • Early insomnia	• ≥4/7 symptoms • Impaired functioning essential • Not due to medications or medical illness (e.g. thyroid disorder)	1. Worry, fear 2. Restless, edgy 3. Sympathetic autonomic overactivity 4. Loss of concentration, mind going blank 5. Irritable 6. Muscle tension 7. Insomnia	• ≥Several months • More days than not • Difficult to control • Related to events or free-floating anxiety • Early insomnia	• ≥4/7 symptoms • Impaired functioning essential • Not due to medications or medical illness (e.g. thyroid disorder)
Panic disorder	Recurrent unexpected panic attacks as abrupt surges of fear, with ≥4/13 symptoms of: 1. Palpitations, tachycardia 2. Sweating 3. Tremor, shaking 4. Short of breath 5. Choking 6. Chest discomfort 7. Nausea 8. Dizzy, light-headed 9. Hot or cold sensations 10. Tingling, paraesthesia 11. Derealisation, depersonalisation 12. Loss of control 13. Fear of dying	• >1 attack • Persistent concern or worry about additional panic attacks or their consequences	• Not due to phobia, social setting, traumatic cue or obsession • Can have comorbid agoraphobia	• Recurrent unexpected panic attacks • Symptoms include palpitations, chest pain, choking sensations, dizziness and feelings of unreality (depersonalisation or derealisation) • Secondary fears of dying, losing control or going mad can occur	• Persistent concerns about, and efforts to avoid, future attacks are essential features of impairment	• Can have comorbid agoraphobia • If panic is situational and expected, resulting from a cue such as an imaging machine, consider part of other anxiety disorder, not panic disorder
Adjustment disorder with anxiety	1. Marked distress out of proportion to stressor event 2. Significant impairment in coping in social, occupational or other areas of functioning	• Onset within 3 months of stressor experience and resolved within 6 months of consequences of the stressor • Not due to other mental disorder	• With anxiety • With depressed mood • With mixed anxiety—depression • With conduct disturbance • With mixed conduct and emotions • Unspecified	1. Preoccupation with stressor or illness 2. Failure to adapt to illness or stressor event 3. Excessive worry, distressing thoughts, rumination about illness or stressor	• Onset within days of stressor, expected to resolve within 6 months • Subthreshold symptomatology, not due to other mental disorder • Has elevated risk of suicide and may lead to more severe mental disorder	• Seen as a single disorder only differentiated by severity (mild, moderate, severe)

DSM-5-TR, American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, fifth edition-Text Revision; GAD, generalised anxiety disorder; ICD-11, World Health Organization International Classification of Diseases, 11th edition.

cancer diagnosis or disease progression. When diagnosing depression in the bereaved patient, ICD-11 requires a longer duration of the depressive state (≥1 month) and the presence of symptoms such as low self-worth or guilt, psychomotor retardation or suicidal thinking, which are unlikely to occur in 'normal' grief.[49]

Demoralisation is clearly differentiated from anhedonic depression, as demonstrated in a network analysis.[50] Comparison of the diagnostic phenomena of adjustment disorder and demoralisation shows that the symptoms of hopelessness, pointlessness and entrapment are more specific to demoralisation.

SCREENING AND ASSESSMENT

A series of recommendations have been developed and disseminated in oncology settings for routine screening for distress as the so-called 'sixth vital sign'.[51] The Edmonton Symptom Assessment System (ESAS)[52] is frequently used as a screening tool because of its brevity and multidimensional domains. Another internationally widely used screening instrument is the Distress Thermometer rating scale, developed by the National Comprehensive Cancer Network.[53] The ESAS or Distress Thermometer is administered with the Problem Checklist to screen for possible cancer-related distress. There are several other screening tools available, including ultra-short or short pen-and-pencil questionnaires or digital instruments.[54,55] In a review of screening instruments, the pooled ability of ultra-short methods to detect depression had a sensitivity of 78.4% and a specificity of 66.8% [positive predictive value (PPV) = 34.2%, negative predictive value (NPV) = 93.4%], while for anxiety the sensitivity was 77.3% and the specificity 56.6% (PPV = 55.2%, NPV = 80.25%).[56]

Table 2. Diagnostic criteria for depressive disorders met in cancer care

Diagnosis	DSM-5-TR criteria[6]			ICD-11 criteria[5]		
	Symptoms	Timeline and threshold for symptoms	Specifiers	Symptoms	Timeline and threshold for symptoms	Qualifiers
Major depression	1. Sad mood 2. Loss of interest or pleasure	• ≥2 weeks' duration • Most of the day • Nearly every day • One of the two listed symptoms is essential	• ≥5/9 symptoms • Impaired functioning essential • Response after loss (e.g. illness) clinically judged to be beyond normal response	1. Sad mood 2. Loss of interest or pleasure	• ≥2 weeks' duration • Most of the day • Nearly every day • One of the two listed symptoms is essential	• ≥5/10 symptoms • Impaired functioning essential • After loss (e.g. illness), markers of severity and longer duration (1 month)
	3. Change in appetite ± weight	5% body weight		3. Loss of concentration, indecisive	Nearly daily	
	4. Sleep disturbance 5. Psychomotor slowing or agitation 6. Fatigue, lethargy 7. Worthless, guilty 8. Loss of concentration, indecisive 9. Suicidal ideation	Insomnia or hypersomnia Must be observable, not merely subjective Nearly daily Nearly daily Nearly daily Thoughts ± plans	• With anxiety • With mixed features • With atypical features • With melancholia • With psychotic features • With seasonal pattern	4. Worthless, guilty 5. Hopeless 6. Suicidal ideation 7. Sleep disturbance 8. Change in appetite/ weight 9. Psychomotor slowing or agitation 10. Fatigue, lethargy	Nearly daily Nearly daily Thoughts ± plans Significant Significant Observable Nearly daily	• With prominent anxiety • With atypical features • With melancholia • With psychotic features • With seasonal pattern
Persistent depressive disorder (dysthymia)	Depressed mood over 2-year period, with ≥2/6 symptoms of: 1. Anorexia 2. Insomnia 3. Fatigue 4. Low self-esteem 5. Poor concentration or indecisiveness 6. Hopelessness	• Most of the day, more days than not[a] • Causing significant distress or impairment in social, occupational or other form of functioning • Can have major depressive episode	1. When no episodes of major depression, designate pure dysthymia 2. With intermittent major depression, indicate if current or not	• Persistent depressed mood over 2-year period, with additional depressive symptoms, without major depression occurring	• Most of the day, more days than not[a]	1. With current episode persistent 2. Use recurrent depressive disorder when exceeds 2 years
Adjustment disorder with depressed mood	1. Marked distress out of proportion to stressor (illness) event 2. Significant impairment in coping in social, occupational or other areas of functioning	• Onset within 3 months of stressor (illness) experience and resolved within 6 months of consequences of the stressor • Not due to other mental disorder	• With depressed mood • With anxiety • With mixed anxiety —depression • With conduct disturbance • With mixed conduct and emotions • Unspecified	1. Preoccupation with stressor or illness 2. Failure to adapt to illness or stressor event 3. Excessive worry, distressing thoughts, rumination about illness or stressor	• Onset within days of stressor; expected to resolve within 6 months • Subthreshold symptomatology, not due to other mental disorder • Has elevated risk of suicide and may lead to more severe mental disorder	Seen as a single disorder only differentiated by severity (mild, moderate, severe)

Common diagnosis currently not incorporated into DSM-5-TR or ICD-11 nosological systems

	Symptoms	Timeline and threshold for symptoms	Specifiers	Risk factors for demoralisation
Demoralisation syndrome	1. Low morale, discouraged 2. Poor coping, feeling a failure 3. Feeling trapped 4. Hopelessness 5. Pointlessness 6. Impairment in functioning 7. Potential suicidal thoughts	• Symptoms persist ≥2 weeks • 4/7 symptoms form threshold for disorder	Can be comorbid with major depression or with adjustment disorder	• Physical and mental illnesses with high symptom burdens that challenge coping • Burdensome treatments • Prolonged or repeated hospitalisations • Poorer education and health literacy • Lower income and socioeconomic deprivation • Being female • Single status (unmarried, separated, divorced, widowed) • Lacking social support

DSM-5-TR, American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, fifth edition-Text Revision; ICD-11, World Health Organization International Classification of Diseases, 11th edition.
[a]DSM-5-TR favours chronicity of disorder; ICD-11 favours distinct type of disorder over emphasis on chronicity.
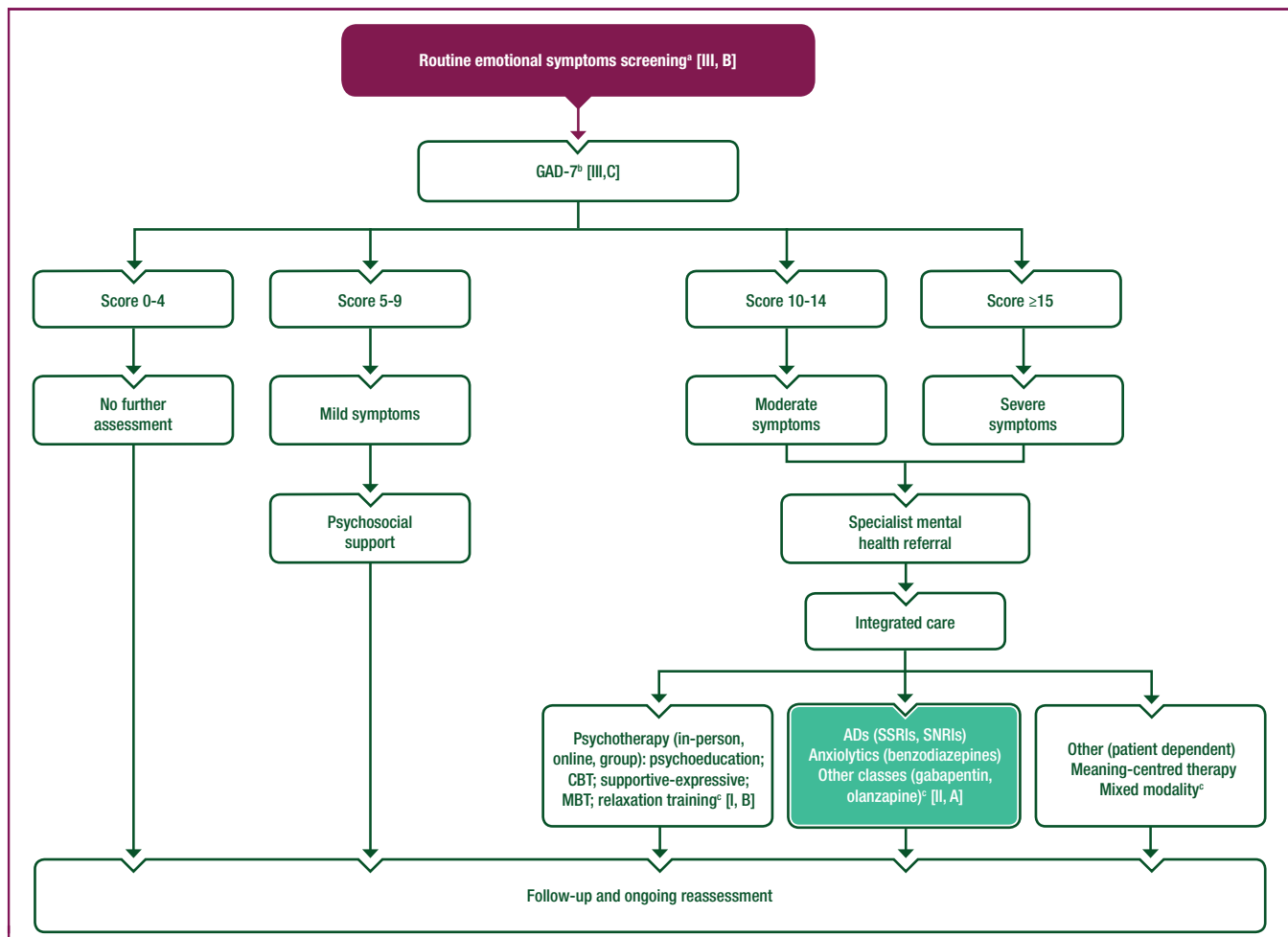
Figure 1. Screening and management of anxiety symptoms/disorders.
Purple: general categories or stratification; white: other aspects of management; turquoise: systemic therapy.
AD, antidepressant; CBT, cognitive behavioural therapy; GAD, generalised anxiety disorder; MBT, mindfulness-based therapy; SNRI, serotonin and norepinephrine re-uptake inhibitor; SSRI, selective serotonin reuptake inhibitor. [a]At diagnosis, treatment, conclusion of treatment, recurrence and when relevant.
[b]Anxious mood (feeling tense, worried), rumination about recurrence is disabling, sleep disturbance, agitation, difficulty in concentration.
[c]As appropriate.

Algorithms for screening for anxiety and depression as part of the more general concept of distress are represented in Figures 1 and 2, respectively, as adaptations of the most widely used national guidelines (e.g. in the USA, Australia, Canada).[57-60] Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101155, summarises the psychometric tools most frequently used in studies to assess anxiety and depression in patients with cancer.

Anxiety

Anxiety may present in many ways, ranging from patients being overtalkative to being withdrawn, and can lead to physical symptoms such as palpitations, sweating, abdominal discomfort and diarrhoea. Assessment of anxiety should include asking the patient whether anxiety was an issue for them before their cancer diagnosis, whether anxiety worsens in certain circumstances (e.g. when attending treatment or clinical review appointments), what their main worries and concerns are, whether they have uncontrolled

physical symptoms such as pain and about any history of alcohol or drug dependence.

Any screening tool employed in the cancer setting should be validated in a cancer population and have acceptable psychometric properties for the population in which it is being used. There are relatively few studies focusing only on screening for anxiety; most studies focus on depression or depression and anxiety, which have a high concordance in patients with cancer. The 14-item HADS[61] (7 items for depression and 7 for anxiety) is the most widely used screening tool. A systematic review and meta-analysis of studies evaluating HADS in patients with cancer found that a score of 8 on the HADS anxiety subscale had a sensitivity of 0.73 and a specificity of 0.65 for the detection of anxiety.[62] The anxiety or depression scores of the ESAS (cut-off $\geq$3) have been shown to be brief and useful methods for screening for anxiety and depression from the time of diagnosis to the end of life in patients with cancer.[63] The GAD-7 scale[64] was devised for the general population and initial research indicated that a cut-off of $\geq$11 was indicative of GAD. Esser et al.[65] compared GAD-7 and HADS
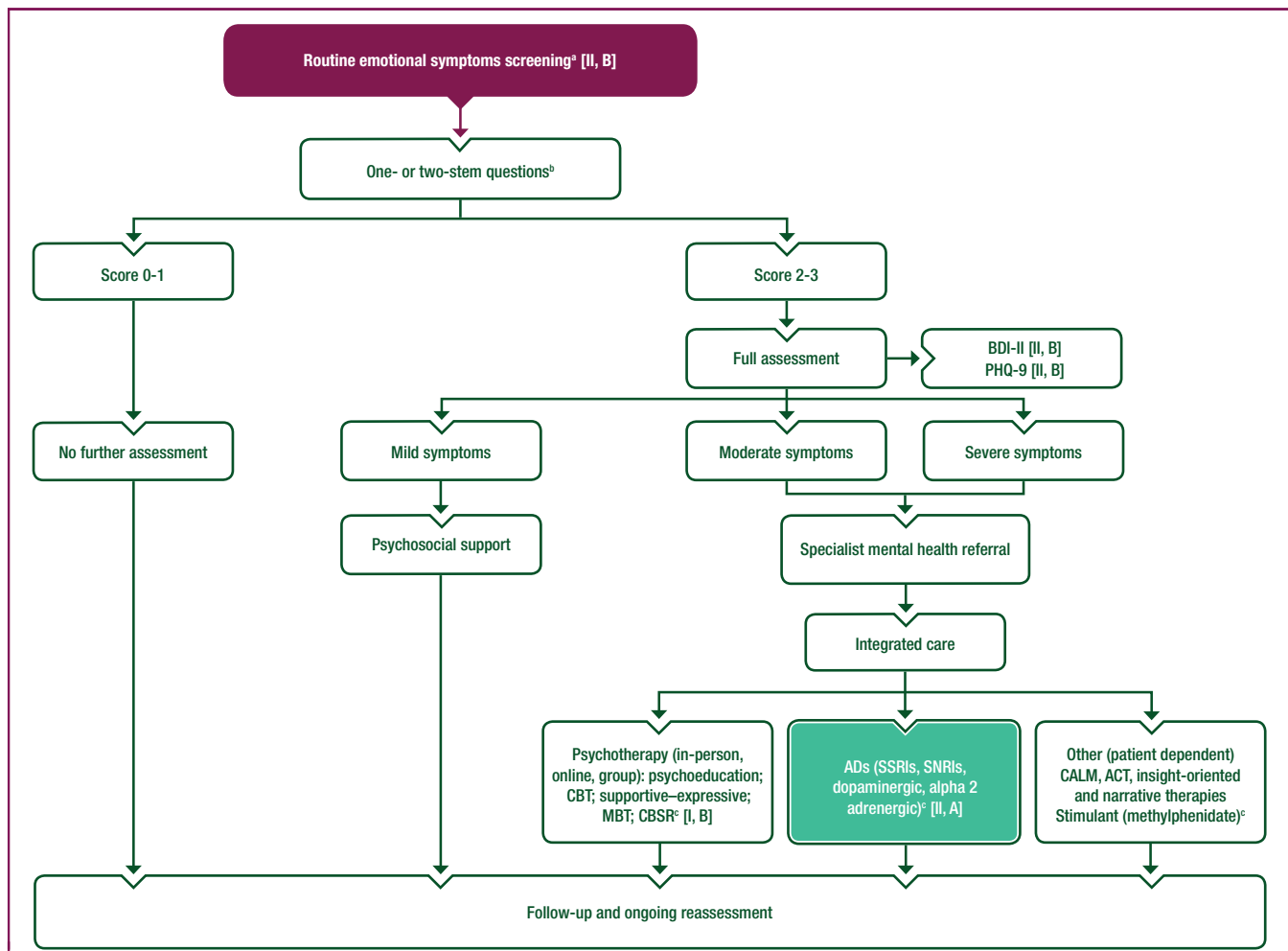
Figure 2. Screening and management of depressive symptoms.
Purple: general categories or stratification; white: other aspects of management; turquoise: systemic therapy.
ACT, acceptance and commitment therapy; AD, antidepressant; BDI-II, Beck Depression Inventory, second edition; CALM, Managing Cancer and Living Meaningfully; CBSR, cognitive behavioural stress reduction; CBT, cognitive behavioural therapy; MBT, mindfulness-based therapy; PHQ-9, Patient Health Questionnaire-9; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]At diagnosis, treatment, conclusion of treatment, recurrence and when relevant.
[b]Depressed mood (feeling down, depressed, helpless/hopeless); anhedonia (little interest or pleasure in doing things).
[c]As appropriate.

anxiety subscale scores in a study of 2141 patients with cancer and found identical areas under the curve with an optimal cut-off of $\geq$7 for GAD-7 and $\geq$8 for the HADS anxiety subscale.

If a cancer survivor is suspected to be experiencing FCR, it is recommended to specifically screen for it. The FCR Inventory (FCRI)[66] has a nine-item FCR severity subscale, referred to as the FCRI-Short Form (FCRI-SF), in which a validated cut-off score of 13 distinguishes 'normal' from 'clinical' FCR.[67] In clinical settings, a further rigorously tested brief scale for FCR is the four-item Concerns About Recurrence Questionnaire (CARQ-4).[68] When compared with the well-validated FCRI-SF, a cut-off of $\geq$12 yielded optimal sensitivity (85%) and specificity (81%) (PPV = 91%, NPV = 70%). For patients with ongoing disease, the concern is not FCR, but rather FoP, a construct which should be considered separately in clinical practice and research. The 12-item FoP questionnaire (FoP-Q-12) has demonstrated good psychometric properties.[69]

Depression

Patients with cancer may not identify with the term 'depression' so it may be more practical to ask if their mood or spirits are low. It is particularly important to consider the possibility of depression in patients who appear withdrawn and who find it difficult to engage with treatment. Awareness of socioeconomic determinants is essential as patients with lower socioeconomic status have been found more likely to report depression and pain and to experience greater global symptom burden than patients with higher socioeconomic status.[70,71]

The simplest approach is to ask patients if they feel depressed or distressed (one-stem question) or if they are in a low mood and have lost interest in their life and activities (low mood and loss of interest; two-stem questions).[72,73] While such an approach can be useful for initial screening, it is not sufficient for assessment. Among validated instruments for assessing depression is the recognised 21-item BDI, second edition (BDI-II) (see

Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.101155). The BDI-II has demonstrated good psychometric testing properties in patients with cancer, including those with advanced cancer.[74] The ability of the BDI-II to distinguish between cognitive—affective symptoms (e.g. pessimism, sadness) and somatic symptoms (e.g. anorexia, fatigability) is of particular relevance when screening for depression in somatic illnesses such as cancer.[74,75]

There are many screening tools for depression, and it is important to use one which has been validated in a cancer population. A meta-analysis by Mitchell et al. on behalf of the Depression in Cancer Care consensus group[76] examined a series of available tools for both screening and assessment of depression at different stages of cancer. The consensus group concluded that the BDI-II and two-stem questions for depression were useful in improving clinical recognition in screening and case finding.

The seven-item HADS depression subscale focuses on the non-somatic symptoms of depression (cut-off score ≥ 8 for mild or borderline cases, ≥ 11 for definite depression). In advanced cancer, a higher threshold may be required, since anhedonia, a major component of the HADS, may be present at the end of life due to increasing physical illness and is not necessarily pathognomonic of a depressive illness in this population.[77]

The PHQ-9, which scores each of the nine DSM criteria for major depression (0 = not at all, 3 = nearly every day), is a self-report instrument with established cut-off scores for mild (5-9), moderate (10-14), moderately severe (15-19) and severe depression (20-27).[78] It has been validated in cancer populations[79] with a threshold score of 10 used to identify cases of clinical depression. The PHQ-9 is recommended as a screening tool by both the National Institute for Health and Care Excellence[80,81] and the American Society of Clinical Oncology,[53] and is very widely used in both clinical and research settings. The six-item Brief Edinburgh Depression Scale (BEDS) was devised and validated against the Present State Examination diagnosis[82] and the HADS[83] for patients with advanced cancer. A cut-off score of 6 out of 18 provides a sensitivity of 72% and a specificity of 83% for the detection of depression, with a PPV of 65.1% and an NPV of 87.1%. For major depression, as the most clinically significant and severe form of depressive disorder, the semi-structured clinical psychiatry interview is the best method for diagnosis.[84]

Recommendations

- Ultra-short methods cannot be used alone to diagnose clinical disorders of anxiety or depression in patients with cancer, but they may be considered as a first-stage screen to identify possible cases [I, B].
- All patients with cancer should be regularly screened and assessed for anxiety in all phases of illness [III, B].
- Validated screening tools should be used to assess anxiety on a regular basis [II, B].
- GAD-7 and HADS are suggested tools to screen for anxiety within all clinical cancer settings [III, C].

- All patients with cancer should be regularly screened and assessed for depression (e.g. feeling down, depressed or hopeless; having little interest or pleasure in doing things; thoughts of suicide) in all phases of illness [II, B].
- Validated screening tools should be used to assess depression on a regular basis [II, B].
- BDI-II and the PHQ-9 self-report instrument are suggested within all clinical cancer settings [II, B] and BEDS within palliative care settings [III, B].

MANAGEMENT

There have been many obstacles to the implementation of anxiety and depression care directly into front-line oncology care.[85,86] The opinions and recommendations of oncologists regarding mental health treatment are paramount to the success of anxiety and depression interventions for patients with cancer.[87,88] Oncology clinicians should have a basic understanding of the available treatments.[89] Oncology clinicians should follow up with patients regarding the uptake of therapeutic recommendations for depression and anxiety and troubleshoot the logistical or psychological difficulties of patients in accepting treatment, with gentle encouragement and reassurance. Furthermore, maintaining a liaison with psycho-oncology units (or programmes) is important for oncologists to ensure more personalised referrals and to receive specific feedback about the psychosocial conditions of the referred patients. Anxiety and depression can emerge in any phase of life and illness course, so it is mandatory to screen and assess psychological symptoms, to follow up if psychopharmacological or psychological treatment is required and to refer those who need specialist help.[90] Effective treatments are available for the prevention and management of anxiety and depressive disorders in various cancer settings,[91] principally with psychotherapeutic and psychopharmacological modalities. In parallel, it is necessary to manage comorbid symptoms like pain and insomnia, as well as other psychosocial factors that may exacerbate anxiety or depressive symptoms.[92]

Psychotherapeutic and psychopharmacological modalities are both efficacious, but pharmacotherapy may be more effective for severe anxiety or depression, while patients with mild to moderate symptoms may benefit from psychotherapy alone.[93-95] The primary psychotherapeutic modalities include psychoeducation, supportive therapy or counselling, relaxation training or mindfulness-based therapy (MBT)[96] [including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT)], cognitive behavioural therapy (CBT), problem-solving therapy, interpersonal therapy (IPT) and supportive—expressive therapy modalities.[97] For patients with advanced cancer and anxiety or depression, supportive—expressive group psychotherapy, meaning-centred therapy, dignity therapy and Managing Cancer and Living Meaningfully (CALM) therapy represent examples of essential first-line therapies for which data from randomised controlled trials (RCTs) are available.[98-100] There is also an expanding interest in online

modalities,[101] which have increased during the COVID-19 pandemic.

Regarding psychopharmacology, the efficacy of AD medications is greater for patients with diagnosable disorders than with subsyndromal symptoms, as in noncancer populations.[102] Methodological limitations should also be considered when extrapolating data from other indications into cancer settings.[103] Furthermore, many treatment studies of depressive symptoms include nondepressed patients at baseline and are therefore limited by a 'floor effect' causing problems in data analysis. Nonselective recruitment can bias the results of trials, causing a type II error (i.e. a benefit exists even though it is not demonstrated).

Psychotherapeutic modalities

Anxiety. High-level evidence exists for the use of psychotherapeutic modalities to treat anxiety disorders during all phases of the cancer trajectory. Although not every cancer setting is represented for each modality, evidence supports psychoeducation, MBT (including MBSR and MBCT), CBT, supportive therapy and blended modalities (e.g. web-based, online and in-person) as efficacious treatments. Other therapies may be efficacious, but the available data are limited, and further investigation is warranted to explore their potential (e.g. IPT). Other therapies have proven efficacy in specific cancer situations for which they were designed (e.g. meaning-centred therapy) (see Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101155). In addition, there is a growing body of research into the efficacy of psychological interventions for FCR, with a meta-analysis of 21 RCTs demonstrating an overall beneficial effect on FCR scores.[104] When compared with traditional CBT, significant benefits were demonstrated with contemporary CBT that aims to change the way in which patients relate to their inner experiences by focusing on cognitive processing and meta-cognitions in FCR.

Depression. Robust data exist for the efficacy of psychotherapy for depression in cancer settings.[105] While all generalisable settings along the cancer trajectory are represented, they are not all represented by each treatment modality. Not all psychotherapeutic modalities have received equally rigorous investigation; some (e.g. psychoeducation) have been studied extensively in certain settings (e.g. breast cancer). A review of three meta-analyses evaluating the efficacy of psychological interventions in patients with breast cancer indicated that short-term treatments seem to be suitable for patients with early breast cancer, while longer-term interventions are more effective for patients with advanced disease.[106] In general, psychoeducational approaches are efficacious both as stand-alone modalities and when combined with other therapies (e.g. psychoeducation added to CBT) or medication (e.g. psychotherapy added to ADs) (see Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101155).

Psychopharmacological agents

Anxiety. Despite the ubiquity of anxiety in the cancer setting and the abundant use of anxiolytic medications, there are limited data supporting their use in cancer settings.[107] Evidence is extrapolated from other settings that may or may not include patients who are medically ill. Many patients receiving systemic anticancer treatments receive anxiolytic medications to prevent and treat nausea (e.g. lorazepam, olanzapine, prochlorperazine). Nevertheless, data supporting their use as anxiolytics in the cancer setting are distinctly absent. Cross-class comparison of anxiolytics in cancer settings is also lacking. Effective classes of medications for the treatment of situational anxiety and anxiety disorders include ADs, benzodiazepines, neuroleptic medications and other sedative or hypnotic medications (see Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101155).

Depression. Psychopharmacological treatment of depression in patients with cancer primarily consists of ADs. It should be noted that a substantial number of patients (10%-15%) already receive ADs as a sleep aid, adjunctive pain medication and/or to target anxiety, even if depression is undiagnosed. These incongruent facts (i.e. prevalent use of ADs while depression remains undertreated) raise the crucial question of which cancer patients are receiving these medications, taking into account the tendency to overuse them in minor depression and underuse them in major depression.[108] Moreover, the guideline recommendations for ADs are generally extrapolated from other settings based on trials with specific exclusion criteria (including the absence of medical disorders), strongly suggesting the need for more studies in cancer and in clinical settings. As a general statement, ADs work to reduce depressive symptoms (up to 70%) but are less efficacious in terms of achieving remission of depression with a single drug ($\sim$30%-40%).[109] Attention to AD administration is therefore paramount, along with the potential use of adjunctive or adjuvant therapies for treatment-refractory patients (e.g. methylphenidate as an add-on therapy to mirtazapine in terminally ill patients with major depressive disorder).[110]

Limited data exist to support the use of psychopharmacological agents to treat depression in patients with cancer, although recommendations for oncologists are available.[111] To date, trials have inconsistently selected for patients who were clinically depressed, which limits the extent to which a benefit may be seen (type II error). The most robust clinical trial data exist for paroxetine, but this AD was controversially associated with reduced levels of the tamoxifen metabolite, endoxifen. Recent reviews, however, indicate that the concurrent use of tamoxifen and ADs has no consistent negative effect on clinical outcomes and survival in patients with breast cancer.[112] There is a general sentiment and consensus that selective serotonin reuptake inhibitors (SSRIs) and related classes have a benign side-effect profile.

Additionally, recent promising data have been gathered on the use of classical (e.g. psilocybin) or atypical (e.g. ketamine) psychedelics for treating depression in palliative care settings[113] (see Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2023.101155), with some studies suggesting that SSRIs are the best choice of treatment if life expectancy is ≥4-6 weeks, whereas psychostimulants or psychedelics can be used if life expectancy is <3 weeks.[114] A number of reviews have concluded that ADs are effective in patients with cancer and depression but more psychopharmacological studies are needed.[105,115,116] These conclusions should be considered in light of all of the aforementioned limitations in study design and noting that ADs may be more efficacious for selected patients who are willing to have their depressive symptoms actively followed and treated (e.g. adequate drug titration, use of adjuvant therapies). It should also be noted that when assessing anxiety and depression, some of the instruments may also measure other dimensions (e.g. activity, symptom interference with daily life, somatic symptoms such as pain) that can be part of the anxiety and depressive disorder spectrum in patients with cancer. In these cases, drugs acting on symptom clusters are preferred, if indicated. Finally, as drug interactions are common in patients with cancer, the involvement of a clinical pharmacologist should be considered to provide knowledge and to carry out psychopharmacological evaluations when necessary.

Recommendations

- The combination of psychotherapeutic and psychopharmacological modalities for the treatment of anxiety and depression is more efficacious than single treatment alone, and is therefore recommended [I, A].
- In patients with anxiety and depressive symptoms the following therapies should be considered: CBT, MBT, psychoeducation and supportive—expressive therapies [I, B].
- Meaning-centred therapy and dignity therapy are recommended in specific cancer settings (e.g. end of life) [I, A].
- Despite limited efficacy data for ADs in patients with cancer, their use is still highly recommended for symptomatic relief given the observed benefits in other settings and their benign side-effect profiles [II, A].
- SSRIs have few significant drug—drug interactions, with the notable exception of tamoxifen metabolism, which is least affected by escitalopram, sertraline and venlafaxine. The only AD to demonstrate a negative clinical outcome is paroxetine, which should be avoided in patients taking tamoxifen [II, E].

CHALLENGES AND SUGGESTIONS FOR FUTURE RESEARCH

More rigorous studies are needed on the incidence and prevalence of anxiety and depression in patients with cancer and on the response to treatment. Although there are data regarding screening for anxiety and depression during the illness trajectory,[117] there are still problems in terms of the representativeness of the data (e.g. cancer site, stage, treatment), varying 40-fold across different types of cancer. There is, therefore, a need for more heterogeneous studies of large samples.[118]

Available guidelines and recommendations indicate principles of implementation of comprehensive screening for anxiety and depression in clinical settings, which is now a standard for accreditation in several countries. Screening, however, is only the first step in a process; a patient who is identified as a 'possible case' should be referred for a more formal specialist assessment and consideration for mental health treatment.[119] Research indicates that many patients (40%-50%) decline help, even when identified as distressed, and only a moderate proportion of cases (25%) accept referrals to, or use, mental health services (e.g. psycho-oncology).[120-122]

This is a significant and challenging problem,[123] underlining the need to improve communication between physicians and patients; the role of oncologists in both screening and motivating patients to be referred and to accept the recommended treatment is extremely important.[124] In a review on this subject, McCarter et al.[125] found a paucity of evidence for strategies to improve rates of referral to psychosocial support and treatment, and stressed the need to establish a strong evidence base supporting the implementation of comprehensive distress screening protocols.[126]

More studies are necessary to understand the predictors and barriers to mental health and psycho-oncology service utilisation among patients with cancer and a diagnosis of anxiety or depression.

METHODOLOGY

This CPG was developed in accordance with the European Society for Medical Oncology (ESMO) standard operating procedures for CPG development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2023.101155.[127] Statements without grading were considered justified standard clinical practice by the authors. Future updates to this CPG will be published on esmo.org as a Living Guideline version or an eUpdate, to be made available at: https://www.esmo.org/guidelines/guidelines-by-topic/supportive-and-palliative-care/anxiety-and-depression-in-adult-cancer-patients.

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