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REVIEW

The use of antidepressants in oncology: a review and practical tips for oncologists

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Background: The use of psychotropic drugs, namely those with an antidepressant profile (ADs), is a mandatory part of an integrated treatment of psychiatric disorders among cancer patients. We aimed to synthetize the most relevant data emerging from published studies to provide tips about the use of ADs in oncology.

Design: A search was made of the major databases over the last 30 years (Embase/Medline, PsycLIT, PsycINFO, the Cochrane Library), including narrative reviews, systematic reviews and meta-analyses summarizing the results from observational studies and randomized clinical trials assessing effectiveness, safety profile, interactions, contraindications and use of ADs in oncology with regard to both psychiatric (depressive spectrum, stress-related, anxiety disorders) and cancer-related symptoms (e.g. pain, hot flashes and fatigue).

Results: The weight of evidence supports the efficacy of ADs for more severe major depression in individuals with cancer and as an adjuvant treatment in cancer-related symptoms, although the methodological limitations of reported randomized controlled trials do not permit definite conclusions. Data also indicate that there should be caution in the use of ADs in cancer patients in terms of their safety profile and potential clinically significant interactions with other prescribed medications. Practical recommendations that have been made for the use of ADs in cancer patients, in the context of a multimodal approach to depression treatment, have been summarized here.

Conclusions: ADs are a relatively safe and effective treatment for more severe major depression in cancer patients. However, more research is urgently needed regarding the efficacy of ADs in different cancer types and cancer settings, their interactions with anticancer agents and their additive benefit when integrated with psychosocial interventions.

Key words: psychopharmacology, antidepressants, depressive disorders, cancer-related symptoms

Introduction

Although emotional distress needing clinical attention can affect 40%–60% of cancer patients [1], a formal diagnosis of a psychiatric disorder according to the usual nosology psychiatric systems, such as the International Classification of Disease of the World Health Organization or the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, can be made in about 25%–30% [2, 3]. Among these, adjustment and stress-related disorders and major depression have been most studied in terms of prevalence, consequences and treatment in oncology [4–8].

Accumulated research over the last 35 years has examined the role of antidepressants (ADs) in the reduction of depressive symptoms and improvement of quality of life among cancer patients [9–11]. Two important qualifications should be noted in the research findings on AD treatment in cancer. The first is that ADs have been shown to be effective in the treatment of other psychiatric disorders, mainly stress-related disorders and anxiety disorders [12, 13]. The second is that ADs have also been used as adjuvant treatment of non-psychiatric cancer-linked symptoms, such as hot flashes, neuropathic pain, nausea and vomiting, fatigue and pruritus [14]. For these reasons, it has been suggested that these medications should be referred to in terms of their pharmacodynamic

profile, which may then be linked to the underlying neurobiological characteristics of the symptoms, the neurotransmitter or molecular system being modified and the mechanism of the action, described as the Neuroscience-Based Nomenclature [15]. This can help clinicians to appreciate the pharmacologic profile of these drugs, the different therapeutic mechanisms and the effects at different doses [16] in the context of an integrated pharmacological and psychological ('PsychopharmOncology') treatment model in oncology [17].

The aims of this narrative review are (i) to summarize the characteristics, the precautions and safety profile of ADs in the treatment of depression, other psychiatric disorders and cancer-related symptoms in cancer patients; and (ii) to suggest guidelines for an appropriate and evidence-based use of ADs in oncology.

Methods

Literature search

A search was made of the major databases from 1997 to 2017 (Embase/Medline, PsycLIT, PsycINFO and the Cochrane Library). Included studies were identified from the reference lists of previous narrative reviews, systematic reviews and meta-analyses summarizing the results from observational studies and randomized clinical trials (RCTs) related to the use of ADs drugs in oncology. When there were no reviews or meta-analyses available, we searched for primary observational studies and RCTs, including searches of the content lists of key journals to identify any additional reviews or meta-analyses missed by the electronic search. Studies published in conference proceedings, qualitative research, commentaries and discussions, letters, or in non-English language journals were excluded.

Search terms

We searched the databases for articles that met the inclusion criteria using pre-specified MESH terms that included 'Cancer (EXP)' or 'Cancer' and 'antidepressants (EXP)' or 'major depression (EXP)' or 'Depressive disorders (EXP)' or 'mood disorders (EXP)' or 'demoralization (EXP)' or 'adjustment disorders with depressed mood (EXP)' or 'PTSD (EXP)' or 'Anxiety disorders (EXP)'. Also cancer-related symptoms (e.g. 'cancer pain'[MH], 'cancer fatigue'[MH], 'hot flash'[MH] AND 'antidepressants'[MH]) were included (see supplementary Table S1, available at *Annals of Oncology* online).

Results

After searching and screening the literature, 4 narrative reviews, 3 systematic reviews, 5 meta-analyses, 4 clinical practice guidelines and 59 clinical trials meeting the inclusion criteria were identified (supplementary Table S1, available at *Annals of Oncology* online). Studies that were incomplete, not sufficiently informative or not examining the role of ADs in a comprehensive way were excluded. The topic areas relative to ADs in oncology were then divided into ADs' characteristics and their use in clinical practice, pharmacokinetics and pharmacodynamics and drug–drug interactions, precautions and side-effects, and clinical disorders (psychiatric and cancer-related syndromes) benefit of ADs.

Antidepressants characteristics and mechanisms of action

There are several different classes of ADs with different mechanisms of action. Some of these drugs, especially the first-generation ADs, such as monoamine oxidase inhibitors (MAOIs), retain a minor role in the treatment of some forms of resistant depression, but are not part of routine care in oncology. They should usually be avoided because of the high risk of potentially lethal drug interactions with other commonly prescribed medications in cancer patients (e.g. opioids). Other first-generation ADs, such as tricyclic antidepressants (TCAs), have several side-effects related to their anticholinergic profile that may be problematic for many cancer patients.

Over the last decades, new classes of ADs with less frequent and less severe adverse effects have been synthetized and marketed. These agents are mainly represented by second-generation ADs and selective ADs (the latter sometimes referred as third-generation ADs). There are also recently marketed ADs (sometimes referred as fourth-generation ADs) (e.g. agomelatine and vortioxetine) for which experience in oncology settings is limited or lacking. Other drugs, such as psychostimulants and hallucinogens, have also been used and are described here according to the specific class of the medication.

Selective serotonin reuptake inhibitors. The selective serotonin reuptake inhibitors (SSRIs) are generally the first-line ADs for the treatment of depression in cancer patients, due to their tolerability. SSRIs comprise a vast class of drugs with a similar side-effect profile (e.g. gastrointestinal disturbance, headache, fatigue or insomnia, sexual dysfunction and transient increased anxiety after initiation of treatment), but there are important differences between each SSRI that may impact on treatment selection (Table 1). Owing to its long half-life and strong cytochrome P450 (CYP450) inhibitory effects, fluoxetine should be used with caution in cancer patients receiving chemotherapy, to avoid the risk of drug interaction with anticancer agents that are metabolized through the CYP450 system. Similarly, paroxetine has prominent P450 inhibitory effects and anticholinergic effects that should be carefully monitored. Sertraline, citalopram and escitalopram have the fewest drug–drug interactions and are the best first-line treatment option. These drugs tend to be well tolerated, although caution is necessary because of the potential for QTc prolongation at higher doses and for bleeding in patients taking aspirin, nonsteroidal anti-inflammatory drugs, warfarin or heparin, because of the antiplatelet effects of SSRIs.

Selective norepinephrine reuptake inhibitors. Reboxetine and teniloxazine (the latter marketed only in Japan) are selective norepinephrine reuptake inhibitors (NRIs) used for the treatment of depression. Reboxetine has been reported to be effective in the treatment of depressed cancer patients [18], but its efficacy has been questioned; more research in cancer patients is needed [19].

Serotonin norepinephrine reuptake inhibitors. Venlafaxine, desvenlafaxine, duloxetine and milnacipran are drugs acting both on the noradrenergic and the serotonergic systems (dual-acting

Table 1. Antidepressants medications and their use in cancer patients

Class and drug	Clinical pearls	Side-effects and precautions
Tricyclics—Reuptake inhibitors 5-HT and NA plus antimuscarinic, antihistaminic and anti-alpha1 actions		
AmitriptylineClomipramine Imipramine	• Effective in pain (low dose) • Sedating profile (amitriptyline) • Activating profile (clomipramine)	• Anticholinergic side-effects in cancer patients, mainly constipation (interaction with opioids) and dry mouth (risk of mucositis) and anticholinergic toxicity (e.g. delirium) • Risk of orthostatic hypotension and cardiac arrhythmias • Weight gain and sedation frequent
Selective serotonin reuptake inhibitor 5-HT		
Fluoxetine	• Used for the treatment of depression, anxiety disorders and stress-related disorders • Used for hot flashes • Minimal risk of discontinuation syndrome due to long half-life • Once weekly formulation available at 90 mg	• All may cause headache, gastrointestinal disturbance, sexual dysfunction, insomnia, restlessness and decreased platelet aggregation • Associated with hyponatremia • Serotonin syndrome can occur • Inhibits conversion of tamoxifen to active metabolite • High potential for drug–drug interactions
Sertraline	• Used for the treatment of depression, anxiety disorders and stress-related disorders • Used for hot flashes	• Few drug–drug interactions • Gastrointestinal side-effects common
Paroxetine	• Used for hot flashes (but not recommended—see precautions)	• High potential for drug–drug interactions via CYP450 enzymes • High risk of discontinuation syndrome due to short half-life • Weight gain • Anticholinergic properties
Citalopram	• Used for the treatment of depression, anxiety disorders and stress-related disorders • Used for hot flashes • Few drug–drug interactions • Sedating profile	• Risk of QTc prolongation
Escitalopram	• Less side-effects • Few drug–drug interactions	• S-enantiomer of citalopram • Sedation
Noradrenaline reuptake inhibitors—Inhibition of NA reuptake, weak effect on 5-HT, inhibition of G protein-coupled inwardly rectifying potassium channels		
Reboxetine	• Activating effect • Least likely to interact with tamoxifen metabolism	• Increased blood pressure at higher doses (monitor blood pressure regularly) • Indirect anticholinergic effects (urinary retention) • May cause cardiovascular effects (tachycardia)
Selective serotonin and noradrenaline reuptake inhibitors—Inhibition of 5-HT and NA reuptake, weak inhibition domopamine reuptake		
Venlafaxine	• Used for neuropathic pain and hot flashes • Least likely to interact with tamoxifen metabolism	• Increased blood pressure at higher doses • High risk of discontinuation syndrome • Nausea, diarrhoea, insomnia, sexual dysfunction and headache
Desvenlafaxine	• See above	• Metabolite of venlafaxine
Duloxetine	• Used for neuropathic pain and hot flashes	• Hepatotoxicity risk and monitor liver function tests • Urinary retention
Levomilnacipran/ Milnacipran	• Used in fibromyalgia	• Only approved in certain countries for depression
Noradrenergic and specific serotonergic antidepressants—Blockade of the pre-synaptic alpha-2 adrenergic inhibitory autoreceptor for norepinephrine and blockade of post-synaptic 5-HT2 and 5-HT3 receptors		
Mirtazapine	• Sleep aid and appetite stimulant • Antiemetic properties • Used for hot flashes • Least likely to interact with tamoxifen metabolism • Minimal sexual dysfunction • Available in orally dissolvable formulation	• Rare risk of agranulocytosis (monitor white blood cell count and absolute neutrophil count) • Increases lipids • Contraindicated in phenylketonuria

Continued

Table 1. *Continued*

Class and drug	Clinical pearls	Side-effects and precautions
Serotonin antagonist and reuptake inhibitors—Blockade of the post-synaptic 5-HT2A receptor and pre-synaptic reuptake of 5HT, norepinephrine and dopamine; Antagonism α1-adrenergic receptor		
Nefazodone	• Minimal sexual dysfunction	• Liver failure (1 per 250 000 patient-years), discontinued in certain countries • Risk of orthostatic hypotension
Trazodone	• Often too sedating to be used as an antidepressant, used for non-habit forming hypnotic effects • Anxiolytic effect • Minimal sexual dysfunction	• Priapism rare side-effect • Avoid post-myocardial infarction
Melatonin agonist at M1 and M2 receptors		
Agomelatine	• Helpful for depression with significant insomnia • No sexual side-effects • No withdrawal effects	• Mild nausea, dizziness, headache, somnolence • Caution in renal or hepatic impairment
Selective dopamine and noradrenaline reuptake inhibitors—Inhibition reuptake norepinephrine and dopamine, release dopamine and noradrenergic (NDRA), non-competitive antagonism on α-3β-2, α-3β-4 and α-4β-2 nicotinic receptors		
Bupropion	• Minimal sexual dysfunction • Useful for smoking cessation • Does not decrease platelet aggregation like serotonergic agents • Central nervous system stimulating effect	• Reduces seizure threshold • Inhibits conversion of tamoxifen to active metabolite • Insomnia and headache
Serotonin modulators and stimulators—Modulators 5-HT, 5-5HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, 5-HT1A receptor partial agonism		
Vilazodone	• May be helpful for depression with significant anxiety • No weight gain or sexual side-effects	• Nausea, vomiting, diarrhoea and headache
Vortioxetine	• Antidepressant properties positive effects on cognitive function (e.g. memory and executive functioning)	• Start at lower dosages due to significant initial gastroparesis
Psychostimulants and other drugs		
Methylphenidate (Dopamine and norepinephrine reuptake inhibitor)	• Rapid improvement of mood • Increase mental alertness • Decrease sense of fatigue • Several types of preparation and routes of administration (transdermal, oral, oral liquid suspension), including extended release (8–12 hours duration)	• Anxiety and agitation • Possible lowering of seizure threshold • Anorexia at higher doses • Exacerbation or precipitation of psychotic symptoms
Modafinil	• Awakening agent for mental alertness • Low abuse potential • No appetite reduction	• Nausea and rhinitis • Palpitations, hypertension and rare cases of chest pain • Risk of Stevens–Johnson syndrome
Ketamine (*N*-methyl-D-aspartate receptor antagonist; dopamine, norepinephrine, 5HT reuptake inhibitor)	• Several types of preparation and routes of administration (transdermal, oral, transmucosal, intravenous) • Rapid effect on depression and suicidal thoughts	• Increase blood pressure, heart and respiratory rate • Nausea, vomiting and anorexia • Hypertonia • Hallucinations, agitation, anxiety, abnormal behaviour
Psilocybin	• Single treatment hallucinatory and mystical experiences provide sustained relief of depression at end of life	• Transient hypertension • Transient headache, paranoia as effects taper off

CYP450, cytochrome P450.

ADs). Venlafaxine works as an SSRI at lower doses and becomes a dual-acting serotonin norepinephrine reuptake inhibitor (SNRI) at doses of 150 mg and above. Desvenlafaxine is the active metabolite of venlafaxine, but has a lesser potential for drug–drug interactions because it is not metabolized by the CYP450 system. Duloxetine is an SNRI at all therapeutic doses (60–120 mg pro die). Dose-dependent hypertension may occur in patients taking venlafaxine at high doses and hepatotoxicity has been described as a rare complication of high dose duloxetine. Milnacipran was originally developed for the treatment of fibromyalgia, but has been shown to be as effective as SSRIs and other SNRIs in the treatment of depression, with similar side-effects (Table 1) [20].

Norepinephrine dopamine reuptake inhibitors. Bupropion is a dual-acting (i.e. noradrenergic and dopaminergic) AD, with activating properties that has been shown to help in improving fatigue and concentration in cancer patients. It tends to be weight-neutral (or, in some cases, to be associated with weight loss) and is not associated with sexual dysfunction. It should be used with caution and not as a first-line treatment option in depressed cancer patients who are cachectic, and should be avoided in depressed patients with significant anxiety, since it may increase agitation, and in patients with seizure disorders, intracranial tumours, eating disorders or alcohol withdrawal, since it decreases the seizure threshold when daily doses exceed 450 mg.

Noradrenergic and specific serotonergic antidepressants. The histaminic receptor agonism and antagonism of 5HT2 and 5HT3 receptors (noradrenergic and specific serotonergic antidepressants) gives mirtazapine anti-anxiety, sleep-inducing, antiemetic and appetite stimulating effects in addition to its antidepressant effect. Side-effects are reported in Table 1.

Serotonin antagonist and reuptake inhibitors. The serotonin antagonist and reuptake inhibitors (SARIs) trazodone and nefazodone have both an antidepressant and anxiolytic profile. Because it is not habit-forming, trazodone is widely used in the treatment of sleep disorders and in the palliation of symptoms in advanced phases of cancer. Orthostatic hypotension is a potential complication of the SARIs, causing dizziness and an increased risk of falling, particularly in elderly or fragile patients. Priapism is also a possible rare effect, although there are no other side-effects on sexual function. Nefazodone has significant side-effects (including liver failure in 1 per 250 000 patient-years) and therefore should be used with caution.

Serotonin modulators and stimulators. Vilazodone and vortioxetine act as SSRIs, but also agonize and antagonize various other serotonin receptors [21]. Vilazodone has partial presynaptic agonism of 5-HT1A, which may give it more anxiolytic properties. Vortioxetine has a novel multimodal mechanism of action which is thought to help restore cognitive deficits associated with depression [22]. However, studies on the use of these newer ADs in oncology are lacking.

Melatonin agonists. Agomelatine has an agonist effect on melatonin M1/M2 receptors and an antagonist action on serotonin (5-HT2C) receptors [23], with a positive effect on sleep and lack of sexual side-effects seen with other ADs. It is contraindicated in patients with renal or hepatic impairment and, because of the possibility of an increase in the levels of liver enzymes, monitoring of liver activity is recommended at the initiation of the treatment and periodically during treatment. Studies on the use of agomelatine in oncology are lacking.

Other drugs. Traditional psychostimulants (methylphenidate and dexamphetamine), which show sympathomimetic properties, have been proposed for the treatment of depression in cancer [24, 25]. The effect of psychostimulants in promoting wakefulness and in elevating mood, with a rapid onset of action of hours to days rather than weeks, would be beneficial in patients with advanced disease. There is some evidence to support their use in the treatment of anorexia, impaired attention and concentration, opiate-induced sedation and pain [26, 27], at low doses that avoid side-effects (Table 1) [28]. However, evidence of their efficacy in the treatment of depression is not clear [29], with some positive results in some studies [30], but not in others [31]. Because of their sympathomimetic effects, caution is advised in patients with hypertension or arrhythmias.

Stimulant-like drugs (e.g. modafinil and armodafinil), which affect histamine projections to the hypothalamus and act as agonists of the noradrenaline receptors, have been proposed for their wakefulness-promoting action in patients with cancer. They seem to lack the tolerance or dependence effects seen with other stimulants but also lack their euphoric effects; data from cancer patients are lacking.

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that has been for a long time used as an anaesthetic agent. Its antidepressant effects and properties have been recently tested, with a rapid effect (one day) observed, although its use is currently reserved for severe and treatment-resistant depression [32]. A few non-controlled studies are available on the rapid response to ketamine in advanced cancer patients [33, 34] for acute depressive symptoms and suicidal ideation in newly diagnosed cancer patients [35]. More data should be collected, however, to establish guidelines for practice and to monitor the potential risk of ketamine treatment [36].

Psilocybin is similarly an old drug repurposed for use to rapidly alleviate depression in cancer patients, particularly related to end-of-life distress [37], although studies are just beginning to emerge.

Drugs that act not only on the monoaminergic system (as the SSRI, NRI, SNRI) but also on other molecular mechanisms, including glutamatergic neurotransmission, may have future significant applications in cancer and other medically ill patients [38, 39].

Pharmacokinetics, pharmacodynamics and potential drug–drug interactions

Information about pharmacokinetics/pharmacodynamics of psychotropic drugs and the main drug–drug interaction in oncology is extremely important, since polypharmacy is common in cancer patients [40, 41]. Most ADs are metabolized through the CYP450 enzyme system and drug–drug interaction is linked to the level of inhibition of CYP450 isoenzymes. Drug interactions between ADs and chemotherapeutic agents may compromise the effectiveness of chemotherapy or increase toxicity of treatment, adversely affecting well-being and survival. However, by virtue of their more selective mechanism of action and receptor profile, newer ADs have a relatively low risk for pharmacodynamic drug interactions, compared with the first-generation ADs (i.e. TCAs and MAOIs). However, the concomitant use of antiepileptics, antimycotics, antibiotics, chemotherapeutic agents and other drugs that cancer patients take and the effect of CYPD26 inhibiting ADs should be carefully monitored [42].

A specific interaction has been reported with the use of SSRIs/SNRIs in breast cancer patients receiving selective estrogen receptor modulators (SERM), such as tamoxifen. Data have accumulated showing that paroxetine, fluoxetine, venlafaxine and bupropion

have significant CYP2D6-inhibiting properties [43–45], which may decrease the plasma concentration of endoxifen (the active metabolite of tamoxifen via CYP2D6) [46]. The consequence in terms of survival of cancer patients is, however, still controversial. Some data indicate a higher risk of recurrence of breast cancer in patients receiving tamoxifen and CYP2D6-inhibiting drugs [47–49], whereas more recent data have not shown such an effect [50, 51]. The International Tamoxifen Pharmacogenomics Consortium has underlined the need for more prospective data on this interaction, controlling for all the possible variables (e.g. type of major alleles of CYP2D6 conferring a decreased CYP2D6 activity, polymorphisms and menopausal state) influencing the metabolic activity [52]. Recommendations have been dispensed to avoid or use with caution ADs with stronger CYPD26-inhibiting action (e.g. paroxetine) in patients on tamoxifen (particularly those with allelic variants of CYP2D6 exposing them to be poor metabolizers) [53, 54]. Also, switching cancer patients receiving paroxetine to weaker CYP2D6-inhibiting ADs (e.g. escitalopram or venlafaxine) has been recommended [55, 56].

Other interactions deserving attention are reported in supplementary Table S2, available at *Annals of Oncology* online.

Other side-effects

Other precautions and side-effects are summarized in Table 1, and in supplementary Table S3, available at *Annals of Oncology* online, including the risk of serotonin syndrome, a potentially life-threatening condition related to drug combinations which alone or combined synergistically increase serotonin to toxic levels. Potential consequences of this include operative bleeding risk during and immediately after surgery, due to the antiplatelet activity of serotonin; discontinuation or SSRI withdrawal syndrome; and a rare (1/1000 to 1/10 000) drug rash with eosinophilia and systemic symptoms, which is a severe cutaneous eruption that has been linked to several common drugs and drug categories, including psychotropic drugs.

Clinical contexts of ADs use

Psychiatric disorders.

Depression: Depressive disorders must be carefully differentiated from normal sadness and physiological depressive conditions [6], but their prevalence in cancer patients appears to be two to three times than in the general population [3, 57]. A systematic review and meta-analysis [58] showed that, irrespective of their class, ADs are more effective than placebo in treating depression among cancer patients. However, ADs should generally be reserved for more severe presentations of depression and always be integrated with psychological therapies, which are the first line of treatment in mild to moderate forms of depression [59].

Stress-related disorders: Stress and stress-related disorders, including acute stress disorders, post-traumatic stress disorders (PTSD) and adjustment disorders are also common and distressing syndromes in cancer patients [60]. Meta-analyses and reviews of the several studies conducted in the area indicate a 12%–25% prevalence of PTSD among cancer patients [61, 62]. The clinical literature on the efficacy of ADs for the treatment of PTSD underlines SSRIs as the preferred initial class of medications [63], although there are no specific treatment outcome data in cancer settings. Adjustment disorders occur in up to 20% of cancer patients [3], where there has been only very limited evidence of benefit of ADs.

Anxiety disorders: For anxiety disorders (e.g. phobias; severe and persistent anticipatory fears, including chemotherapy-induced anticipatory nausea and vomiting; social anxiety, etc.), SSRIs, SNRIs and mirtazapine are the drugs of choice in cancer patients, sometimes together with benzodiazepines [64].

Sleep disorders: Sleep/wake cycle dysregulation, as part of depressive, stress-related and anxiety disorders or as complications of medical procedures, is common in cancer patients and should be properly addressed [65]. In addition to the use of hypnotics, mostly benzodiazepines, ADs with sedative components (e.g. mirtazapine and trazodone) may be useful.

Cancer-related symptoms/syndromes

Clinical practice, supported by scientific evidence, has shown that ADs can be used to improve non-psychiatric cancer-related symptoms, such as loss of appetite, sleep disturbances, pain, anxiety and fatigue, which remarkably interfere with quality of life.

Pain. Pain is one of the most disabling conditions in cancer patients. The efficacy of ADs, as a supplement to the primary analgesics, has been underlined by several reviews [66–68]. The use of ADs as a co-adjuvant treatment in cancer pain has also been recommended in the European Society of Medical Oncology (ESMO) Guidelines for cancer pain management [69]. Among the several classes, the old TCAs and more recently SNRIs (venlafaxine and duloxetine) have been suggested to be effective in the treatment of neuropathic pain in cancer patients on chemotherapy [70, 71]. However, a recent meta-analysis [72] has underscored the heterogeneity of patient samples in the available studies and the importance of balancing the likelihood of benefit against the risk of adverse effects of ADs combined with opioid or antiepileptic drugs for cancer pain.

Hot flashes. Hot flashes secondary to the use of SERM or aromatase inhibitors may cause negative affect, fatigue, sleep difficulties and overall poor quality of life [73]. ADs, especially SSRIs and SNRIs, have been shown to be effective in treating hot flashes, although caution is required in use of SSRIs and SNRIs for hot flashes because of the potential for CYP2D6 inhibiting effects.

Appetite and nausea/vomiting. The anti-histaminergic properties of mirtazapine have shown it to be useful in counteracting nausea, chemotherapy-induced anorexia/cachexia and severe weight loss [74]. A phase II trial confirmed its beneficial impact on appetite, sleep disturbances, anxiety, pain and quality of life, as well as depression in cancer patients [75].

Fatigue. Fatigue is also a common symptom in cancer patients, with studies investigating the possible adjuvant benefit of psychotropic drugs [76]. The antidepressant norepinephrine dopamine reuptake inhibitor bupropion has been suggested to reduce cancer-related fatigue [77], based on dopaminergic activity.

Table 2. Practical tips in the use of ADs in cancer patients

Practical tips

- Start the treatment at low doses followed by a period of dose titration to achieve an optimum individualized response (low doses may help to avoid unwanted initial side-effects, particularly in patients in poor physical conditions)
- Consider to use ADs according to their profile: for patients with anxiety symptoms or sleep disorder, use ADs with a sedative profile; for patients with low energy or psychomotor retardation, use ADs with an activating profile (see Table 1)
- Inform and reassure patients of latency period (beneficial effects usually start within 2–4 weeks of their initiation, with the full effect in about 4–6 weeks) and possible side-effects, in order to avoid premature dropout, especially if patients are receiving other medications
- Treat the patient for 4–6 months in order to avoid relapses or recurrence of episodes after remission. Treat the patients for longer periods, if previous major depressive episodes were present (major recurrent depression)
- Regularly monitor the patient's physical variables and concomitant use of medications for cancer (e.g. steroids, antiemetics, antibiotics, antiestrogen and chemotherapy agents)
- Discontinue medications by tapering the dose by 50% over a couple of weeks to reduce the risk of withdrawal symptoms that can be distressing and may be mistaken for symptoms of cancer illness or relapse into depression
- Patients at higher risk of suicidality should be prescribed a limited quantity of antidepressant medications and monitored in follow-up more frequently

Factors to be considered when prescribing ADs in cancer

- Past psychiatric history (e.g. assess for past positive treatment responses to an antidepressant)
- Concurrent medications (e.g. assess for potential drug–drug interactions)
- Somatic symptom profile (e.g. a sedating antidepressant may be preferable for those with prominent insomnia; cachectic patients may benefit from antidepressants that stimulate weight gain)
- Potential for dual benefit (e.g. duloxetine for neuropathic pain, venlafaxine for hot flashes)
- Type of cancer (e.g. avoid bupropion in those with central nervous system cancers due to elevated seizure risk)
- Co-morbidities (e.g. avoid psychostimulants or tricyclic antidepressants in those with symptomatic cardiac disease)
- Cancer prognosis (e.g. in setting of terminal disease, the rapid onset of action of psychostimulants/ketamine may be preferable)

AD, antidepressant.

Among psychostimulants, methylphenidate [78] and modafinil have also been considered [79], with some contrasting results [80, 81] and further research needed [82].

Guidelines for the use of ADs in cancer care

Based on the recommendations of scientific bodies for the treatment of AD in psychiatric and primary care populations [83–87], several guidelines have been developed for oncology [88–92] and palliative care [93]. The most significant steps, general rules and caveats when prescribing ADs in cancer care and treating cancer patients are summarized in Table 2.

Table 3 provides practical guidance on the most commonly used first-line ADs for treating major depression in cancer patients, based on extrapolation from practice in other medical populations [94]. Level of evidence in cancer populations is provided based on CANMAT criteria [11], with the strength of the recommendation based on Grade Levels [95].

Discussion

ADs have been shown to be effective in the treatment of cancer patients with more severe major depression and in those with other cancer-related distressing symptoms [58, 96]. The efficacy of ADs is positively associated with length of treatment, and no difference has been reported between ADs and placebo in terms of overall acceptability [97, 98]. There are, however, limitations and general cautions to be taken into consideration.

It should be underscored that that there is still a debate ongoing about the effect of ADs in the treatment of both major depression and persistent forms of depression, with some data suggesting an overestimation of the effect of ADs due to selective publishing and selection of patients who have a high likelihood of response in RCTs. More sound methodological studies are needed to clarify the benefit compared with placebo, since many reported studies of ADs have been too small to prove clinical relevance [99, 100]. In the specific setting of oncology, the paucity of data and the limited volume and methodology of reported RCTs have been noted as problems to be resolved in future studies [101]. More specific data are also needed regarding follow-up response (>12 weeks) and dropouts. Current evidence is based on studies with small sample sizes and wide confidence intervals, and inconsistency due to statistical or clinical heterogeneity. Larger RCTs comparing commonly used ADs to placebo (or other ADs) in people with cancer and depressive disorders are urgently needed to better inform clinical practice [102–104]. This is even more necessary with regard to the psychopharmacological treatment of other psychiatric disorders, such as PTSD, or anxiety disorders in cancer patients [62, 105].

More information is also needed about the way in which cancer care professionals use ADs. Recent research has confirmed a gradual increase in the rate of AD prescription, with the intent of addressing the symptoms of depression [106, 107], among cancer patients, including long survivors [108]. A recent review indicates that the prescribing patterns of ADs in oncology is related to several patient variables, including gender (females > men), ethnicity (Caucasians receiving more SSRIs than other ethnic groups)

Table 3. First-line ADs in cancer patients

Generic name	Optimal indication	Standard adult dose	Level of evidence/grade of recommendation
Citalopram/Escitalopram	• Few CYP450 drug interactions • Escitalopram may have more rapid onset of action	Start: 10–20 mg o.d./(5–10 mg q.h.s.) Goal: 20–40 mg/(10–20 mg) Max: 40 mg o.d./(20 mg q.h.s.)	• Level III[a] evidence • Strong, moderate quality
Venlafaxine/Desvenlafaxine	• Optimal choice for patients on tamoxifen • Consider for prominent hot flashes	Start: 37.5–75 mg q.a.m./(50 mg) Goal: 75–225 mg/(50–100 mg) Max: 300 mg q.a.m./(100 mg)	• Level III[a] evidence • Strong, low quality
Bupropion XL	• Consider for prominent fatigue • Aids sexual function	Start: 150 mg q.a.m. Goal: 150–300 mg Max: 450 mg q.a.m.	• Level III[a] evidence • Strong, low-quality
Duloxetine	• Separate indications for neuropathic and chronic pain	Start: 30 mg q.a.m. Goal: 30–60 mg Max: 120 mg q.a.m.	• Level III[a] evidence • Strong, low-quality
Mirtazapine	• Consider for prominent insomnia, anorexia/cachexia, diarrhoea	Start: 7.5–15 mg q.h.s. Goal: 15–45 mg Max: 60 mg q.h.s.	• Level III[a] evidence • Strong, low-quality

[a]CANMAT Level III Evidence: non-randomized, controlled prospective studies or case series or high-quality retrospective studies.
AD, antidepressant; CYP450, cytochrome P450.

and treatment (more in patients with extensive cancer treatment) [109, 110], with only few studies reporting data on exact dose or follow-up regimens [111]. However, the need for correct assessment and diagnosis of depression and other psychopathological conditions is extremely important. A large number of cancer patients suffer from emotional distress not requiring AD treatment (e.g. mild–moderate distress, adjustment disorders with depressed mood, etc.), while a minority can be diagnosed with severe forms of depression needing AD treatment. A more integrated liaison between psychiatry and oncology is needed to address this overuse, as well as the opposite problem of undertreatment of depressed cancer patients who would benefit from ADs. Walker et al. [112] showed, for example, that of 1538 patients diagnosed with major depression, 1130 (73%) were not receiving effective AD treatment, while Fisch et al. [113] found that among 3106 cancer patients, only one-fourth of those with clinically significant depression were properly treated. The continuous, coordinated and comprehensive role of primary care for cancer patients and their families may also help in this regard at all stages of cancer [114].

A third related issue is the need for collaborative care integrating psychopharmacology and psychosocial intervention. In general clinical psychiatry, this has been shown to be more effective than single interventions in both depressive and anxiety disorders [101, 115]. Evidence also indicates that a sequential integration of psychotherapy and pharmacotherapy is a viable strategy for preventing relapse and recurrence in severe forms of depression (e.g. major depression) and that discontinuation of ADs may be feasible when psychotherapy is provided [116]. In oncology, there is a marked need for the integration of pharmacological and psychosocial intervention [117]. This is important because psychosocial intervention is the treatment of choice for mild and moderate forms of depression and because collaborative care treatment programmes are cost-effective for cancer patients with elevated symptoms of depression [118]. They have been associated with improvement of psychological and somatic symptoms, health, and quality of life compared with usual care. A collaborative care model that incorporates a stepped care approach by integrating pharmacologic, psychological and practical management [59] can improve the effectiveness of the treatment of psychosocial disorders in patients with cancer [119] and can maximize the treatment outcome of depression [98, 120].

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References

1. Brocken P, Prins JB, Dekhuijzen PN, van der Heijden HF. The faster the better?—A systematic review on distress in the diagnostic phase of suspected cancer, and the influence of rapid diagnostic pathways. Psychooncology 2012; 21: 1–10.
2. Singer S, Das-Munshi J, Brähler E. Prevalence of mental health conditions in cancer patients in acute care—a meta-analysis. Ann Oncol 2010; 21: 925–930.
3. Mitchell AJ, Chan M, Bhatti H et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol 2011; 12: 160–174.
4. Walker J, Holm Hansen C, Martin P et al. Prevalence of depression in adults with cancer: a systematic review. Ann Oncol 2013; 24(4): 895–900.
5. Caruso R, Nanni MG, Riba M et al. Depressive spectrum disorders in cancer: prevalence, risk factors and screening for depression: a critical review. Acta Oncol 2017; 56(2): 146–155.
6. Caruso R, Nanni MG, Riba M et al. Depressive spectrum disorders in cancer: diagnostic issues and intervention. A critical review. Curr Psychiatry Rep 2017;19(6): 33. doi: 10.1007/s11920-017-0785-7.
7. Krebber AM, Buffart LM, Kleijn G et al. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. Psychooncology 2014; 23(2): 121–130.
8. Cordova MJ, Riba MB, Spiegel D. Post-traumatic stress disorder and cancer. Lancet Psychiatry 2017; 4(4): 330–338.
9. Rodin G, Katz M, Lloyd N et al. Treatment of depression in cancer patients. Curr Oncol 2007; 14(5): 180–188.
10. Grassi L, Nanni MG, Uchitomi Y, Riba M, Pharmacotherapy of depression in people with cancer. In D Kissane, M Maj, N Sartorius (eds), Depression and Cancer. London: Wiley 2011; 151–175.
11. Li M, Fitzgerald P, Rodin G. Evidence-based treatment of depression in patients with cancer. J Clin Oncol 2012; 30(11): 1187–1196.
12. Caruso R, Grassi L, Nanni MG, Riba M. Psychopharmacology in psycho-oncology. Curr Psychiatry Rep 2013; 15(9): 393.
13. Thekdi SM, Trinidad A, Roth A. Psychopharmacology in cancer. Curr Psychiatry Rep 2015; 17(1): 529.
14. Grassi L, Caruso R, Hammelef K et al. Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: a review. Int Rev Psychiatry 2014; 26(1): 44–62.
15. Zohar J, Stahl S, Moller HJ et al. A review of the current nomenclature for psychotropic agents and an introduction to the neuroscience-based nomenclature. Eur Neuropsychopharmacol 2015; 25(12): 2318–2325.
16. Fitzgerald P, Li M, Grassi L, Rodin G. Pharmacotherapy of depression in cancer patients. In L Grassi, M Riba (eds), Psychopharmacology in Oncology and Palliative Care. Berlin: Springer 2014; 145–161.
17. Grassi L, Riba M, Psychopharmacology in Oncology and Palliative Care. A Practical Manual. Heidelberg: Springer-Verlag 2014.
18. Grassi L, Biancosino B, Marmai L et al. Effect of reboxetine on major depressive disorder in breast cancer patients: an open-label study. J Clin Psychiatry 2004; 65: 515–520.
19. Eyding D, Lelgemann M, Grouven U et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 2010; 341: c473.
20. Nakagawa A, Watanabe N, Omori IM et al. Milnacipran versus other antidepressive agents for depression. Cochrane Database Syst Rev 2009; (3): CD006529.
21. Kraus C, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity—links between molecular, functional and structural pathophysiology in depression. Neurosci Biobehav Rev 2017; 77: 317–326.
22. Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol 2015; 19(2): pii: pyv082. doi: 10.1093/ijnp/pyv082.
23. Liu J, Clough SJ, Hutchinson AJ et al. MT1 and MT2 melatonin receptors: a therapeutic perspective. Annu Rev Pharmacol Toxicol 2016; 56: 361–368.
24. Portela MA, Rubiales AS, Centeno C. The use of psychostimulants in cancer patients. Curr Opin Support Palliat Care 2011; 5(2): 164–168.
25. Malhi GS, Byrow Y, Bassett D et al. Stimulants for depression: on the up and up? Aust N Z J Psychiatry 2016; 50(3): 203–207.
26. Yennurajalingam S, Palmer JL, Chacko R, Bruera E. Factors associated with response to methylphenidate in advanced cancer patients. Oncologist 2011; 16(2): 246–253.
27. Andrew B, Ng CG, Jaafar NR. The use of methylphenidate in cancer patients: a review. Curr Drug Targets 2017; doi:10.2174/1389450118666170317162603. [Epub ahead of print]
28. Lasheen W, Walsh D, Mahmoud F et al. Methylphenidate side effects in advanced cancer: a retrospective analysis. Am J Hosp Palliat Care 2010; 27(1): 16–23.
29. McIntyre RS, Lee Y, Zhou AJ et al. The efficacy of psychostimulants in major depressive episodes: a systematic review and meta-analysis. J Clin Psychopharmacol 2017; 37(4): 412–418.
30. Centeno C, Sanz A, Cuervo MA et al. Multicentre, double-blind, randomised placebo-controlled clinical trial on the efficacy of methylphenidate on depressive symptoms in advanced cancer patients. BMJ Support Palliat Care 2012; 2(4): 328–333.
31. Sullivan DR, Mongoue-Tchokote S, Mori M et al. Randomized, double-blind, placebo-controlled study of methylphenidate for the treatment of depression in SSRI-treated cancer patients receiving palliative care. Psychooncology 2016; doi:10.1002/pon.4220. [Epub ahead of print]
32. Schwartz J, Murrough JW, Iosifescu DV. Ketamine for treatment-resistant depression: recent developments and clinical applications. Evid Based Mental Health 2016; 19(2): 35–38.
33. Irwin SA, Iglewicz A, Nelesen RA et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med 2013; 16(8): 958–965.
34. Iglewicz A, Morrison K, Nelesen RA et al. Ketamine for the treatment of depression in patients receiving hospice care: a retrospective medical record review of thirty-one cases. Psychosomatics 2015; 56(4): 329–337.
35. Fan W, Yang H, Sun Y et al. Ketamine rapidly relieves acute suicidal ideation in cancer patients: a randomized controlled clinical trial. Oncotarget 2017; 8(2): 2356–2360.
36. Singh I, Morgan C, Curran V et al. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. Lancet Psychiatry 2017;4(5): 419–426.
37. Barrett FS, Griffiths RR. Classic hallucinogens and mystical experiences: phenomenology and neural correlates. Curr Top Behav Neurosci 2017; doi:10.1007/7854_2017_474. [Epub ahead of print]
38. Catena-Dell'Osso M, Fagiolini A, Rotella F et al. Glutamate system as target for development of novel antidepressants. CNS Spectr 2013; 18(4): 188–198.
39. Dhir A. Investigational drugs for treating major depressive disorder. Expert Opin Investig Drugs 2017; 26(1): 9–24.
40. Yap KY, Tay WL, Chui WK, Chan A. Clinically relevant drug interactions between anticancer drugs and psychotropic agents. Eur J Cancer Care (Engl) 2011; 20(1): 6–32.
41. Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. CNS Drugs 2012; 26(1): 39–67.
42. Levin TT, Cortes-Ladino A, Weiss M, Palomba ML. Life-threatening serotonin toxicity due to a citalopram-fluconazole drug interaction: case reports and discussion. Gen Hosp Psychiatry 2008; 30(4): 372–377.
43. Desmarais JE, Looper KJ. Interactions between tamoxifen and antidepressants via cytochrome P450 2D6. J Clin Psychiatry 2009; 70: 1688–1697.
44. Caraci F, Crupi R, Drago F, Spina E. Metabolic drug interactions between antidepressants and anticancer drugs: focus on selective serotonin reuptake inhibitors and hypericum extract. Curr Drug Metab 2011; 12: 570–577.

45. L'Espérance S, Frenette S, Dionne A, Dionne JY. Comité de l'évolution des pratiques en oncologie (CEPO) Pharmacological and non-hormonal treatment of hot flashes in breast cancer survivors: CEPO review and recommendations. Support Care Cancer 2013; 21: 1461–1474.
46. Henry NL, Stearns V, Flockhart DA et al. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. Am J Psychiatry 2008; 165: 1251–1255.
47. Kelly CM, Juurlink DN, Gomes T et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ 2010; 340: c693.
48. Chubak J, Bowles EJ, Yu O et al. Breast cancer recurrence in relation to antidepressant use. Cancer Causes Control 2016; 27(1): 125–136.
49. Damodaran SE, Pradhan SC, Umamaheswaran G et al. Genetic polymorphisms of CYP2D6 increase the risk for recurrence of breast cancer in patients receiving tamoxifen as an adjuvant therapy. Cancer Chemother Pharmacol 2012; 70(1): 75–81.
50. Valachis A, Garmo H, Weinman J et al. Effect of selective serotonin reuptake inhibitors use on endocrine therapy adherence and breast cancer mortality: a population-based study. Breast Cancer Res Treat 2016; 159(2): 293–303.
51. Haque R, Shi J, Schottinger JE et al. Tamoxifen and antidepressant drug interaction in a cohort of 16,887 breast cancer survivors. J Natl Cancer Inst 2015; 108(3): pii: djv337, doi: 10.1093/jnci/djv337.
52. Province MA, Goetz MP, Brauch H, International Tamoxifen Pharmacogenomics Consortium et al. CYP2D6 genotype and adjuvant tamoxifen: meta-analysis of heterogeneous study populations. Clin Pharmacol Ther 2014; 95(2): 216–227.
53. Zembutsu H, Sasa M, Kiyotani K et al. Should CYP2D6 inhibitors be administered in conjunction with tamoxifen? Expert Rev Anticancer Ther 2011; 11(2): 185–193.
54. Zembutsu H, Nakamura S, Akashi-Tanaka S et al. Significant effect of polymorphisms in cyp2d6 on response to tamoxifen therapy for breast cancer: a prospective multicenter study. Clin Cancer Res 2017; 23(8): 2019–2026.
55. Binkhorst L, Bannink M, de Bruijn P et al. Augmentation of endoxifen exposure in tamoxifen-treated women following SSRI switch. Clin Pharmacokinet 2016; 55(2): 249–255.
56. Miguel C, Albuquerque E. Drug interaction in psycho-oncology: antidepressants and antineoplastics. Pharmacology 2011; 88(5-6): 333–339.
57. Robson A, Scrutton F, Wilkinson L, MacLeod F. The risk of suicide in cancer patients: a review of the literature. Psychooncology 2010; 19(12): 1250–1258.
58. Laoutidis ZG, Mathiak K. Antidepressants in the treatment of depression/depressive symptoms in cancer patients: a systematic review and meta-analysis. BMC Psychiatry 2013; 13: 140.
59. Li M, Kennedy EB, Byrne N et al. Management of depression in patients with cancer: a clinical practice guideline. J Oncol Pract 2016; 12(8): 747–756.
60. Caruso R, Nanni MG, Riba MB et al. The burden of psychosocial morbidity related to cancer: patient and family issues. Int Rev Psychiatry 2017;29(5): 389–402.
61. Smith MY, Redd WH, Peyser C, Vogl D. Post-traumatic stress disorder in cancer: a review. Psychooncology 1999; 8(6): 521–537.
62. Rustad JK, David D, Currier MB. Cancer and post-traumatic stress disorder: diagnosis, pathogenesis and treatment considerations. Pall Supp Care 2012; 10: (3):213–223.
63. Baldwin DS, Anderson IM, Nutt DJ et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 2014; 28(5): 403–439.
64. Spiegel D, Riba MB. Managing anxiety and depression during treatment. Breast J 2015; 21(1): 97–103.
65. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. J Clin Oncol 2001; 19: 895–908.
66. Jongen JL, Huijsman ML, Jessurun J et al. The evidence for pharmacologic treatment of neuropathic cancer pain: beneficial and adverse effects. J Pain Symptom Manage 2013;46(4): 581–590.
67. Verdu B, Decosterd I, Buclin T et al. Antidepressants for the treatment of chronic pain. Drugs 2008; 68: 2611–2632.
68. Bennett MI. Effectiveness of antiepileptic or antidepressant drugs when added to opioids for cancer pain: systematic review. Palliat Med 2011; 25: 553–539.
69. Ripamonti C, Santini D, Maranzano E, on behalf of the ESMO Guidelines Working Group et al. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 2012; 23(Suppl 7): 139–154.
70. Smith EM, Pang H, Cirrincione C, Alliance for Clinical Trials in Oncology et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013; 309: 1359–1367.
71. Matsuoka H, Makimura C, Koyama A et al. Pilot study of duloxetine for cancer patients with neuropathic pain non-responsive to pregabalin. Anticancer Res 2012; 32: 1805–1809.
72. Kane CM, Mulvey MR, Wright S et al. Opioids combined with antidepressants or antiepileptic drugs for cancer pain: systematic review and meta-analysis. Palliat Med 2017; 269216317711826. doi: 10.1177/0269216317711826. [Epub ahead of print].
73. Morrow PK, Mattair DN, Hortobagyi GN. Hot flashes: a review of pathophysiology and treatment modalities. Oncologist 2011; 16: 1658–1664.
74. Kast RE, Foley KF. Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT3 antagonists with good antinausea effects. Eur J Cancer Care 2007; 16: 351–354.
75. Riechelmann RP, Burman D, Tannock IF et al. Phase II trial of mirtazapine for cancer-related cachexia and anorexia. Am J Hosp Palliat Care 2010; 27: 106–110.
76. Breitbart W, Alici-Evcimen Y. Update on psychotropic medications for cancer-related fatigue. J Natl Compr Canc Netw 2007; 5: 1081–1091.
77. Minton O, Richardson A, Sharpe M et al. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst 2008; 100: 1155–1166.
78. Mücke M, Mochamat CH, Peuckmann-Post V et al. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev 2015; (5): CD006788.
79. Conley CC, Kamen CS, Heckler CE et al. Modafinil moderates the relationship between cancer-related fatigue and depression in 541 patients receiving chemotherapy. J Clin Psychopharmacol 2016; 36(1): 82–85.
80. Gong S, Sheng P, Jin H et al. Effect of methylphenidate in patients with cancer-related fatigue: a systematic review and meta-analysis. PLoS One 2014; 9(1): e84391.
81. Spathis A, Fife K, Blackhall F et al. Modafinil for the treatment of fatigue in lung cancer: results of a placebo-controlled, double-blind, randomized trial. J Clin Oncol 2014; 32(18): 1882–1888.
82. Mücke M, Mochamat CH, Peuckmann-Post V et al. Pharmacological treatments for fatigue associated with palliative care: executive summary of a Cochrane Collaboration systematic review. J Cachexia Sarcopenia Muscle 2016; 7(1): 23–27.
83. Bauer M, Pfennig A, Severus E, World Federation of Societies of Biological Psychiatry. Task Force on Unipolar Depressive Disorders et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World J Biol Psychiatry 2013; 14(5): 334–385.
84. Bauer M, Severus E, Köhler S, WFSBP Task Force on Treatment Guidelines for Unipolar Depressive Disorders et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. Part 2: maintenance treatment of major depressive disorder—update 2015. World J Biol Psychiatry 2015; 16(2): 76–95.
85. Cleare A, Pariante CM, Young AH, and the members of the Consensus Meeting19 Endorsed by the British Association for Psychopharmacology. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British

Association for Psychopharmacology guidelines. J Psychopharmacol 2015; 29(5): 459–525.
86. Gelenberg AJ, and Work Group On Major Depressive Disorder Practice Guideline For The Treatment of Patients With Major Depressive Disorder Third Edition. American Psychiatric Association, 2010; http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf
87. Baldwin DS, Anderson IM, Nutt DJ et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the © British Association for Psychopharmacology. J Psychopharmacol 2014;28(5): 403–439.
88. Ramasubbu R, Taylor VH, Samaan Z, Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and select comorbid medical conditions. Ann Clin Psychiatry 2012; 24(1): 91–109.
89. Butow P, Price MA, Shaw JM et al. Clinical pathway for the screening, assessment and management of anxiety and depression in adult cancer patients: Australian Guidelines. Psychooncology 2015; 24(9): 987–1001.
90. Andersen BL, DeRubeis RJ, Berman BS, American Society of Clinical Oncology et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol 2014; 32(15): 1605–1619.
91. Li M, Kennedy EB, Byrne N et al. The Management of Depression in Patients with Cancer. Toronto: Cancer Care Ontario; 2015 May 11. Program in Evidence-based Care Guideline No: 19-4.
92. Howell D, Keshavarz H, Esplen MJ, on behalf of the Cancer Journey Advisory Group of the Canadian Partnership Against Cancer et al. A Pan Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress, Depression, and Anxiety in Adults with Cancer. Toronto: Canadian Partnership Against Cancer and the Canadian Association of Psychosocial Oncology, July 2015.
93. Rayner L, Price A, Hotopf M, Higginson IJ. The development of evidence-based European guidelines on the management of depression in palliative cancer care. Eur J Cancer 2011; 47: 702–712.
94. Kennedy SH, Lam RW, McIntyre RS et al. CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. Can J Psychiatry 2016; 61(9): 540–560.
95. Schunemann HJ, Jaeschke R, Cook DJ et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med 2006; 174(5): 605–614.
96. Riblet N, Larson R, Watts BV, Holtzheimer P. Reevaluating the role of antidepressants in cancer-related depression: a systematic review and meta-analysis. Gen Hosp Psychiatry 2014; 36(5): 466–473.
97. Hart SL, Hoyt MA, Diefenbach M et al. Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer. J Natl Cancer Inst 2012; 104(13): 990–1004.
98. Ostuzzi G, Benda L, Costa E, Barbui C. Efficacy and acceptability of antidepressants on the continuum of depressive experiences in patients with cancer: systematic review and meta-analysis. Cancer Treat Rev 2015; 41(8): 714–724.
99. Bschor T, Kilarski LL. Are antidepressants effective? A debate on their efficacy for the treatment of major depression in adults. Expert Rev Neurother 2016; 16: 367–374.
100. Meister R, von Wolff A, Mohr H et al. Comparative safety of pharmacologic treatments for persistent depressive disorder: a systematic review and network meta-analysis. PLoS One 2016; 11(5): e0153380.
101. Li M, Kennedy EB, Byrne N et al. Systematic review and meta-analysis of collaborative care interventions for depression in patients with cancer. Psychooncology 2017; 26(5): 573–587.
102. Toftegård Andersen L, Voigt Hansen M, Rosenberg J, Gögenur I. Pharmacological treatment of depression in women with breast cancer: a systematic review. Breast Cancer Res Treat 2013; 141(3): 325–330.
103. Carvalho AF, Hyphantis T, Sales PM et al. Major depressive disorder in breast cancer: a critical systematic review of pharmacological and psychotherapeutic clinical trials. Cancer Treat Rev 2014; 40(3): 349–355.
104. Ostuzzi G, Matcham F, Dauchy S et al. Antidepressants for the treatment of depression in people with cancer. 2015;(6): CD011006. doi: 10.1002/14651858.CD011006.pub2.
105. Traeger L, Greer JA, Fernandez-Robles C et al. Evidence-Based Treatment of Anxiety in Patients With Cancer. J Clin Oncol 2012; 30: 1197–1205.
106. Ng CG, Boks MP, Zainal NZ, de Wit NJ. The prevalence and pharmacotherapy of depression in cancer patients. J Affect Disord 2011; 131: 1–7.
107. Grassi L, Nanni MG, Uchitomi Y, Riba M, Pharmacotherapy of depression in people with cancer. In DW Kissane, M Maj, N Sartorius (eds), Depression and Cancer. Chichester: Wiley 2011; 151–176.
108. Hawkins NA, Soman A, Buchanan Lunsford N et al. Use of medications for treating anxiety and depression in cancer survivors in the United States. J Clin Oncol 2017; 35(1): 78–85.
109. Fisch MJ, Sherman LK, Adamus AT et al. Trends in antidepressant prescribing at a comprehensive cancer center. J Clin Oncol 2004; 22(14 Suppl): 6132.
110. Lal LS, Miller LA, Arbuckle R et al. Disparities in outpatient antidepressant prescribing patterns and determinants of resource utilization at a tertiary care cancer center. J Support Oncol 2009; 7(6): 237–244.
111. Sanjida S, Janda M, Kissane D et al. A systematic review and meta-analysis of prescribing practices of antidepressants in cancer patients. Psychooncology 2016; 25(9): 1002–1016.
112. Walker J, Hansen CH, Martin P et al. Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. Lancet Psychiatry 2014; 1(5): 343–350.
113. Fisch MJ, Zhao F, Manola J et al. Patterns and predictors of antidepressant use in ambulatory cancer patients with common solid tumors. Psychooncology 2015; 24(5): 523–532.
114. Rubin G, Berendsen A, Crawford SM et al. The expanding role of primary care in cancer control. Lancet Oncol 2015; 16: 1231–1272.
115. Archer J, Bower P, Gilbody S et al. Collaborative care for depression and anxiety problems. Cochrane Database Syst Rev 2012; 10: CD006525.
116. Guidi J, Fava GA, Fava M, Papakostas GI. Efficacy of the sequential integration of psychotherapy and pharmacotherapy in major depressive disorder: a preliminary meta-analysis. Psychol Med 2011; 41: (2): 321–331.
117. Walker J, Sharpe M. Integrated management of major depression for people with cancer. Int Rev Psychiatry 2014; 26(6): 657–668.
118. Duarte A, Walker J, Walker S et al. Cost-effectiveness of integrated collaborative care for comorbid major depression in patients with cancer. J Psychosom Res 2015; 79(6): 465–470.
119. Sharpe M, Walker J, Holm Hansen C, SMaRT (Symptom Management Research Trials) Oncology-2 Team et al. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. Lancet 2014; 384(9948): 1099–1108.
120. Rodríguez Vega B, Palao A, Torres G et al. Combined therapy versus usual care for the treatment of depression in oncologic patients: a randomized controlled trial. Psychooncology 2011; 20(9): 943–952.