Antidepressant Therapy in Patients with Cancer: A Clinical Review

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Abstract

Background: The prevalence of major depressive disorder (MDD) by DSM criteria among cancer patients is about 14%–15% in oncological, hematological, and palliative services and the number is risen up to 20%–25% when other depressive disorders are also included. Like MDD patients in general, patients with cancer are thought to be underdiagnosed and undertreated. Untreated depression in cancer patients may lead to having distressed symptoms and signs, decreased quality of life, higher suicide risk, greater psychological burden on the family, longer hospital stays, poorer anticancer treatment compliance, as well as even increased risk for mortality. Methods: In this review, the authors reviewed published articles on the use of antidepressant use for patients with cancer, to familiarize the readers with the use of antidepressants. Results: Antidepressants have been found to be more effective than placebo in relieving depressive symptoms in patients with cancer, and the efficacy is positively associated with length of treatment. Although the rate of antidepressant prescription is increasing, still about 75% of cancer patients with depression have not yet received antidepressant treatment. Besides the use in treating mood and anxiety symptoms, antidepressants have also been found to have versatile rôles as palliative treatment for cancer-related symptoms – pain, hot flushes, nausea, anorexia/cachexia, and fatigue. Furthermore, antidepressants have been studied for their anticancer potentials. They can inhibit tumor growth through either indirectly regulating immunity by enhancing cytotoxic activity and modulating cytokine production, or directly initiating cancer cell death and arresting cancer cell proliferation. We also found important drug-drug interaction between antidepressants and tamoxifen. Conclusion: Besides treating depressive and anxiety disorders, antidepressants are effective in treating cancer-related symptoms (pain, hot flushes, nausea, anorexia/cachexia, and fatigue). Cancer patients are eager to receive more effective treatment against their cancer as well as comorbid depression, and physicians should be more aggressive in providing every beneficial regimen – including an antidepressant.

Key words: Anorexia/cachexia, fatigue, nausea, pain
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Introduction

In a cross-country meta-analysis [1], the prevalence of major depressive disorder (MDD) by DSM criteria among cancer patients is about 14%–15% in oncological, hematological and palliative care settings, and it is risen up to 20%–25% when other depressive disorders – such as dysthymic and minor depressive disorders – are also included. A Scottish study [2] revealed that the prevalence of MDD is highest in patients with lung cancer (13.1%), followed by those with gynecological cancer (10.9%), breast cancer (9.3%), colorectal cancer (7.0%), and genitourinary cancer (5.6%).

Depression is often unrecognized partly because that clinicians tend to presume all cancer patients being “understandably depressed [3],” and that depressive symptoms defined in DSM-5 such as appetite and weight changes, fatigue, and psychomotor retardation are indistinguishable from cancer symptoms. However, Brenne et al., found that many other symptoms such as despair, anxiety, and social withdrawal are common in depressed patients with incurable cancer [4]. Chochinov et al. also suggested that simply asking a question “Are you depressed most of the time?” is proven to be a good simple tool to screen for depression in the patients with advanced cancer, showing excellent sensitivity and specificity [5].

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Depressive symptoms are emerged markedly after diagnosis of cancer, which typically reaches the highest prevalence in the first 6 months, and become lesser in severity over the time after adjustment to the shock of being diagnosed with cancer and the side effects of anticancer treatments [6].

In cancer patients, depression may lead to a decreased quality of life, higher suicide risk, greater psychological burden on the family, longer hospital stays, and poorer anticancer treatment compliance [7]. The result of a meta-analysis shows that depression, defined categorically or dimensionally, is associated with increased risk for mortality in cancer patients after controlling for confounding medical variables [8].

Antidepressants for Depression in Cancer Patients

A meta-analysis of 19 studies [9] shows that antidepressants – particularly selective serotonin-reuptake inhibitors (SSRIs) and mianserin – are more effective than placebo in relieving depressive symptoms in patients with cancer, and the efficacy is positively associated with length of treatment. While SSRIs and tricyclic antidepressants (TCAs) are not different from placebo in overall acceptability, the “other antidepressant” group – including bupropion, venlafaxine, and mianserin – has less dropout rate than placebo does [10].

In 2016, Sanjida et al. reviewed 38 articles and found that the prevalence of prescribing antidepressants to cancer patients is 15.6% [9]. The prescription is remarkably less common in studies from Asia (7.4%), but more common in female (22.6%) or breast cancer patients (22.6%). SSRIs are the most frequently prescribed antidepressants in that review [9].

In the United States of America, the average rate of antidepressant use among cancer patients is 18.3%, compared with 12.3% among adults without a cancer history in 1999–2012, and the prevalence of use among cancer patients was increased nearly doubled, from 10.6% in 1999–2000 to 20.8% in 2011–2012 [11]. Over the same period, a smaller increase of 7.2% has been observed among adults without a cancer history [11].

In a study to analyze the use of antidepressants in depressive patients with cancer (patient group) and without cancer (control group) [12], German investigators found that after a 1-year follow-up, less patients receive antidepressants than controls (66.5% vs. 72.8%) [12]. TCAs were given less frequently to patients than to controls (31.2% vs. 38.2%); by contrast, 7.0% of patients with cancer and 4.2% of controls receive benzodiazepines [12]. However, an Australian study showed that 17.2% of cancer patients receive antidepressants and that they are 42% more likely to get antidepressant therapy than noncancer patients. Cancer patients with the comorbid disease, receiving opioids, corticosteroids, or benzodiazepines, and those death is approaching, are more likely to be treated with an antidepressant [13].

Antidepressant for Cancer-related Symptoms

Antidepressant has been lauded for its versatile use clinically [14,15], including some distressing cancer-related symptom [10]. The symptoms listed below are some frequently seen clinical symptoms in patients with cancer which is treatable with antidepressants.

Pain

Cancer-related pain is frequent and debilitating and is reported by more than 70% of cancer patients [16]. Studies showed that around two-thirds to three quarters of pains are related to tumor itself, 10%–20% to cancer treatments, and about 10% to comorbid diseases [17]. ICD-11 has been released by the World Health Organization in 2018 (www.who.int/browsable11-m/en), listing cancer-related pain as a separate entity which includes chronic cancer pain (code: MG30.10) and chronic post-cancer treatment pain (code: MG30.11). Chronic cancer pain is a chronic pain caused by the primary cancer or metastases. However, chronic post-cancer treatment pain is caused by any treatment given to treat the primary tumor or metastases, including chemotherapy, radiotherapy, surgery, and hormone therapy.

Pain can be classified as neuropathic or nociceptive. Neuropathic pain is caused by direct injury to nerves or nerve roots, which is due to tumor infiltration or treatment such as chemotherapy and radiation therapy. Nociceptive pain is due to tissue damage with activating nociceptors secondary to tumor invasion into bone, joints, or connective tissues, or is associated with invasive procedures including lumbar puncture, biopsy and surgical intervention [18]. In a review of 19 studies comprising 11,063 cancer patients [19], Bennett et al. found that 6,569 (59.4%) have nociceptive pain, 2,102 (19%) neuropathic pain, 2,227 (20.1%) mixed-mechanism pain, and 165 (1.5%) those are classified as having unknown or other causes.

Besides nonopioids (acetaminophen and non-steroid anti-inflammatory drugs) and opioids as suggested by the WHO’s three-step analgesic ladder for treating cancer pain (www.who.int/cancer/palliative/painladder/en/), adjuvant analgesics, including antidepressants and anticonvulsants which have analgesic properties, to reduce opiate doses and their adverse effects, and can be used at any step of the ladder [20]. In a randomized double-blind crossover trial in 231 patients with chemotherapy-induced neuropathy [21], Smith et al., found that 60 mg/day of duloxetine over a period of 5 weeks is effective in reducing neuropathic pain. Another randomized controlled trial in 48 patients [22] also showed that short-term treatment with venlafaxine around oxaliplatin treatment can reduce the risk of chemotherapy-induced neuropathic pain. Furthermore, Nishihara et al. [23] found that low-dose imipramine (5 mg Q12H) and mirtazapine (7.5 mg BID) combined with a pregabalin 25 mg Q8H are more effective in treating pain associated with bone metastases than pregabalin 50 mg Q8H alone.

Hot flushes

Patients with breast cancer or prostate cancer are likely to have hot flushes during or after treatment. In women, treatments such as chemotherapy, hormone therapy, or ovariectomy can cause premature menopause and develop hot flushes. In men, castration and treatment with certain hormones can also cause this symptom [24]. Although hormone replacement therapy has been a mainstay of treatment for hot flushes in healthy
menopausal women, it is contraindicated for patients with breast and prostate cancer due to an increased risk of cancer recurrence [24].

Hot flushes can cause chills, night sweats, anxiety, and insomnia, hence have negative impact on patients’ quality of life [25]. SSRIs and SSRIs are found to be effective in managing hot flushes, and venlafaxine (an serotonin and norepinephrine reuptake inhibitors [SNRI]) and paroxetine (an SSRI) have been studied more extensively and are more consistent in effectively reducing the frequency and severity of hot flushes in cancer patients [26]. Studies also show that duloxetine and mirtazapine are effective in improving hot flushes in breast cancer patients [27, 28].

### Nausea

Nausea and vomiting are common symptoms in cancer patients. While the most common cause is the administration of chemotherapy, many complications of advanced cancer such as gastroparesis, bowel and outlet obstructions, and brain tumors may lead to nausea or vomiting as well [29].

SSRI- and SNRI-induced side effect of nausea, especially during the medication initiation, can cause patients’ nonadherence, particularly if given at close range with chemotherapies. SSRI and SNRI treatments should start 10–15 days before chemotherapy to avoid the overlapping and potentiation of such side effects [7].

Mirtazapine itself blocks 5-HT1 receptor and thus is linked to an anti-nausea effect [14]. Two case reports are identified, to specifically report mirtazapine use in treating nausea in cancer patients [26].

### Anorexia/cachexia

Anorexia/cachexia is prevalent in cancer patients, which is characterized by anorexia, decreased food intake, and irreversible skeletal muscle mass loss. It is possibly due to excessive systemic inflammation and hyper-catabolism and is worsened by anticancer therapy [30]. Cachexia may account for up to 20% of cancer deaths [31].

The relevant anti-histaminergic activity and the blockage of 5-HT2c receptor of mirtazapine can help increase food intake, results in having considerable weight gain [14], improving cancer cachexia in cancer patients. An open-label trial of mirtazapine for 8 weeks in nondepressed patients with cancer-related cachexia/anorexia showed that mirtazapine helps improve appetite and health-related quality of life, although the high attrition rate due to poor clinical condition, death, or study contamination (start of highly emetogenic chemotherapies). SSRI and SNRI treatments should start 10–15 days before chemotherapy to avoid the overlapping and potentiation of such side effects [7].

### Fatigue

Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [33]. Cancer-related fatigue is found in around 50%–90% of the cancer patients [34]. Bupropion has a dual effect on norepinephrine (NE) and dopamine neurotransmitter systems, and thus shares actions with psychostimulants [14]. A 4-week open-label study of the effects of bupropion sustained release on 21 cancer patients with and without depression showed that improvement has been found for symptoms of fatigue and depression. When dividing the patients into two groups, – depressed and non-depressed based on a cutoff score of 17 on the Hamilton Depression Rating Scale – the investigator found that both groups show improvement in fatigue and depressive symptoms, but only non-depressed group shows improved quality of life [35].

### Actions of Mechanism of Antidepressants for Treating Cancer-related Symptoms

The therapeutic rationale for choosing antidepressants is basically based on their clinical classification of transmissions of three monoamines (serotonin, NE, and dopamine) in the brain [14, 15, 36]. Dealing with the side effects of antidepressant is also based on the same concept of those three monoamines.

As shown in Table 1, pain – even all kinds of pain – can be improved with the SNRIs and mirtazapine [14, 15]. Although not shown in clinical review in cancer patient here, monoamine oxidase inhibitor (MAOI) (such as moclobemide) is also expected to improve pain because the use of an MAOI can improve 5-HT and NE transmission too [15, 36]. Anecdotally, SNRIs (venlafaxine or duloxetine) in continuous daily use can improve periodic severely abdominal cramping in cancer patients after gastrointestinal operations.

The neuronal fibers of transmitting 5-HT and NE from Raphe nucleus and locus coeruleus, respectively, to regulate mood and anxiety symptoms ascendingly and to improve pain symptom descendingly [14]. The patients with depressive/anxiety disorder and pain have low levels of brain-derived neurotrophic factors [14, 15]. The use of SNRIs, mirtazapine, and MAOIs can improve the brain level of BDNF, resulting in improving the pain in cancer patients with pain. Due to unbearable and

| Table 1. Common cancer-related symptoms and suggested antidepressants for treatment |
|----------------------------------------|-------------------------------|
| Cancer-related symptoms                | Suggested antidepressants     |
| Chemotherapy-induced neuropathic pain  | SNRIs (duloxetine, venlafaxine)|
|                                       | [21, 22]                      |
| Bone metastases-associated nociceptive pain | TCA (imipramine) or mirtazapine combined with pregabalin [23] |
| Hot flashes                            | SSRIs, SNRIs, mirtazapine [26-28] |
| Nausea                                 | Mirtazapine [14, 26]          |
| Anorexia/cachexia                      | Mirtazapine [14, 32]          |
| Fatigue                                | Bupropion [14, 35]            |

The numbers in brackets are references cited in this review. They are listed as reference entries in the references section. SNRIs, serotonin and norepinephrine reuptake inhibitors (including venlafaxine, milnacipran, duloxetine, desmethylvenlafaxine, levomilnacipran); TCA, tricyclic antidepressants (including imipramine, desipramine, amitriptyline, nortriptyline, etc.); SSRIs, selective serotonin reuptake inhibitors (including fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram)
dangerous side effects (such as dry mouth and cardiotoxicity), TCAs are not drugs of choice in modern psychopharmacology. Usually, SNRIs can be used substituting TCAs to give their comparable therapeutic benefit without those unwanted (strong anticholinergic and antihistaminergic) side effects [14].

5-HT and NE also play a decisive role in stabilizing the thermoneutral zone. As sex hormone levels decline, NE levels rise, causing an elevation in core body temperature. Furthermore, diminished sex hormone levels are also associated with low 5-HT levels, leading to an upregulation of 5-HT receptors in the hypothalamus and reset of the natural thermostat [37]. While many clinical trials have demonstrated the effectiveness of SSRIs and SNRIs in treating hot flushes, the authors would like to recommend to use a dual action antidepressant, i.e., an SNRI instead of an SSRI for a broader range of benefits. The uses of mirtazapine to mitigate anorexia/cachexia and nausea are based on mirtazapine’s own direct pharmacological blockade of 5-HT2c and 5-HT3 receptors, respectively.

Not shown in the clinic review (Table 1), a preliminary study suggested that agomelatine can be a novel treatment of chronic fatigue syndrome [38]. Agomelatine, sharing similar pharmacological function with bupropion through improving both DA and NE transmissions [36], is anticipated to be used in improving cancer-related fatigue as well. However, newer serotonergic antidepressants (such as vilazodone and vortioxetine) are not expected to have more additional benefits besides those from SSRIs in patients with cancer besides their better tolerability.

Immunomodulatory Effects of Antidepressant Drugs

Animal studies show that fluoxetine and mirtazapine administration increase CD8+ cytotoxic cells [39, 40]. Human studies also reveal that SSRIs – including fluvoxamine, escitalopram, and fluoxetine – give cytotoxic effects through increasing natural killer cells counts or activity [41-43]. Besides their cytotoxic effect, growing evidence indicates that antidepressants modulate the cytokine production [44]. For example, studies show that antidepressants with different mechanisms, such as TCAs (imipramine), SSRIs (fluoxetine), and SNRI (venlafaxine) consistently reduce the IFN-γ/IL-10 ratio [45].

In addition to the direct effect mediated through lymphocytes, Hernández et al. [46] also found that after a 52-week fluoxetine use, cortisol levels are found to be decreased by 30% compared to baseline. Antidepressants also down-regulate glucocorticoid receptor sensitivity [47], restore negative feedback by cortisol on the hypothalamic-pituitary-adrenal (HPA) axis [14, 48], and normalize HPA hyperactivity.

In 1863, German physician Virchow first made a connection between inflammation and cancer [49]. Recent work confirmed that immunity protects against cancer development and shape the character of emerging tumors through the process of immunoediting [50]. The antidepressant drugs can regulate the immune system and hence modulate tumor progression. For example, Fang et al. found that mirtazapine-treated mice have higher IL-12 and interferon-γ levels, more infiltrating CD4+/CD8+ T cells, less tumor necrosis factor-α, as well as produce tumor growth inhibition, compared with those never received mirtazapine [40].

Anticancer Potentials of Antidepressant Drugs

Some earlier clinical studies suggested that use of antidepressants – including SSRIs and TCAs – can increase the risk of breast cancer and ovarian cancer [51, 52]. However, later epidemiological studies – including those using Taiwan’s National Health Insurance Research Database – show that antidepressant prescription is not associated with risk of cancers of breast, ovary, and colorectum [53-55].

Contrariwise, increasing studies show that antidepressants may have anticancer effects. Beside their immunomodulatory effect as the aforementioned, antidepressants are found to eliminate cancer cells through modulating oxidative stress, suppressing angiogenesis, inhibiting tumor proliferation, as well as inducing apoptosis and autophagy. Details of action of the mechanism are discussed as followed:

Oxidative stress modulation

Overproduction of reactive oxygen species (ROS) has been detected in almost all cancers and is involved with their initiation, promotion, and progression of the cancer cells. Meanwhile, cancer cells also express increased antioxidant activity to detoxify from ROS, suggesting that cancer cells function under an exquisite balance of ROS levels [56]. Chemotherapy can increase intracellular ROS disproportionally, and induce cancer cell cycle arrest and apoptosis [56].

Imipramine, clomipramine, and citalopram can also increase intracellular ROS, cause the loss of mitochondrial membrane potential, activate caspase, and finally lead to the apoptosis of human myeloid leukemia cells [57, 58]. Amitriptyline has been found to increase ROS and to irreversibly damage mitochondria, and to reduce antioxidant activity, exerting anticancer potentials for lung, cervical and liver cancers [59]. Nortriptyline has been reported to increase the ROS production and induce mitochondria-mediated and death receptor-mediated apoptosis in human bladder cancer cells [60]. The cytotoxic effects of citalopram on liver cancer cells are also associated with an increased ROS formation [61].

Contrariwise, some reports also exist to show that fluoxetine acts as antioxidant, to decrease the melanoma-induced oxidative changes in mice spleen [62], and to lower the activity of superoxide dismutase levels in the brain of hepatoma-bearing mice [63].

Angiogenesis

The new growth of the vascular network, so-called angiogenesis, is important since an adequate supply of oxygen and nutrients is necessary for the proliferation and metastatic spread of cancer cells. Many proteins have been identified as angiogenic activators, and among them, vascular endothelial growth factor (VEGF) is receiving more attention [64]. Kannen et al. have found fluoxetine-induced reduction of VEGF expression and the antiproliferative potential of fluoxetine on colon cancer cells in vitro [65]. Contrariwise, Kubera et al. [66] have found the promotestatic effect of desipramine in young melanoma-bearing mice, which is connected with an
increased VEGF and metalloproteinase-9 (MMP-9) plasma levels. MMPs degrade basement membrane and extracellular matrix components, increasing the migration, invasion, and metastasis of tumor cells [66].

**Cell cycle arrest**

Deregulation of the cell cycle and uncontrolled proliferation are hallmarks of the cancer cells. The cell cycle is controlled by regulating cyclin-dependent kinases (CDKs) through their activator cyclins and CDK inhibitors (also known as CKIs) [67]. The p53 protein can also arrest the cell cycle at checkpoints and initiate apoptosis, hence plays an important anti-cancer rôle [68].

Stepulak et al. [69] found that fluoxetine can slow down the cell cycle progression and inhibition of proliferation of lung and colon cancer cells *in vitro*, which are associated with the decreased expression of cyclin A and cyclin D1, as well as the increased expression of p21 (CKI-1) and p53 genes. Fluoxetine also decreases c-fos and c-jun expression, which are transcriptional activators to regulate the expression of genes during cell proliferation [69].

Kinjo et al. also found that desipramine decreases the expression of the proliferating cell nuclear antigen gene, causing an increase in the expression of CKI p21 and p27 genes, and induces cell cycle arrest of mice skin squamous carcinoma cells [70].

**Apoptosis and autophagy**

Apoptosis and autophagy are two pivotal mechanisms in mediating cell survival and death. Apoptosis — or programmed cell death — is the result of a cascade of caspase activation which is initiated by extrinsic (death receptor-mediated) or intrinsic (mitochondrial-mediated) stimuli [71]. The apoptotic signaling pathway is impaired or perverted during the formation of cancer, and restoring apoptosis as a therapeutic strategy to cancer treatment has been intensively studied [72]. On the other hand, autophagy maintains cellular homeostasis through degrading and recycling damaged intracellular proteins and organelles in lysosomes and provides substrates for energy generation and biosynthesis in stress. As a result, autophagy is regarded as a double-edged sword that in some cases can induce cancer cell death, and in others provides cancer cells nutrient and promotes their survival [72].

Levkovitz et al. found that paroxetine, fluoxetine, and clomipramine cause apoptosis in glioma and neuroblastoma cell lines, which is preceded through rapid increase in activated c-jun levels, cytochrome c release from mitochondria, and increased caspase-3-like activity [73]. A study also showed that fluoxetine induces apoptosis in neuroblastoma through mitogen-activated protein kinase pathways and histone hyperacetylation [74].

Studies showed that fluoxetine induces autophagy in the chemotherapy resistant Burkitt’s lymphoma and triple negative breast cancer, resulting in having a novel therapeutic implications in cancer therapy [75, 76]. Contrariwise, autophagy inhibition may also be beneficial for the therapy of some advanced tumors [77].

**Drug-drug Interaction in Cancer Patients Using Antidepressants**

Most antidepressants are metabolized through the cytochrome P450 (CYP) enzyme system, and many drug interactions are a result of induction or inhibition of CYP enzymes. Tamoxifen, a hormone therapy drug for estrogen receptor-positive breast cancer, is mainly metabolized through the CYP2D6 to endoxifen, which is 30-100 times stronger than tamoxifen and is responsible for most of the clinical effects [78]. Antidepressants that inhibit CYP2D6 enzymes can hinder tamoxifen’s antitumor effect and increase risk for cancer recurrence, adversely affecting well-being and survival. Accumulating data have shown that fluoxetine, bupropion, and particularly paroxetine, are strong inhibitors of CYP2D6, and should, therefore, be better avoided in patients treated with tamoxifen, especially those with poor metabolizer phenotype of CYP2D6 [79].

One population-based cohort study showed that paroxetine use during tamoxifen treatment is associated with an increased risk of death from breast cancer [80]. However, Haque et al. examined nearly 16,900 early stage breast cancer survivors who took tamoxifen for an average of 3 years [81]. Among them, about a half also took antidepressants. During the 14-year follow-up, more than 17% of the survivors developed subsequent breast cancer. Recurrence rates are similar in those who took paroxetine and those who did not, and there is no such association for other antidepressants either [81].

Due to the paradoxical finding on some antidepressants use in tamoxifen-treated patients, clinicians must carefully weigh the benefits against risks of concurrent use of tamoxifen and antidepressants with potent CYP2D6 inhibition profile. Pragmatism suggests preferential avoidance of antidepressants known to inhibit CYP2D6, and those imparting less inhibition, such as sertraline, citalopram, and escitalopram are reasonable alternatives [82].

Analgesic drugs such as tramadol, codeine, hydrocodone, oxycodone, and fentanyl, as well as antiemetics of 5-HT3 antagonists, such as ondansetron, granisetron, and metoclopramide, are often used in cancer patients as palliative treatment. But they may act synergistically with serotonergic antidepressants and increase the risk of serotonin syndrome [79]. Among those medications, tramadol is metabolized by CYP2D6 to the active metabolite, hence CYP2D6-inhibiting antidepressants can decrease the analgesic activity of tramadol [83].

**Conclusion**

The use of antidepressants in cancer patients is indicated when depression interferes with the patient’s quality of life or with adherence to anti-cancer treatment. Moreover, antidepressants have been shown to be effective in treating other distressing cancer-related symptoms, such as pain, hot flushes, nausea, cachexia, and fatigue.

Although the research showed the rate of antidepressant prescription is increasing, depression is still overlooked in most of the cancer patients, hence those who might benefit from antidepressants are often left untreated. Walker et al. found that among 1,538 cancer patients with MDD, about 370 (24%) are taking antidepressants [2]. Park et al. [84] designed a placebo-controlled antidepressant clinical trial in oncology patients, yet no one was enrolled for the trial. One of the recruitment difficulties is that patients were reluctant to be enrolled in any placebo-controlled studies [84].
We suggest that cancer patients are keen to receive more effective treatment for their cancer as well as comorbid depression and that physicians should be more aggressive in providing every beneficial regimen – including an antidepressant. After reading this review, we hope that you will think of the use of an antidepressant when you get a chance to see a cancer patient – regardless in consultation, outpatient, or inpatient psychiatric services.

Acknowledgment

Some off-label indications are mentioned in this review. The readers are advised to read the package insert carefully before prescribing antidepressants to the patients.

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Conflicts of Interest

There are no conflicts of interest.

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