Treatment of depressive symptoms in patients with cancer

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ABSTRACT

Depression is the most common psychological condition in patients with cancer. These patients often have worse outcomes, such as decreased adherence to treatment and increased suicide rates. Since depression is common and often under recognized in this patient population, guidelines recommend screening every patient with cancer for depression. Both psychotherapy and pharmacotherapy are shown to be effective to treat depression in patients with cancer. Psychotherapy, specifically cognitive behavioral therapy, is preferred in patients with more mild depressive symptoms, while pharmacotherapy is used for more severe depression. Dignity therapy and supportive-expressive therapy are also recommended for patients near the end of life. Pharmacotherapeutic options for treatment include antidepressants and psychostimulants. Guidelines recommend SSRIs, SNRIs, or mirtazapine as first line treatment, with TCAs often avoided due to side effects. Psychostimulants, such as modafinil and methylphenidate, can be used as well, and are especially effective for patients near the end of life. SSRIs may also be useful to prevent the development of depression in patients taking drugs known to cause depression, such as interferon alfa. Treatment of depression in patients with cancer should be based on patient specific symptoms and situation. This article will review both non-pharmacologic and pharmacologic treatment options in patients with cancer and comorbid depression.

KEY WORDS

Cancer, depression, treatment, pharmacotherapy, psychotherapy

PSYCHOTHERAPY

In patients with a diagnosis of cancer, the most common psychological condition is depression[1]. Depression is three times more common in patients with cancer than in the general population[1]. Depressive symptoms in these patients can range from feelings of sadness to a clinical diagnosis of major depression. Major depression is present in 16% of patients with cancer, with minor depression and dysthymia present in about 22%. Rates of depression are highest in patients closest to the end of life and those with certain types of cancer, including pancreatic, gastric, lung, and oropharyngeal[1].

Patients with cancer and depression often have worse outcomes than those without depression. Patients with cancer who also exhibit depression are three times as likely to be nonadherent with their medication, leading to possible treatment failures or cancer recurrences[2]. These patients are also twice as likely to complete suicide compared to the general population. Suicide risk factors include older patients, males, and certain types of cancer, including head and neck cancers and multiple myeloma2. Due to the overlap of symptoms, such as fatigue, insomnia, and anorexia, depression is also under diagnosed in patients with cancer1. The National Comprehensive Cancer Network (NCCN) provides guidelines for Distress Management, which encompasses any psychosocial problems found in patients with cancer. These guidelines recommend that every patient be screened during their initial visit to the oncologist. NCCN has developed a screening tool, "Distress Thermometer," which asks patients to rank their stress during the past week on a scale of 0-10. A score of 4 or higher indicates that a patient should be referred to mental health services2.

The treatment of depression in this patient population involves both psychotherapy and pharmacotherapy. While pharmacotherapy is recommended more for severe depression, psychotherapy is recommended for depression of all severity levels[1].

Cognitive behavioral therapy is the most commonly recommended psychotherapy for these patients and has the most evidence from clinical trials in patients with major depression. Most other therapies only have evidence from clinical trials in patients with subclinical depression. It has been shown in clinical trials to reduce depression and anxiety, as well as pain and fatigue related to cancer[2]. Supportive psychotherapy is also recommended in the NCCN guidelines. One specific type of supportive therapy, dignity therapy, has been shown to improve depressive symptoms in clinical trials[2]. Dignity therapy is an individualized type of psychotherapy that gives patients the opportunity to discuss their preferences and legacy they want passed along after death. Patients receive an edited transcript of the session to share with friends and family[3]. Dignity therapy was found to be effective in patients with a life expectancy of less than 6 months[1]. One review recommends specific types of psychotherapy based on the patient's stage of disease[1]. For patients recently diagnosed with cancer, psychoeducation, CBT, relaxation strategies, and problem-solving approaches are recommended. For those with more advanced cancer, the recommended psychotherapy is supportive-expressive therapy that focuses on processing fear associated with death[1]. Family and couples therapy is recommended by the NCCN guidelines to lessen distress. Studies have shown that family and couples therapy is associated with less distress and more relationship satisfaction, as well as reducing the effects of grief in families[2].

PHARMACOTHERAPY

Several clinical trials have examined the use of antidepressants in the treatment of depression in patients with cancer. There is not one particular class of antidepressant that has shown more benefit than another. Choice of antidepressant should be based on the efficacy, side effect profile, potential drug-drug interactions, and the individual needs of the patient. Selective serotonin reuptake inhibitors are often used as first line therapy, while tricyclic antidepressants are often avoided due to high incidence of side effects and potential for death in the event of an overdose[4,5]. Antidepressants with trials exhibiting positive results in patients with cancer include paroxetine, fluoxetine, citalopram, escitalopram, sertraline, duloxetine, mirtazapine, and bupropion. The antidepressant with the most Level I evidence is mianserin, an analogue of mirtazapine which is not approved for use in the United States. Other medications with evidence from clinical trials include alprazolam, methylphenidate, and modafanil[1].

One open-label study assessed the efficacy of sertraline for all types of depression in patients with cancer undergoing chemotherapy. Twenty-seven patients took sertraline for 12 weeks, starting at a dose of 25mg, with a possibility to titrate up to 100mg. The primary outcome was change in the Montgomery Asberg Depression Rating Scale (MADRS), with 15 patients showing >50% improvement at endpoint. The mean MADRS score at baseline was 28.4, which dropped to 13.26 at 12 weeks. There was also a significant reduction in fatigue, reduced appetite, anhedonia, and suicidal thoughts from baseline to endpoint[6].

Another study looked at the use of escitalopram in patients with cancer in palliative care. Eighteen patients who met DSM-IV criteria for depressive disorder were treated with escitalopram 10mg for 2 weeks. Patients were evaluated using Hospital Anxiety and Depression Scale (HADS) and Mental Adjustment to Cancer Scale (Mini-MAC). At endpoint, there was a significant reduction in anxiety, as measured by HADS, and in hopelessness-helplessness, as measured by Mini-MAC[7].

A double-blind, randomized controlled trial examined the use of fluoxetine in patients with breast cancer. Patients determined to have depressive symptoms, as identified by a two-item screening survey were given either fluoxetine 20mg or placebo for 6 months. Patients with clinical depression were excluded. Depression was assessed using the Brief Zung Self-Rating Depression Scale (BZSDS). Almost 80% of patients taking fluoxetine had a significant reduction in depressive symptoms at endpoint, which was significantly more than placebo[8].

One open-label trial looked at mirtazapine for the treatment of major depression in oncology patients. Only patients with a DSM-IV diagnosis of major depression and a Hamilton Rating Scale for Depression score of >18 were included. Twenty-one patients took mirtazapine for 24 weeks, with a >50% reduction of HAM-D score defined as a positive response. All twenty-one patients achieved the primary end-point, with mean HAM-D scores falling from 21.4 at baseline to 2.6 after six months[9]. Mirtazapine can also have the added benefits of appetite stimulation and sedation at low doses. Insomnia and loss of appetite were two of the inclusion criteria for the trial. Several patients

experienced weight gain during the study and an improvement was also noted in insomnia, particularly for patients on the 15 mg/day dose[9].

Another open-label study examined bupropion SR for depression and fatigue in patients with cancer. Patients took bupropion for four weeks after titrating to 300 mg or the maximum tolerable dose. Nine of the patients were identified as depressed at baseline, based on HAM-D scores >17. Both depressed and non-depressed patients showed significant drop in HAM-D scores at the endpoint, with depressed patients showing a greater drop in HAM-D scores than non-depressed patients.[10]

A prospective, 12-week, case-control study compared the use of duloxetine in patients with depression and cancer versus patients with depression only. Patients included had either major depression or adjustment disorder with depressed mood, as defined by DSM-IV criteria. Patients received duloxetine 30mg initially, which was titrated to 60mg after one week, and could be increased to 120mg after one month based on response. The HADS, Clinical Global Impression-Severity (CGI-S), and MADRS were all used in the assessment. In patients with both cancer and depression, scores significantly improved on each of the depression scales at both four and twelve weeks. These results were not significantly different from those of the patients with depression only, suggesting a similar response to antidepressants between the two groups[11].

There have also been a number of trials that examine the prophylactic use of antidepressants in oncology patients to prevent the development of depression. One study looked at citalopram use in patients with head and neck cancer. Patients were randomized to either citalopram or placebo for 12 weeks. Patients received placebo or citalopram 20mg, titrated to 40mg after one week. The HAM-D was used in the assessment, with the cutoff for depression defined at ≥15. The CGI-S scale was obtained as a secondary endpoint. There was not a significant difference in the number of patients who developed depression according to the HAM-D at the end of the study, but there was a significant difference for the secondary endpoint. None of the patients in the citalopram group had a CGI-S rating worse than "mildly ill", but 30% of the placebo group did in comparison[12].

Another study looked at paroxetine for the prevention of depression in patients with malignant melanoma who were taking inferferon alfa, of which depression is a common side effect. Forty patients were randomized to either paroxetine or placebo, starting two weeks prior to interferon alfa therapy and continuing for 12 weeks after initiation of therapy. Patients took paroxetine 10mg initially and increased to 20mg after one week; the dose could be titrated up to 40mg based on response. The HAM-D was used for the assessment of depression. The development of depression was significantly lower in the paroxetine group compared to placebo, with only 2 of 18 patients developing depression on paroxetine versus 9 of 20 in the placebo group. The HAM-D scores of patients in the paroxetine group were not significantly different from baseline to endpoint, but were nearly 50% lower than the scores of those in the placebo group[13].

Psychostimulants have also been examined for the treatment of depression in patients with cancer. In one open-label study, methylphenidate was used in patients with advanced cancer identified as being depressed by a palliative care physician. Thirty patients received methylphenidate for seven days, with a starting dose of 5mg BID titrated up to 15mg BID based on response. Depression was resolved in all patients, with significant improvement noted in other symptoms as well, including fatigue, concentration, anorexia, and sedation[14].

A retrospective study examined the use of methylphenidate or dextroamphetamine in hospitalized cancer patients with depression. Out of a total of 59 patients, 44 were treated with dextroamphetamine and 15 were treated with methylphenidate. Patients' improvement on the stimulant was rated retrospectively based on chart review by a psychiatrist using the CGI-S. Most patients showed improvement in depression, with 71% of the dextroamphetamine patients and 80% of the methylphenidate patients showing marked or moderate levels of improvement[15].

Another study found improvement in depression with modafinil use. In this randomized, double-blinded, crossover study, thirty patients received either modafinil or placebo for four days and then crossed over to the alternative treatment for four more days. The Edmonton Symptom Assessment System was used to assess multiple symptoms present in patients with cancer, including depression. Depression improved significantly compared to placebo in patients taking modafinil[16].

GUIDELINES

Palliative care guidelines from British Columbia provide an algorithm for pharmacological treatment of depression in patients with advanced disease (see Table 1). Medication choice is based on life expectancy. Psychostimulants are recommended for patients with a life expectancy of less than one month, while antidepressants are recommended for patients with a life

expectancy of greater than three months. Psychostimulant choice is further stratified by age; modafinil is the drug of choice for those over the age of 65, with methylphenidate and dextroamphetamine also being options for those aged less than 65. For those being treated with an antidepressant, SSRIs, SSNRIs, and mirtazapine are first line treatments with TCAs as a second line[4].

Table 1. British Columbia Medical Services Commission Treatment Algorithm[4]

Life Expectancy	Treatment Recommendation
<1 month	Age >65 years: modafinil Age ≤65 years: methylphenidate or dextroamphetamine or modafinil
1-3 months	Psychostimulant + Antidepressant
>3 months	Antidepressant First line: SSRI or SSNRI or mirtazapine Second line: TCA

CONCLUSION

Since depression is often underdiagnosed in patients with cancer due to the overlap of symptoms, it is important for every patient to be screened for depression. Treatment guidelines recommend screening for depression using the Distress Thermometer. With decreased medication adherence and increased suicide rates, it is crucial that depression be identified to improve patient outcomes. Psychotherapy is useful for patients with depression of all severity levels, with cognitive-behavioral therapy being the treatment of choice. Pharmacotherapy is indicated for patients with more severe levels of depression, as these patients have been shown to benefit more from antidepressant therapy. First line treatments include SSRIs and SNRIs, with TCAs usually avoided due to side effects and fatality risk. Other antidepressants that have been shown to be effective in this patient population are mirtazapine, bupropion, and duloxetine. SSRIs may also be useful in preventing the development of depression, particularly in patients receiving medications with a high risk for causing depression, such as interferon alfa. Psychostimulants, such as methylphenidate and modafinil, are also useful for the treatment of depression, especially for patients near the end of life. These medications can improve other cancer-related symptoms as well, such as fatigue and concentration. Ultimately, treatment of depression in cancer patients is based on the severity of depression and duration of life remaining, and should be patient specific.

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