

Cancer-related depression and potential pharmacologic therapies

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Depression in stem-cell transplant and chemotherapy-treated oncology patients has received increased attention in psychooncology research during the past decade. Depression is believed to negatively impact quality of life, long-term psychological adjustment, and survival rates. With the occurrence of depression in oncology patients reaching 15%—2 to 3 times greater than in the general population—improved diagnostic methods are needed, as well as interventions that are both timely and effective (1).

Patients and health care providers may be reluctant to initiate therapy, as many of the symptoms can be explained as natural responses to the diagnosis and treatment of cancer. Physical depressive symptoms (e.g., sleep and appetite disturbances, psychomotor retardation, decreased energy) are common in oncology patients and act as confounders to such early diagnoses. Studies of hematopoietic stem cell transplant patients show that physical limitations peak around 90 days after transplant and improve about 1 year after transplant but do not significantly change throughout the 3- to 5-year full-recovery process. Physical recovery often occurs before emotional stability, yet complete recovery is a slow process that may worsen before improving. Further stem cell study results show that during a 5-year time period, 22% of patients report symptoms consistent with clinical depression, and an additional 31% could be classified as having mild depression (2).

There are currently no recommendations concerning the preferred pharmacologic class or dosage to be used in oncology patients. Appropriate strategies for intervention and treatment should include both pharmacological and psychological therapies, much like regimens used in patients with other significant medical problems (1). It is difficult to study the effects of psychopharmacologic agents in oncology patients since full results may be delayed by 6 to 8 weeks. Furthermore, due to inadequate studies representative of the oncology population, dosing of antidepressants must be highly individualized. Practice trends favor screening all oncology patients for depression and providing treatment to a wide spectrum, including patients with depressive disorders and those with clinically diagnosed depression (1).

Current pharmacological treatment options mimic therapies utilized in the primary care setting and include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors

(SSRIs), serotonin norepinephrine reuptake inhibitors, and psychostimulants. Most data are anecdotal from small cohort studies in patients with a variety of malignancies.

TRICYCLIC ANTIDEPRESSANTS

Historically, TCAs were among the first therapies used to treat cancer depression. A small trial conducted in 1978 showed improvement in the Hamilton Depression Rating Scale score for 39 oncology patients taking imipramine (3). Another study of 42 patients with cancer showed improvement in depressive symptoms prior to improvement in physical symptoms with trimipramine compared with placebo (4). Unfortunately, use of TCAs for depression has been abandoned due to numerous intolerable adverse effects including anticholinergic effects, cardiac conduction abnormalities, sedation, and weight gain.

Although there are high toxicities associated with overdose, low-dose TCAs are among the best of studied antidepressants for adjuvant analgesia. Unlike the gradual improvements in cognitive symptoms experienced from TCA use, rapid effects are seen when TCAs are employed for analgesia (5). Such research has led to increased attention for the use of amitriptyline to ameliorate chemotherapy-induced neuropathy. At low doses, amitriptyline has been shown to improve various neuropathic symptoms and may additionally improve quality of life (6).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Commonly requested and employed depression therapy includes SSRIs; however, these agents may have questionable benefit during the postchemotherapy time period since adequate responses are delayed up to 4 weeks. Potential adverse effects of SSRI therapy include nausea, headache, and sexual dysfunction in addition to the numerous cytochrome P450 drug interactions (7) (*Table*). Antidepressant medications must be carefully examined because agents differ greatly in adverse effect profiles. Potentially harmful drug interactions that occur with

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Table. Antidepressant agents and cytochrome P450 inhibition*

Agent	2C9/2C19	2D6
Clomipramine	No effect	↓/↑
Fluoxetine	↓/↑	↑↑↑
Sertraline	↓/↑	↑
Paroxetine	No effect	↑↑↑
Citalopram/escitalopram	No effect	↓/↑
Bupropion	No effect	↑↑↑
Venlafaxine	No effect	No effect
Duloxetine	No effect	↑↑
Mirtazapine	No effect	No effect
Methylphenidate	No effect	No effect
Dextroamphetamine	No effect	No effect

*From reference 18.

No effect indicates no inhibition; ↑, 1.25–2-fold increase in the plasma area under the curve (AUC) values or 20%–50% decrease in clearance; ↑↑, >2-fold increase in the plasma AUC values or 50%–80% decrease in clearance; ↑↑↑, >5-fold increase in the plasma AUC values or >80% decrease in clearance; ↓/↑, all other inhibition.

chemotherapy agents complicate SSRI use in the oncology population. Additional issues with therapy include age-related differences in drug metabolism, since children and adolescents metabolize SSRIs more rapidly than adults and therefore require vigilant dose titration (1).

In 1996, a double-blind, placebo-controlled trial of fluoxetine therapy for anxiety and depressive symptoms was conducted in 115 cancer patients. Results showed improvements in all assessments performed, yet the authors concluded that the 5-week trial may not provide adequate time for therapeutic response in patients with significant medical comorbidities (8). A subsequent study examined the safety and efficacy of fluoxetine and desipramine in 40 depressed women with advanced cancer. After the 6-week, double-blind, placebo-controlled trial, both treatments were shown to improve depression and anxiety symptoms, with statistical improvement seen among the various measurement scales used. Fluoxetine was shown to offer greater benefits regarding quality of life issues (e.g., improvement of pain and mood) (9).

MIRTAZAPINE

Mirtazapine is a tetracycline amine that antagonizes presynaptic alpha-2 adrenergic receptors to inhibit serotonin and norepinephrine release. Additional blockade occurs at serotonin 5-HT_{2A} and 5-HT₃ receptors, resulting in decreased gastrointestinal adverse effects. At low doses, mirtazapine also possesses antihistaminic properties that can improve nausea and insomnia. Mirtazapine may further be useful in the cancer-cachexia setting due to the side effects of increased appetite and weight gain. These drug effects are attractive to oncology patients, as they can potentially enhance quality of life and avoid both polypharmacy and multiple drug interactions.

In a 6-week study, mirtazapine was compared with imipramine and placebo for superiority in sleep improvement and the

decrease of anxiety and depression in oncology patients. After the study period, significant improvements and superiority were seen by the mirtazapine group for patient-perceived anxiety and depression. Effects of initial, middle, and late insomnia also improved statistically in the mirtazapine group. Study visits occurred every 2 weeks, with the most impressive results seen at the first and second visits (10). Further small studies showed benefits of mirtazapine at both the 15-mg and 30-mg daily doses against the mild symptoms of depression, loss of appetite, and decline in cognition function. Eating-related symptoms were the first to improve (11).

BUPROPION

Bupropion is a dopamine-reuptake inhibitor structurally unrelated to existing classes of antidepressants. Improvement of fatigue, functional status, and depression most closely resemble the dopaminergic and noradrenergic activities of psychostimulants. Potential drug interactions and contraindications (e.g., seizure disorder) should be carefully investigated prior to initiation. Adverse effects of use include increased anxiety, insomnia, and altered appetite and weight, with either loss or gain possible. Bupropion has been studied in open-label fashion to investigate overall effects on quality of life, depression, and fatigue. A 4-week, dose titration study of 21 mixed-site cancer patients resulted in significant improvement in depressive symptoms and physical quality of life. Similar effects were seen with fatigue in this small cohort of patients followed for a short period of time (12). A similar study was conducted in 15 patients with a variety of malignancies and histories of antidepressant use. Thirteen patients reported symptom improvement within 2 to 4 weeks with minimal adverse effects, validating the use of bupropion as an alternative therapy for depression (13).

PSYCHOSTIMULANTS

Low-dose psychostimulant agents are being introduced as off-label antidepressant therapy due to their potential for rapid clinical effects and alleviation of physical symptoms. Immediate drug benefits occur and are sustained over a 3- to 8-hour time period, providing considerable advantage to terminally ill patients (14). Such effects are marked by increased alertness, elevation of mood and self-esteem, improvement in cognitive function and physical performance, and a normalization of poor appetite (15). Caution should be used in patients with uncontrolled hypertension, cardiac abnormalities, or glaucoma.

A small study of methylphenidate 10 mg by mouth twice daily, titrated to a total of 80 mg daily or adequate response, was conducted for patients with cancer, depression, and contraindications to other acceptable therapies. Twenty-three of the 30 patients enrolled showed moderate to marked improvement in depressive symptoms within days of starting therapy. Only two patients withdrew due to intolerable side effects. In a similar study, 30 of 41 patients showed an improvement in depressive symptoms by day 7 of therapy with methylphenidate (16).

Added benefits of stimulants may also include the enhancement of narcotic analgesia when coadministered with opioids and reduction of opioid-induced sedation. Studies show that

patients treated with dextroamphetamine and morphine sulfate experience 50% to 100% more pain relief than those with placebo and morphine (17). The combination is used to decrease total daily narcotic use, thereby decreasing opioid-induced sedation.

CONCLUSION

Depressive symptoms naturally arise from the stress and anticipation of cancer diagnosis, treatment, and remission. This depression is a concern for patients, family members, and caregivers alike, as it can introduce significant morbidity and increased health care costs. The overall decrease in physical and mental functioning can be associated with decreased survival. Careful attention should be placed on identification and treatment strategies, including psychotherapy in combination with pharmacotherapy to prevent unnecessary roadblocks to recovery. This is of utmost importance since cancer-related depression is frequently underdiagnosed and undertreated. Published data only exist for small cohorts of patients that have a wide variety of malignancies. Larger, more disease-specific randomized trials are needed before strong recommendations can be made regarding patient-specific antidepressant therapies. Psychotherapy is always recommended alone or as an adjunct to pharmacologic regimens for cancer depression. Until these large-scale trials are conducted and have conclusive results, physicians should carefully consider all potential adverse effects, drug interactions, and patient-reported histories of antidepressant use prior to initiating pharmacologic therapy for depression. Choice of antidepressant therapy should be highly individualized and monitored frequently for efficacy and toxicity.

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