CME

The Use of Antidepressants in Cancer Treatment

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CME EDUCATIONAL OBJECTIVES

1. To understand how prescribing antidepressants in patients with cancer differs from prescribing in non-cancer-related major depressive disorder (MDD).
2. To become familiar with the types of patient-rated and physician-rated distress scales available for cancer patients.
3. To name various non-pharmacological interventions for MDD in cancer patients and to know when it is appropriate to incorporate them into treatment.

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Drs. Trinidad, Simopoulos, and Flosnik have disclosed no relevant financial relationships.

doi: 10.3928/00485713-20110829-06

A 52-year-old male suffered from recurrent acute lymphocytic leukemia and twice was admitted to the hospital for chemotherapy. Among the agents used during his hospitalizations was fludarabine phosphate, given intravenously at 60 mg daily; this agent potentially caused various neuropsychiatric symptoms.[1] He was concomitantly on furosemide, dexamethasone, amlodipine, insulin, amylase, ondansetron and oxycodone, as needed, for pain. The patient had no history of depression before his cancer diagnosis, although he had a medical history of chronic pancreatitis and diabetes mellitus type 2.

DIAGNOSIS

Major Depressive Disorder in Recurrent Acute Lymphocytic Leukemia

During the first hospitalization, he was referred to the psychiatric clinic. In bedside psychotherapy, the patient described terminal insomnia, feelings of hopelessness and helplessness, poor energy levels, diminished concentration, intermittent thoughts that life was not worth living, and vague somatic complaints.

Psychotherapy concluded after 10 twice-weekly sessions; the patient attained euthymia and was discharged. The psychotherapy was provided by a senior psychiatry resident who helped the patient express his feelings, understand the treatment protocol for cancer, and who acted as liaison for the primary and oncology teams and the patient to educate him on his condition.

Less than 6 months later, he was readmitted with recurrence of acute lymphocytic leukemia (ALL), this time requiring a prolonged hospital stay. He developed bilateral, moderate-to-severe shooting pain in his lower extremities. The patient also experienced daily low mood, irritability, lack of sleep, increasing hopelessness, and suicidal thinking. Thirty milligrams of duloxetine was added to treat his chemotherapy-associated neuropathic pain, and also to alleviate his depression.

The patient was prescribed 30 mg of the serotonin-norepinephrine reuptake inhibitor (SNRI) for treatment of his concurrent depressive symptoms and somatic complaints. While there is minimal evidence for drug-drug interaction between fludarabine and selective serotonin reuptake inhibitors (SSRI), duloxetine was selected as initial treatment because of its efficacy in treating depressive symptoms combined with somatic complaints in the cancer population.

After a few days, the pain improved and the patient's suicidal ideations subsided, but his depression remained. He did not attain baseline euthymia. He remained in the hospital for long and complicated chemotherapy cycles, followed by long-term outpatient psychotherapy to cope with the persistent stresses of his illness and feelings of demoralization despite taking the appropriate antidepressant.

DISCUSSION

In this presented case, it is both explicit and implicit that antidepressant prescribing will depend on a wide variety of factors: the nature of the cancer and its attendant treatment including the exact chemotherapeutic agents used, the premorbid condition of the patient (including such important factors as alcohol or substance abuse, family supports, and genetic loading), associated symptoms such as neuropathies, and the availability of a multidisciplinary staff to not only detect the emergence of depression, but also to advocate for its definitive treatment.

The protracted treatments and lengthy hospital stay following recurrence of the patient's ALL taxed his emotional and physical reserves, precipitating major depressive disorder (MDD). The antidepressant choice subsumed the consideration of the neuropathy. Although duloxetine is indicated for certain forms of neuropathy, this patient's neuropathy was multifactorial and duloxetine's efficacy for this particular type is unestablished;[1] however, this patient improved, which suggests that this antidepressant was chosen appropriately. Full remission from MDD, however, was difficult to achieve because of the protracted hospital stay and the attendant discomforts of chemotherapy.

ANTIDEPRESSANTS AND PAIN MANAGEMENT

The patient's competing medical issue, manifested primarily by unrelenting, intractable pain, warrants further consideration, as it highlights critical clinical factors that influence a consulting psychiatrist's care and decision-making. A psychiatrist must choose an antidepressant agent that will treat both the psychic and somatic manifestations of physical and mental illness. Patients with depressive symptoms may frequently experience and report painful somatic symptoms only, believing that mood symptoms are somehow secondary in importance, or are evidence of perceived weakness. Somatic symptoms in both depressed, non-medically ill and depressed medically ill patients include back pain, headaches, muscle tension, gastrointestinal disturbances, and fatigue.[2,3]

Kroenke et al reported finding a link between depression and somatic symptoms, and a correlation between the number of symptoms reported by a patient and the likelihood of a mood/anxiety disorder. As the number of physical symptoms increased, so did the likelihood of a patient having a psychiatric diagnosis. Additionally, painful physical symptoms were found to contribute to the development of a more severe depression, as demonstrated in the patient.[4]

The comorbidity of depressive and somatic symptoms is well-established. The patient was treated with duloxetine, an SNRI, as opposed to an SSRI, based on burgeoning evidence that depressive and pain symptoms share a common neurobiological pathway. Low levels of both serotonin and norepinephrine have been implicated in the development of depression, evidenced by the efficacy of antidepressant medications that function at a receptor level to increase the levels of these neurotransmitters. Such medications include: the SSRIs, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and SNRIs. Although the precise mechanisms remain to be elucidated, it has been suggested

that both serotonergic and noradrenergic projections from the brainstem are involved in spinal pathways that modulate painful physical symptoms. In the depressive state, these pathways are disrupted and an individual may experience increased perceptions of pain.[5] Although it is difficult to fully discern the etiology of the patient's somatic complaints, it is noteworthy that both his pain and depressive symptoms improved only after introduction of a dual-acting antidepressant.

An SNRI was elected as first-line treatment for the patient, despite the fact that, in general, all antidepressants are thought to have comparable efficacy. A review of the literature demonstrates that significantly greater remission (HAM-D $\leq$ 7) rates have been found with SNRIs versus SSRIs. In a pooled analysis of data from eight studies, patients prescribed venlafaxine were more likely to achieve remission compared with SSRI-treated patients (45% vs. 35%, $P < .001$).[6]

Further pooled analysis of six studies comparing duloxetine and an SSRI also demonstrated that dual-acting antidepressants may offer more clinical benefit than single-acting medications.[7] Moreover, in double blind, placebo-controlled trials of duloxetine in the treatment of major depression and painful physical symptoms associated with depression (back, shoulder pain, global pain), greater remission rates were found than with placebo.[8] It was theorized that such efficacy would maximize the chances of effectively treating the patient. Still, the patient did not achieve a full euthymic state, despite some measurable improvement.

DEMORALIZATION VERSUS DEPRESSION

This clinical reality belies a second point about the treatment of hospitalized patients with competing psychiatric issues: that such patients often also suffer from profound demoralization, a state for which no medication exists and psychotherapy is crucial. Demoralization is commonly confused with depression, as they share disturbances in energy, appetite, and sleep. However, it may be differentiated from major depression in that responsivity of mood is usually preserved: Removal of adversity restores a full capacity of enjoyment.[9] The patient in this case was chronically ill and never able to return to prior, premorbid functioning. He continued to struggle with existential postures of vulnerability, including confusion, isolation, despair, and helplessness;[8] he would have benefited from ongoing outpatient treatment on discharge from the hospital.

CANCER AND MDD

Antidepressant prescribing in cancer differs from prescribing in non-cancer MDD. The clinician will need to consider a greater number of potentially influential factors (Sidebar 1). A straightforward remission from depression, usually simple to measure and to determine in non-cancer cases of MDD, may be hard to come by or to measure in patients with cancer. Some forms of depression have symptoms that resemble cancer and/or its treatment, including: fatigue, appetite changes, and sleep disturbances. It is often helpful to deploy structured rating scales such as the Beck Depression Inventory and cancer specific rating scales of distress (Sidebar 2) to track the efficacies of each medication trial over time.[10-14]

Apart from psychotherapy, other helpful nonpharmacological measures include: physical activity; self-help and support groups; yoga and other systematic relaxation efforts.[8-12] These measures should be strongly considered if antidepressants are not an option, such as when a patient is not yet willing to take them or cannot afford them.

SIDEBAR 1.

Factors to Consider When Choosing Antidepressants in Cancer

1. Neurospsychiatric effects of the cancer.
2. Neuropsychiatric side effects of chemotherapy.
3. Antidepressant interaction with each of the other drugs.
4. Readiness of the patient to accept antidepressants.
5. Availability of both outpatient and inpatient psychiatric followup.
6. Comorbid medical conditions.
7. Affordability of the antidepressant.

Source: Trinidad AC, Simopoulos E, Flosnik D.

SIDEBAR 2.

Distress Rating Scales for Cancer Patients

Self-Rated Scales:

1. Distress thermometer (DT).
2. Zung Self-Rating Depression Scale.
3. Hospital Anxiety and Depression Scale (HADS).

Clinician-Rated Scales:

1. PO-Bado (Psycho-oncology) Scale.
2. Psychosocial Adjustment to Illness Scale (PAIS).

Source: Trinidad AC, Simopoulos E, Flosnik D.

CONCLUSION

Cancer often is accompanied by secondary complications such as major depression.[15,16] Even if there are no pre-existing histories of depression, genetic or constitutional vulnerabilities might be unmasked by cancer diagnosis and treatment.[17,18] In addition to comprehensive support and surveillance by a qualified multidisciplinary oncology team, antidepressants can be useful adjuncts in treating depressive symptoms.[19-23]

Prescribing antidepressants to patients with cancer depends on: the nature of the cancer; the exact chemotherapeutic agents utilized; the patient's premor-

bid conditions (including such important factors as alcohol or substance abuse, family supports, and genetic loading); the readiness of the patient to accept antidepressants; associated symptoms such as neuropathies; and the availability of a multidisciplinary staff to detect the emergence of depression and advocate for its definitive treatment.[24]

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