Oncology and psychiatry intersect

Depression, SSRIs, cancer and drug interactions

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ABSTRACT

Major depressive disorder (MDD) is a highly prevalent and critically disabling medical condition. Numerous factors have been associated with the onset of MDD, including both environmental and heritable components. Depression has been found to be common among cancer patients, who often face uncertain treatment courses. In the present case, a 51-year-old woman presents to her family physician with an ongoing episode of severe depression, characterized by low energy, insomnia and speech latency. In addition to a past medical history significant for MDD, this woman has a 1-year history of estrogen-receptor positive invasive ductal carcinoma (IDC). She previously underwent a unilateral mastectomy and reconstruction is pending. As she began adjuvant oral tamoxifen therapy, her ongoing selective serotonin reuptake inhibitor (SSRI) was changed from fluoxetine to escitalopram, owing to the propensity for drug interactions between certain SSRIs (including fluoxetine) and the cytochrome P450 (CYP) 2D6 enzyme that is responsible for metabolizing tamoxifen into its active metabolite. Over the course of her recent escitalopram treatment, this woman's depressive symptoms have returned. Following assessment, including the Patient Health Questionnaire (PHQ)-9, this woman is referred to adult outpatient psychiatry for management. This case illustrates some of the major features of MDD, and uniquely focuses on the balance required in managing a patient's depression and maintaining their cancer treatment program. A discussion of factors contributing to the onset of depression in cancer patients is included, with focus on the role of reconstructive surgeries for breast cancer patients.

CASE PRESENTATION

The following case has been created by the authors, and is not based on a real-life patient encounter.

Ms. Patmore is a 51-year-old premenopausal female who presents to her family physician's office with an ongoing episode of severe depression. She is accompanied by her daughter, who reports her mother's inability to sleep, a lack of appetite, low energy and speech latency.¹ Past medical history is significant for major depressive disorder (MDD) diagnosed five years ago and managed effectively in the past three years with the selective serotonin reuptake inhibitor (SSRI) fluoxetine (20 mg per day). Ms. Patmore's daughter reports their family's recent concerns that Ms. Patmore is becoming increasingly depressed, with similar characteristics as her initial depressive episodes five years previously.

Ms. Patmore has a recent (1 year) history of estrogen-receptor positive invasive ductal carcinoma (IDC; T1N1 disease) that was identified on routine mammogram. She underwent a unilateral mastectomy 10 months ago and surgical reconstruction is pending. Post-operatively, Ms. Patmore began adjuvant therapy with oral tamoxifen (20 mg per day) as her cancer was found to be estrogen receptor (ER) positive.² Her daughter reports that at that time, fluoxetine was replaced with the SSRI escitalopram (20 mg per day), owing to the propensity for drug interactions between certain SSRIs (including fluoxetine) and the cytochrome P450 (CYP) 2D6 enzyme, which metabolizes tamoxifen to its active metabolite, endoxifen.³ Over the past three months, Ms. Patmore's depressive symptoms have returned and worsened.

INITIAL INVESTIGATIONS

Ms. Patmore is presenting with characteristic signs of MDD (lack of appetite, depressed mood, insomnia, fatigue).¹ Her medical history suggests that her recent change in SSRI may have affected her, as well as the recent physical and psychological stresses related to her cancer diagnosis and mastectomy. On arrival, her vitals are within normal limits. An electrocardiogram (ECG) and bloodwork (including CBC, a comprehensive metabolic panel and thyroid stimulating hormone (TSH)), are ordered to investigate a mood disorder secondary to an underlying medical cause, such as hypothyroidism.⁴ Ms. Patmore's daughter denies any history of mania or bipolar disorder, as well as use of illicit drugs, alcohol, or cannabis consumption.^{4,5}

The Patient Health Questionnaire (PHQ)-2 is administered and found to be positive. The PHQ-9 is subsequently administered and is positive for severe depression (total score > 20).⁶ Owing to her history of MDD and use of SSRIs, Ms. Patmore is referred to adult outpatient general psychiatry for further assessment and treatment planning.

MDD & DEPRESSION IN CANCER

MDD is a highly prevalent and critically disabling medical condition worldwide.⁷ MDD is characterized by a depressed mood, a lack of interests, impaired concentration, fatigue, suicidal ideation and often disturbed sleep and/or eating patterns.¹ MDD affects twice as many women as men, causing considerable impairment.⁸ The disorder not only causes a reduction in health, similar to other chronic disease (e.g. arthritis, asthma, diabetes), but also substantially worsens health when it is co-morbid with these diseases.⁹ As such, health care providers should not overlook the presence of depression in patients who have chronic physical disorders.^{9,10} Numerous factors have been associated with the

development of MDD, including both environmental and heritable components.⁸ Presently, MDD is managed using pharmacological treatments and/or psychotherapy, both of which have demonstrated efficacy.¹¹ Second generation antidepressants such as SSRIs and selective serotonin norepinephrine reuptake inhibitors (SNRIs) are the most commonly used pharmacological agents.¹² Cognitive behavioral therapy (CBT) is the foremost form of psychotherapy and focuses on modifying maladaptive thinking patterns through structured, goal-oriented sessions.¹³

Depression is common among cancer patients, with prevalence rates as much as four times higher than in the general population.¹⁴ It has been suggested that co-morbid depression may be associated with worse prognoses, as well as increased mortality rates.¹⁵ Depressive symptoms typically develop during the first year after cancer diagnosis and are in large part thought to extend from the psychological distress faced by patients.¹⁶ Patients facing long-lasting, demanding and uncertain treatments experience shock and stress, providing an opportunity for psychological instability.¹⁷ Physical changes experienced by cancer patients, including chemotherapy-induced alopecia, have also been significantly associated with depression.¹⁸ The burden of emotional pain and distress patients and their families experience dealing with cancer has led to the creation of a new cancer care field called psychosocial oncology, or psycho-oncology.¹⁹ Psychosocial oncology programs focus on interventions to improve patients' experiences, by providing supports that address the social, psychological, emotional, spiritual and functional aspects of patients' lives.

For patients facing breast cancer specifically, the profound mutilating effects of surgery — even when completed with curative intent — can dramatically influence a patient's body image and psychological well-being.²⁰ Partial and complete mastectomy of diseased and contralateral breasts has become increasingly frequent, in part related to the increasing use of breast MRI (magnetic resonance imaging) for screening.²¹ The co-occurrence between mastectomy and depression in breast cancer survivors has been described.²² Breast reconstruction is therefore increasingly a solution for breast cancer patients who undergo ablative surgery in order to help restore patients' sense of self, as is access to psychosocial oncology services.

CYP2D6 INTERACTIONS WITH TAMOXIFEN

Owing to the prevalence of depression and MDD in cancer patients, efforts are increasingly being made to manage patients' depressive symptoms as they undergo their cancer treatment. Many considerations are taken into account with regard to the pharmacological management of depression for a given patient. In breast cancer, where many patients receive post-operative hormone therapy (estrogen receptor blockers or aromatase inhibitors) to reduce the risk of recurrence, consideration is required regarding which antidepressants are simultaneously prescribed.⁴ An example is in the case of the anti-estrogen drug tamoxifen. Tamoxifen is metabolized by CYP2D6, which converts tamoxifen into its active metabolite endoxifen.³ A subset of anti-depressant medications function as inhibitors of CYP2D6, including the SSRIs paroxetine and fluoxetine, as well as bupropion, a norepinephrine-dopamine

reuptake inhibitor.⁴ As such, the use of antidepressants targeting CYP2D6 should be reviewed in cancer patients receiving hormonal therapy with tamoxifen, given alternative antidepressants exist. The SSRIs citalopram and escitalopram, the SNRIs desvenlafaxine and venlafaxine, and the noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine are weak/non-CYP2D6 inhibitors and therefore safer treatment options unlikely to alter the efficacy of tamoxifen when co-prescribed.²³⁻²⁵ Of note, alternatives to tamoxifen (such as the aromatase inhibitors (AIs) anastrozole and exemestane) may be prescribed to postmenopausal patients, as these agents are not affected by anti-depressant medications.²⁶ However, AIs are not generally prescribed to premenopausal patients whose ovaries still produce estrogen. Instead, premenopausal patients with estrogen receptor expression are likely to receive tamoxifen, either alone or in combination with either chemical ovarian suppression (via luteinizing hormone-releasing hormone (LHRH) agonists, such as goserelin) or ablation.²⁶

CASE CONTINUATION

Ms. Patmore is evaluated by adult outpatient general psychiatry for MDD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). A diagnosis of MDD is confirmed. Mirtazapine (15 mg per day) is prescribed to replace Ms. Patmore's current antidepressant, escitalopram. Although daily fluoxetine previously worked well for Ms. Patmore, it is a strong CYP2D6 inhibitor, making it a non-ideal choice alongside daily tamoxifen which she will continue to take for up to 5 years.²⁷ Mirtazapine is known to have a rapid onset and good tolerability, with efficacy apparent as early as two weeks after treatment initiation.²⁵ Additionally, mirtazapine promotes appetite and is less likely to cause nausea or vomiting compared to other antidepressants (due to blockade of 5-HT₃ receptors).^{25,28} The possibility of adding psychotherapy to Ms. Patmore's treatment plan is also discussed. Studies examining combined pharmacological treatment and psychotherapy suggest that the combination may be more effective than treating MDD with either modality alone.²⁹ Regular outpatient follow-up appointments are scheduled to monitor the efficacy of mirtazapine and explore additional management possibilities, including psychotherapy.

CONCLUSIONS

At follow up over the next several weeks, Ms. Patmore's MDD is found to be improving with mirtazapine. The initial signs at presentation (insomnia, lack of appetite, fatigue and speech latency) all show gradual improvement with daily mirtazapine. Ms. Patmore returns for follow-up appointments through outpatient psychiatry. She also continues to be monitored by her family physician and medical oncologist regarding her tamoxifen therapy and any signs of cancer recurrence. Breast reconstruction is scheduled in 6 months' time.

In summary, this case explores a 51 year-old premenopausal patient with poorly controlled MDD following a change in antidepressant medication intended to avoid a potential drug interaction with tamoxifen via the enzyme CYP2D6.

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