Manic and nonadherent, with a diagnosis of breast cancer

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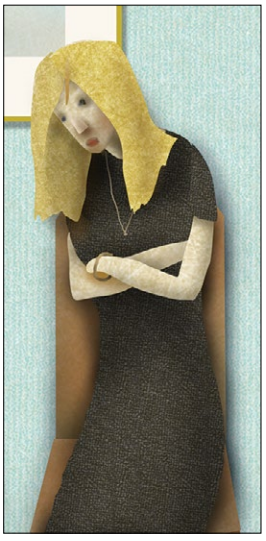
Ms. A, age 58, is admitted with new-onset agitation and auditory hallucinations. She has a history of bipolar disorder and recently had a diagnosis of breast cancer. How would you care for her?



DAVE CUTLER FOR CURRENT PSYCHIATRY

CASE Diagnosis, mood changes

Ms. A, age 58, is a white female with a history of chronic bipolar I disorder who is being evaluated as a new patient in an academic psychiatric clinic. Recently, she was diagnosed with ER+, PR+, and HER2+ ductal carcinoma. She does not take her prescribed mood stabilizers.

After her cancer diagnosis, Ms. A experiences new-onset agitation, including irritable mood, suicidal thoughts, tearfulness, decreased need for sleep, fast speech, excessive spending, and anorexia. She reports that she hears the voice of God telling her that she could cure her breast cancer through prayer and herbal remedies. Her treatment team, comprising her primary care provider and surgical oncologist, consider several medication adjustments, but are unsure of their effects on Ms. A's mental health, progression of cancer, and cancer treatment.

What is the most likely cause of Ms. A's psychiatric symptoms?

a) anxiety from having a diagnosis of cancer
b) stress reaction
c) panic attack
d) manic or mixed phase of bipolar I disorder

The authors' observations

Treating breast cancer with concurrent severe mental illness is complex and challenging for the patient, family, and health care providers. Mental health and oncology clinicians must collaborate when treating these patients because of overlapping pathophysiology and medication interactions. A comprehensive evaluation is required to tease apart whether a patient is simply demoralized by her new diagnosis, or if a more serious mood disorder is present.

Worldwide, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among women.[1] The mean age of women diagnosed with breast cancer is 61 years; 61% of these women are alive 15 years after diagnosis, representing the largest group of female cancer survivors.

The incidence of breast cancer is reported to be higher in women with bipolar disorder compared with the general population.[2-4] This positive correlation might be associated with a high rate of smoking, poor health-related behaviors, and, pos-

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Disclosures
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How would you handle this case?

Answer the challenge questions throughout this article

sibly, medication side effects. A genome-wide association study found significant associations between bipolar disorder and the breast cancer-related genes BRCA2 and PALB2.[5]

Antipsychotics and prolactin

Antipsychotics play an important role in managing bipolar disorder; several, however, are known to raise the serum prolactin level 10- to 20-fold. A high prolactin level could be associated with progression of breast cancer. All antipsychotics have label warnings regarding their use in women with breast cancer.

The prolactin receptor is overexpressed in >95% of breast cancer cells, regardless of estrogen-receptor status. The role of prolactin in development of new breast cancer is open to debate. The effect of a high prolactin level in women with diagnosed breast cancer is unknown, although available preclinical data suggest that high levels should be avoided. Psychiatric clinicians should consider checking the serum prolactin level or switching to a treatment strategy that avoids iatrogenic prolactin elevation. This risk must be carefully weighed against the mood-stabilizing properties of antipsychotics.[6]

TREATMENT Consider comorbidities

Ms. A receives supportive psychotherapy in addition to quetiapine, 400 mg/d, and valproic acid, 1,500 mg/d. This regimen helps her successfully complete the initial phase of breast cancer treatment, which consists of a single mastectomy, adjuvant chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab). She is now on endocrine therapy with tamoxifen.

Ms. A, calm, much improved mood symptoms, and euthymic, has questions regarding her mental health, cancer prognosis, and potential medication side effects with continued cancer treatment.

Which drug used to treat breast cancer might relieve Ms. A's manic symptoms?

a) cyclophosphamide
b) tamoxifen
c) trastuzumab
d) pamidronate

The authors' observations

Recent evidence suggests that tamoxifen reduces symptoms of bipolar mania more rapidly than many standard medications for bipolar disorder. Tamoxifen is the only available centrally active protein kinase C (PKC) inhibitor,[7] although lithium and valproic acid also might inhibit PKC activity. PKC regulates presynaptic and postsynaptic neurotransmission, neuronal excitability, and neurotransmitter release. PKC is thought to be overactive during mania, possibly because of an increase in membrane-bound PKC and PKC translocation from the cytosol to membrane.[7,8]

Preliminary clinical trials suggest that tamoxifen significantly reduces manic symptoms in patients with bipolar disorder within 5 days of initiation.[7] These findings have been confirmed in animal studies and in 1 single-blind and 4 double-blind placebo-controlled clinical studies over the past 15 years.[9]

Tamoxifen is a selective estrogen-receptor modulator used to prevent recurrence in receptor-positive breast cancer. Cytochrome P450 (CYP) 2D6 is the principal enzyme that converts tamoxifen to its active metabolite, endoxifen. Inhibition of tamoxifen conversion to endoxifen by CYP2D6 inhibitors could decrease the efficacy of tamoxifen therapy and might increase the risk of breast cancer recurrence. Although antidepressants generally are not recommended as a first-line agent for bipolar disorder, several selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are potent, moderate, or mild inhibitors of CYP2D6[10] (***Table 1***). Approximately 7% of

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women have nonfunctional CYP2D6 alleles and have a lower endoxifen level.[11]

Treating breast cancer

The mainstays of breast cancer treatment are surgery, radiation therapy, chemotherapy, hormone therapy, and targeted monoclonal antibody therapy. The protocol of choice depends on the stage of cancer, estrogen receptor status, expression of human epidermal growth factor receptor 2 (HER-2), treatment history, and the patient's menopausal status. Overexpression of HER-2 oncoprotein, found in 25% to 30% of breast cancers, has been shown to promote cell transformation. HER-2 overexpression is associated with aggressive tumor phenotypes, lymph node involvement, and resistance to chemotherapy and endocrine therapy. Therefore, the HER-2 oncoprotein is a key target for treatment. Often, several therapies are combined to prevent recurrence of disease.

Breast cancer treatment often can cause demoralization, menopausal symptoms, sleep disturbance, impaired sexual function, infertility, and disturbed body image. It also can trigger psychiatric symptoms in patients with, or without, a history of mental illness.

Trastuzumab is a recombinant humanized monoclonal antibody against HER-2, and is approved for treating HER-2 positive breast cancer. However, approximately 50% of patients with HER-2 overexpression do not respond to trastuzumab alone or combined with chemotherapy, and nearly all patients develop resistance to trastuzumab, leading to recurrence.[12] This medication is still used in practice, and research regarding antiepileptic drugs working in synergy with this monoclonal antibody is underway.

OUTCOME Stability achieved

Quetiapine and valproic acid are first-line choices for Ms. A because (1) she would be on long-term tamoxifen to maintain cancer remission maintenance and (2) she is in a manic phase of bipolar disorder.

Table 1

Psychotropic medications that inhibit CYP2D6

Inhibitor status	Drug
Weak (Safe with tamoxifen)	Citalopram Escitalopram Venlafaxine
Moderate (Use with caution)	Amiodarone Duloxetine Sertraline Thioridazine
Strong (Avoid with tamoxifen)	Bupropion Fluoxetine Paroxetine Quetiapine

CYP: cytochrome P450

Tamoxifen also could improve her manic symptoms. This medication regimen might enhance the action of cancer treatments and also could reduce adverse effects of cancer treatment, such as insomnia associated with tamoxifen.

After the team educates Ms. A about how her psychiatric medications could benefit her cancer treatment, she becomes more motivated to stay on her regimen. Ms. A does well on these medications and after 18 months has not experienced exacerbation of psychiatric symptoms or recurrence of cancer.

The authors' observations

There are 3 major classes of mood stabilizers for treating bipolar disorder: lithium, antiepileptic drugs, and atypical antipsychotics.[13] In a setting of cancer, mood stabilizers are prescribed for managing mania or drug-induced agitation or anxiety associated with steroid use, brain metastases, and other medical conditions. They also can be used to treat neuropathic pain and hot flashes and seizure prophylaxis.[13]

Valproic acid

Valproic acid can help treat mood lability, impulsivity, and disinhibition, whether

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Breast cancer treatment can trigger psychiatric symptoms in patients with, or without, a history of mental illness

Table 2

Risk-benefit profile of mood-stabilizing medications in breast cancer patients

Drug	Risks	Benefits
Antimanic		
Lithium	Toxicity Inducer of oncogenic signaling in ER+ cells Inhibits cancer cell apoptosis	Granulocyte-stimulating and leukocyte demargination, ameliorates neutropenia associated with chemotherapy Increased ionizing radiation sensitivity
Antiepileptics		
Valproic acid	Hematologic adverse effects Hepatotoxicity CYP450 enzyme inhibition	Histone deacetylase inhibitor that induces cell cycle arrest, activates apoptosis, and inhibits cell metastasis Increases action of breast cancer treatment and induces solid breast cancer tumor regression Restores ER+ phenotype, allowing for more targeted breast cancer treatment
Carbamazepine	Hematologic suppression Hepatotoxicity CYP450 enzyme inducer	Reduction of HER-2 proto-oncogene by histone acetylation Synergistic effect when combined with trastuzumab
Lamotrigine	Stevens-Johnson syndrome (rash)	No specific beneficial effect on breast cancer treatment or prognosis
Antipsychotics		
Quetiapine	Metabolic disturbances Low risk of elevating prolactin	Alleviates tamoxifen-induced insomnia
Olanzapine	Moderate increase in prolactin level Metabolic disturbances	Reduces otherwise refractory nausea Leads to weight gain and improved appetite in cachexia
Risperidone, paliperidone, all first-generation antipsychotics	High increase in prolactin level	
Ziprasidone, asenapine, quetiapine, clozapine, aripiprazole	Metabolic disturbances No or minimal increase in prolactin level	
Iloperidone, lurasidone	Moderate increase in prolactin level	

CYP: cytochrome P450; HER-2: human epidermal growth factor receptor 2

Clinical Point

Valproic acid reduces cancer cell viability and could act as a powerful antiproliferative agent in estrogen-sensitive breast cancer cells

these symptoms are due to primary psychiatric illness or secondary to cancer metastasis. It is a first-line agent for manic and mixed bipolar states, and can be titrated quickly to achieve optimal benefit. Valproic acid also has been described as a histone deacetylase (HDAC) inhibitor, known to attenuate apoptotic activity, making it of interest as a treatment for cancer.[14] HDAC inhibitors have been shown to:

- induce differentiation and cell cycle arrest
- activate the extrinsic or intrinsic pathways of apoptosis
- inhibit invasion, migration, and angiogenesis in different cancer cell lines.[15]

In regard to breast cancer, valproic acid inhibits growth of cell lines independent of estrogen receptors, increases the action of such breast cancer treatments as tamoxifen, raloxifene, fulvestrant, and letrozole, and induces solid tumor regression.[14] Valproic acid also reduces cancer cell viability and could act as a powerful antiproliferative agent in estrogen-sensitive breast cancer cells.[16]

Valproic acid reduces cell growth-inducing apoptosis and cell cycle arrest in ERα-positive breast cancer cells, although it has no significant apoptotic effect in ERα-negative cells.[16] However, evidence does support the ability of valproic acid to restore an estrogen-sensitive phenotype in ERα-negative breast cancer cells, allowing successful treatment with the anti-estrogen tamoxifen in vitro.[10]

Antipsychotics

Antipsychotics act as dopamine D2 receptor antagonists within the hypothalamic-pituitary-adrenal axis, thus increasing the serum prolactin level. Among atypicals, risperidone and its active metabolite, paliperidone, produce the greatest increase in the prolactin level, whereas quetiapine, clozapine, and aripiprazole minimally elevate the prolactin level.

Hyperprolactinemia correlates with rapid breast cancer progression and inferior prognosis, regardless of breast cancer receptor typing. Therefore, prolactin-sparing antipsychotics are preferred when treating a patient with comorbid bipolar disorder and breast cancer. Checking the serum prolactin level might help guide treatment. The literature is mixed regarding antipsychotic use and new mammary tumorigenesis; current research does not support antipsychotic choice based on future risk of breast cancer.[6]

Other adverse effects from antipsychotic use for bipolar disorder could have an impact on patients with breast cancer. Several of these medications could ameliorate side effects of advanced cancer and chemotherapy. Quetiapine, for example, might improve tamoxifen-induced insomnia in women with breast cancer because of its high affinity for serotonergic receptors, thus enhancing central serotonergic neurotransmitters and decreasing excitatory glutamatergic transmission.[17]

In any type of advanced cancer, nausea and vomiting are common, independent of chemotherapy and medication regimens. Metabolic derangement, vestibular dysfunction, CNS disorders, and visceral metastasis all contribute to hyperemesis. Olanzapine has been shown to significantly reduce refractory nausea and can cause weight gain and improved appetite, which benefits cachectic patients.[18]

Last, clozapine is one of the more effective antipsychotic medications, but also carries a risk of neutropenia. In patients with neutropenia secondary to chemotherapy, clozapine could increase the risk of infection in an immunocompromised patient.[19] Granulocyte colony stimulating factor might be useful as a rescue medication for treatment-emergent neutropenia.[19]

Treatment considerations

Cancer patients might be unable or unwilling to seek services for mental health during their cancer treatment, and many who have a diagnosis of psychiatric illness might stop following up with psychiatric care when

NEXT MONTH IN
CASES THAT TEST YOUR SKILLS

Police find Ms. P, age 56, behaving bizarrely in the middle of the road. She describes racing thoughts, pressured speech, decreased need for sleep, and delusions—symptoms that began 10 years ago, when she was a high-functioning senior executive accountant.
How would you diagnose her condition?

Follow this case in the February 2016 issue of
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Prolactin-sparing antipsychotics are preferred when treating a patient with comorbid bipolar disorder and breast cancer

Clinical Point

Changing an effective mood stabilizer to gain benefits in breast cancer prognosis is not recommended in most cases

Related Resources

- Agarwala P, Riba MB. Tailoring depression treatment for women with breast cancer. Current Psychiatry. 2010;9(11): 39-40,45-46,48-49.
- Cunningham R, Sarfati D, Stanley J, et al. Cancer survival in the context of mental illness: a national cohort study. Gen Hosp Psychiatry. 2015;37(6):501-506.

Drug Brand Names

Amiodarone • Cordarone
Aripiprazole • Abilify
Asenapine • Saphris
Bupropion • Wellbutrin
Carbamazepine • Tegretol
Citalopram • Celexa
Clozapine • Clozaril
Cyclophosphamide • Cytoxan, Neosar
Doxorubicin • Doxil, Adriamycin
Duloxetine • Cymbalta
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Lurasidone • Latuda
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Quetiapine • Seroquel
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Risperidone • Risperdal
Sertraline • Zoloft
Tamoxifen • Nolvadex
Thioridazine • Mellaril
Trastuzumab • Herceptin
Valproic acid • Depakene
Venlafaxine • Effexor
Ziprasidone • Geodon

cancer treatment takes priority. It is critical for clinicians to be aware of the current literature regarding the impact of mood-stabilizing medication on cancer treatment. Monitoring for drug interactions is essential, and electronic drug interaction tools, such as Lexicomp, may be useful for this purpose.[13] Because of special vulnerabilities in this population, cautious and judicious prescribing practices are advised.

The risk-benefit profile for medications for bipolar disorder must be considered before they are initiated or changes are made to the regimen (***Table 2, page 54***). Changing an effective mood stabilizer to gain benefits in breast cancer prognosis is not recommended in most cases, because benefits have been shown to be only significant in preclinical research; currently, there are no clinical guidelines. However, medication adjustments should be made with these theoretical benefits in mind, as long as the treatment of bipolar disorder remains effective.

Regardless of what treatment regimen the health team decides on, several underlying issues that affect patient care must be considered in this population. Successfully treating breast cancer in a woman with severe mental illness only can be accomplished when her mental illness is under control. Once she is psychiatrically stable, it is important for her to have a basic understanding of how cancer can affect the body and know the reasons behind treatment.

It is imperative that physicians provide their patients with a general understanding of their comorbid disorders, and find ways to help patients remain adherent with treatment of both diseases. Many patients feel demoralized by a cancer diagnosis and adherence to a medication regimen might be a difficult task among those with bipolar disorder who also are socially isolated, lack education, or have poor recall of treatment recommendations.[20]

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Bottom Line

Managing comorbid bipolar disorder and breast cancer might seem daunting, but treatments for the 2 diseases can work in synergy. You have an opportunity to educate patients and colleagues in treating bipolar disorder and comorbid breast cancer. Optimizing care using known psychopharmacologic data can not only lead to better outcomes, but might additionally offer some hope and reason to remain treatment-adherent for patients suffering from this complex comorbidity.

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This month's quickpoll

How would you describe your experience making the transition from ICD-9 to ICD-10?

- ☐ Great! I don't have problems using the new codes
- ☐ I've had some problems, but it's going more smoothly than expected
- ☐ I've had a lot of trouble. For example, I find it difficult to map a patient's diagnosis to the new codes
- ☐ I don't have experience with ICD-10. Office staff does our billing and coding

See **"What psychiatrists must know to make the mandated transition to ICD-10"** *pages 25,26,28-32*

Visit CurrentPsychiatry.com to answer the Quick Poll and see how your colleagues responded.

NOVEMBER POLL RESULTS

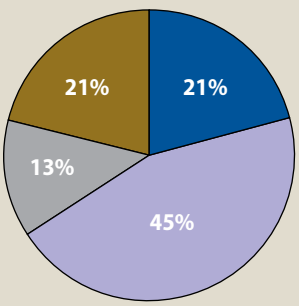
Ms. A, age 78, is brought to your clinic by her caregiver. She describes feeling "fretful recently, and kind of depressed, too." During the evaluation, you notice that Ms. A has a large bruise on her arm. When you ask about the bruise, she replies, in a noticeably low voice, that she fell. Based on your evaluation, you suspect that Ms. A might have been abused; on the other hand, her medications include an oral anticoagulant known to increase the risk of falls and easy bruising. **How would you proceed?**

21% Document the interaction and report to Adult Protective Services

45% Administer the Comprehensive Geriatric Assessment, and then make a decision as to whether to report suspected abuse

13% Assess her capacity to make decisions and report to Adult Protective Services, if necessary

21% Ask Ms. A if she will accept help with circumstances in her home, if offered



SUGGESTED READING:
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Data obtained via CurrentPsychiatry.com, November 2015.