Managing schizophrenia in a patient with cancer: A fine balance

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How would you handle this case?

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Ms. B, age 60, has schizophrenia, which has been stable on clozapine for 2 decades when she is diagnosed with cancer. How do you manage her psychiatric illness during chemotherapy?

CASE Stable with a new diagnosis

Ms. B, age 60, has a history of schizophrenia, which has been stable on clozapine, 500 mg/d, for more than 2 decades. After a series of hospitalizations in her 20s and 30s, clozapine was initiated and she has not required additional inpatient psychiatric care. She has been managed in the outpatient setting with standard biweekly absolute neutrophil count (ANC) monitoring. She lives independently and is an active member in her church.

After experiencing rectal bleeding, Ms. B is diagnosed with rectal carcinoma and is scheduled to undergo chemotherapy and radiation treatment.

How would you manage Ms. B's psychiatric illness at this time?

a) continue clozapine and the current monitoring schedule
b) continue clozapine and increase ANC monitoring to weekly
c) discontinue clozapine and switch to another antipsychotic
d) discontinue clozapine and monitor her closely

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The authors' observations

Both clozapine and chemotherapy carry the risk of immunosuppression, presenting a clinical challenge when choosing an appropriate management strategy. However, the risks of stopping clozapine after a long period of symptom stability are substantial, with a relapse rate up to 50%.[1] Among patients taking clozapine, the risk of agranulocytosis and neutropenia are approximately 0.8% and 3%, respectively, and >80% of agranulocyotis cases occur within the first 18 weeks of treatment.[2,3] Although both clozapine and chemotherapy can lead to neutropenia and agranulocytosis, there currently is no evidence of a synergistic effect on bone marrow suppression with simultaneous use of these therapies[2] nor is there evidence of the combination leading to sustained marrow suppression.[4]

Because of Ms. B's positive response to clozapine, the risks associated with discontinuing the medication, and the relatively low risk of clozapine contributing to neutropenia after a long period of stabilization, her outpatient psychiatric providers decide

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to increase ANC monitoring to weekly while she undergoes cancer treatment.

TREATMENT Neutropenia, psychosis

Ms. B continues clozapine during radiation and chemotherapy, but develops leukopenia and neutropenia with a low of 1,220/µL white blood cells and an ANC of 610/µL. Clozapine is stopped, consistent with current recommendations to hold the drug if the neutrophil count is <1,000/µL in a patient without benign ethnic neutropenia, and her outpatient provider monitors her closely. The treatment team does not restart an antipsychotic immediately after discontinuing clozapine because of the risk that other antipsychotics can cause hematologic toxicity or prolong granulocytopenia associated with clozapine.[5]

Approximately 2 weeks later, Ms. B is admitted to a different hospital for altered mental status and is found to have hyponatremia and rectal bleeding. The workup suggests that her rectal carcinoma has not fully responded to initial therapies, and she likely will require further treatment. Her mental status improves after hyponatremia resolves, but she reports auditory hallucinations and paranoia. Risperidone, 4 mg/d, is initiated to target psychosis.

After discharge, Ms. B develops bilateral upper extremity tremor, which she finds intolerable and attributes to risperidone. She refuses to continue risperidone or try adjunctive medications to address the tremor, but is willing to consider a different antipsychotic. Olanzapine, 10 mg/d, is initiated and risperidone is slowly tapered. During this time, Ms. B experiences increased paranoia and believes that the Internal Revenue Service is calling her. She misses her next appointment.

Later, the fire department finds Ms. B wandering the streets and brings her to the psychiatric emergency room. During the examination, she is disheveled and withdrawn, and unable to reply to simple questions about diet and sleep. When asked why she was in the street, she says that she left her apartment because it was "too messy." The treatment team learns that she had walked at least 10 miles from her apartment before sitting down by the side of the road and being picked up by the fire department. She reveals that she left her apartment and continued walking because "a man" told her to do so and threatened to harm her if she stopped.

When Ms. B is admitted to the psychiatric service, she is paranoid, disorganized, and guarded. She remains in her room for most of the day and either refuses to talk to providers or curses at them. She often is seen wearing soiled clothing with her hair mussed. She denies having rectal carcinoma, although she expressed understanding of her medical condition <2 months earlier.

What is the appropriate next step in management?

a) continue olanzapine at the present dosage
b) continue to increase olanzapine until Ms. B experiences therapeutic effect
c) resume clozapine
d) resume clozapine and add lithium
e) taper olanzapine and initiate a different antipsychotic

The authors' observations

Clozapine is considered the most efficacious agent for treatment-resistant schizophrenia.[6] Although non-compliance is the most common reason for discontinuing clozapine, >20% of patients stop clozapine because of adverse effects.[7] Clozapine often is a drug of last resort because of the need for frequent monitoring and significant side effects; therefore deciding on a next step when clozapine fails or cannot be continued because of other factors can pose a challenge.

Ms. B's treatment team gave serious consideration to restarting clozapine. However, because it was likely that Ms. B would undergo another round of chemotherapy and possibly radiation, the risk of neutropenia recurring was considered too high.

continued

Clinical Point

Among patients taking clozapine, the risk of agranulocytosis and neutropenia are approximately 0.8% and 3%, respectively

Clinical Point

Although structurally similar to clozapine, loxapine is not known to cause agranulocytosis

Table

When to consider loxapine

The patient was trialed on clozapine with good response, but it had to be stopped secondary to intolerable side effects
The patient is unable to comply with the monitoring required for clozapine
The patient has preexisting neutropenia or heart disease
The patient developed agranulocytosis on clozapine and retrial is not clinically prudent
The patient is overweight, has type 2 diabetes mellitus or metabolic syndrome

Lithium has been used successfully to manage neutropenia in patients taking clozapine and, for some, adding lithium could help boost white cell count and allow a successful rechallenge with clozapine.[3,8] However, because of Ms. B's medical comorbidities, including cancer and chronic kidney disease, adding lithium was not thought to be clinically prudent at that time and the treatment team considered other options.

Olanzapine. Although research is limited, studies suggest olanzapine is the most commonly prescribed medication when a patient has to discontinue clozapine,[7] with comparable response rates in those with refractory schizophrenia.[9] Therefore, Ms. B was initially maintained on olanzapine, and the dosage increased to 30 mg over the course of 16 days in the hospital. However, she did not respond to the medication, remaining disorganized and paranoid without any notable improvement in her symptoms therefore other treatment options were explored.

Loxapine. Previous limited case reports have shown loxapine to be effective in treating individuals with refractory schizophrenia, either alone or in combination with other antipsychotics.[10,11] FDA-approved in 1975, loxapine was among the last of the typical antipsychotics brought to the U.S. market before the introduction of clozapine, the first atypical.[12] Loxapine is a dibenzoxazepine that has a molecular structure similar to clozapine.[13] Unlike clozapine, however, loxapine is not known to cause agranulocytosis.[14] Research suggests that although clozapine is oxidized to metabolites that are cytotoxic, loxapine is not, potentially accounting for their different effects on neutrophils.[15]

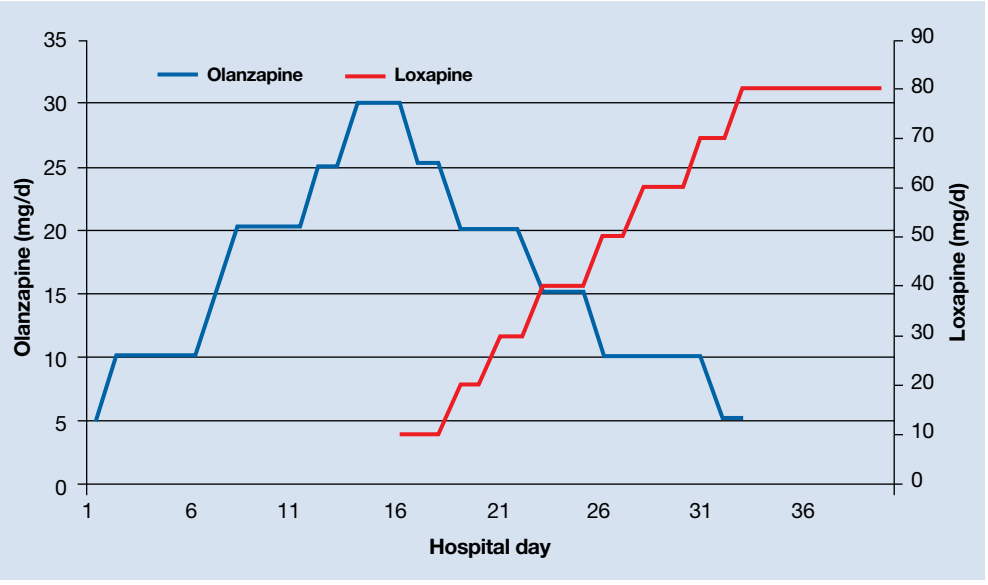
The efficacy of loxapine has shown to be similar to other typical and atypical antipsychotics, with approximately 70% of patients showing improvement.[14] However, loxapine may be overlooked as an option, possibly because it was not included in the CATIE trial and was the last typical antipsychotic to be approved before atypicals were introduced.[12] First available in oral and IM formulations, there has been increased interest in loxapine recently because of the approval of an inhaled formulation in 2012.[16]

Although classified as a typical antipsychotic, studies have suggested that loxapine acts as an atypical at low dosages.[17,18] Previous work suggests, however, that the side effect profile of loxapine is similar to typical antipsychotics.[14] At dosages <50 mg, it results in fewer cases of extrapyramidal side effects than expected with a typical antipsychotic.[18]

Loxapine's binding profile seems to exist along this spectrum of typical to atypical. Tissue-based binding studies have shown a higher 5-HT2 affinity relative to D2, consistent with atypical antipsychotics.[19] Positron emission tomography studies in humans show 5-HT2 saturation of loxapine to be close to equal to D2 binding in loxapine, thus a slightly lower ratio of 5-HT2 to D2 relative to atypicals, but more than that seen with typical antipsychotics.[20] These differences between *in vitro* and *in vivo* studies may be secondary to the binding of loxapine's active metabolites, particularly 7- and 8-hydroxyloxapine, which have more dopaminergic activity. In addition to increased 5-HT2A binding compared with typical antipsychotics, loxapine also has a high affinity for the D4 receptors, as well as interacting with

Figure

Dosage titration of olanzapine and loxapine



other serotonin receptors 5-HT3, 5-HT6, and 5-HT7. Of note this is a similar pattern of binding affinity as seen in clozapine.[19]

Loxapine is a reasonable treatment alternative for individuals with schizophrenia who have not responded to other antipsychotics and for whom clozapine is a poor choice (***Table***). Loxapine may be considered in those with a history of clozapine-induced agranulocytosis or myocarditis; those with preexisting neutropenia, such as benign ethnic neutropenia, or heart disease in which the risks of clozapine may outweigh the benefits; and those resistant to the intensive monitoring that clozapine requires. Loxapine also should be considered in those who responded well to clozapine in the past but are unable to continue the medication for other reasons, such as in Ms. B's case.

It should be noted, however, that loxapine may not be an appropriate treatment in all forms of cancer. Similar to other first-generation antipsychotics, it increases prolactin levels, and thus may have a negative clinical impact on patients with prolactin receptor positive breast cancers.[21,22] Finally, although clozapine can result in significant weight gain, dyslipidemia, and hyperglycemia, unlike many antipsychotics, loxapine has been shown to be weight neutral or result in weight loss,[14] making it an option to consider for patients with type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, or cardiovascular disease.

OUTCOME Improvement, stability

Ms. B begins taking loxapine, 10 mg/d, gradually cross-tapered with olanzapine, increasing loxapine by 10 mg every 2 to 3 days (***Figure***). After 8 days, when the dosage has reached 40 mg/d, Ms. B's treatment team begins to observe a consistent change in her behavior. Ms. B comes into the interview room, where previously the team had to see her in her own room because she refused to come out. She also tolerates an extensive interview, even sharing parts of her history without prompting, and is able to discuss her treatment. Ms. B continues to express some paranoia regarding the treatment team. On day 12, receiving loxapine, 50 mg/d, Ms. B

Clinical Point

Consider loxapine in patients who have not responded to other antipsychotics and for whom clozapine is a poor choice

Clinical Point

Loxapine may not be appropriate treatment in all forms of cancer because it increases prolactin levels

says that she likes the new medication and feels she is doing well with it. She becomes less reclusive and begins socializing with other patients. By day 19, receiving loxapine, 80 mg/d, a nurse, who knows Ms. B from the outpatient facility, visits the unit and reports that Ms. B is at her baseline.

At discharge, Ms. B is noted to be "bright," well organized, and neatly dressed and wearing makeup. Her paranoia and auditory hallucinations have almost completely resolved. She is social, engages appropriately with the treatment team, and is able to describe a plan for self-care after discharge including following up with her oncologist. Her white blood cell counts were carefully monitored throughout her admission and are within normal limits when she is discharged.

One year later, Ms. B remains taking loxapine, 70 mg/d. Although she continues to report mild paranoia, she is living independently in her apartment and attends church regularly.

Related Resources

- Clozapine REMS. www.clozapinerems.com/CpmgClozapineUI/home.u.
- Irwin KE, Henderson DC, Knight HP, et al. Cancer care for individuals with schizophrenia. Cancer. 2014;120(3):323-334.
- Rahman T, Kaklamani V. Manic and nonadherent, with a diagnosis of breast cancer. Current Psychiatry. 2016;15(1):51-57.

Drug Brand Names

Clozapine • Clozaril
Lithium • Eskalith, Lithobid
Loxapine • Loxitane, Adasuve
Olanzapine • Zyprexa
Risperidone • Risperdal

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Bottom Line

Cancer treatment can present challenges when managing psychiatric illness. Loxapine is an alternate treatment for individuals with schizophrenia who have not responded to other antipsychotics and for whom clozapine is a poor choice. Consider loxapine for patients with significant adverse effects to clozapine, comorbid medical conditions that preclude its use, or those who are poor candidates for frequent blood monitoring.

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