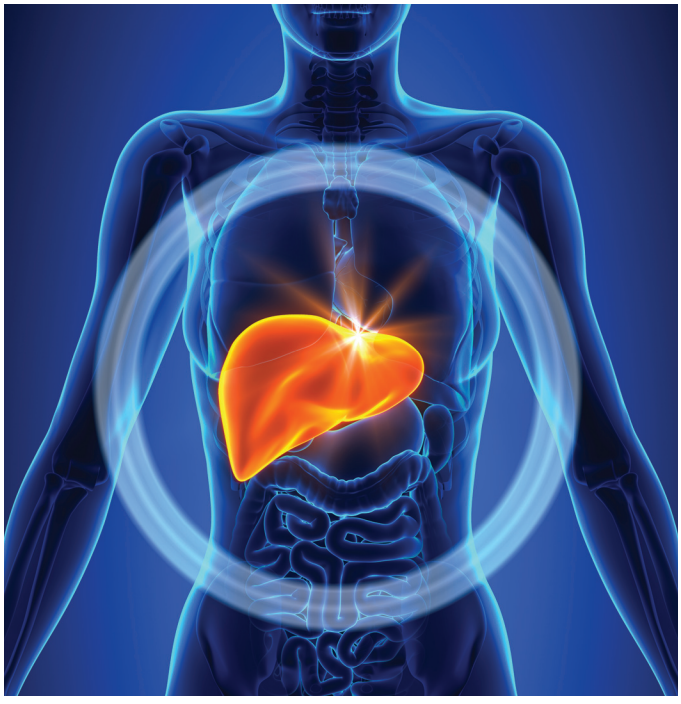
75-Year-Old Woman With Elevated Liver Enzymes

Marilyn J. Miller, PhD, CRNP, CS-P



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A 75-year-old woman, Gladys, was brought to the psychiatric clinic in a manic state by her concerned sister. The patient was disheveled, dehydrated, and having difficulty expressing her thoughts. Vital signs included a blood pressure of 200/94 mm Hg; pulse, 88 beats/min; temperature, 98.4°F; and respiratory rate, 20 breaths/min. Psychiatric history included a diagnosis of schizoaffective disorder with inconsistent adherence to treatment regimens, particularly mood stabilizers; and attention-deficit/hyperactivity disorder, for which she took methylphenidate regularly. Medical history was significant for asthma, osteoporosis, hypertension, type 2 diabetes, and hypothyroidism.

Gladys tended to become involved in personal relationships that adversely affected her mental health. This, in fact, had just happened: A "friend" had taken advantage of her kindness and then abruptly moved away, triggering the patient's current decompensation. She was referred for admission for psychiatric evaluation and treatment.

During the three-week hospitalization, Gladys was diagnosed with bipolar I disorder. She agreed to take mood-stabilizing medication primarily to alleviate her insomnia during manic episodes. She was discharged on a multidrug regimen for her coexisting conditions (see Table 1, next page). Of note, her blood pressure at discharge was 148/66 mm Hg.

At outpatient follow-up five days later, the patient reported feeling better and stronger. However, five weeks after discharge, Gladys returned with complaints of tiredness during the day (though sleeping well at night), severe dry mouth, aching joints, and poor appetite. Her blood pressure was 100/50 mm Hg. She denied abdominal pain or change in the color of her urine or stool. She also denied use of alcohol, illicit drugs, or OTC medications. Laboratory results revealed

Marilyn J. Miller is an adult nurse practitioner/psychiatric clinical specialist practicing in the Maryland VA Health Care System.

TABLE 1
Patient's Medications

Drug (dosage)	Indication
Albuterol (1 spray qid prn)	Asthma
Calcium carbonate/vitamin D (600 mg/400 IU bid)	Osteoporosis
Clonazepam (1 mg qhs)	Sedation
Diltiazem XR (240 mg/d)	Hypertension
Glyburide (5-mg tabs: 2 w/ breakfast, 1 w/dinner)	Type 2 diabetes
Levothyroxine (0.025 mg/d)	Hypothyroidism
Lisinopril/hydrochlorothiazide (10/12.5 mg/d)	Hypertension
Lorazepam (0.5 mg q4hr prn)	Anxiety
Methylphenidate (10 mg bid)	Attention-deficit/ hyperactivity disorder
Quetiapine (100 mg qhs)	Mood stabilization

elevated levels of several liver enzymes (see Table 2, page 36), all of which had been normal when she was admitted to the hospital two months earlier.

DISCUSSION

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels may result from a variety of factors. Mild elevations are commonly caused by alcohol consumption, hemochromatosis, medications, nonalcoholic fatty liver disease, and viral hepatitis (with which elevations may range from mild to marked).[1] Moderate to marked elevations of ALT and AST are commonly seen with acute biliary obstruction, alcoholic hepatitis, toxic injury, and ischemic injury.[2]

Abnormal liver enzyme levels are common with use of psychotropic drugs, such as antipsychotics and mood stabilizers.[3] In a systematic review that examined the effects of antipsychotics on liver function tests, a median 4% of patients experienced elevated ALT, AST, or gamma-glutamyl transferase (GGT) levels (defined as more than triple the normal level) or alkaline phosphatase (ALP) level (defined as more than twice the normal level).[3] Of the studies reviewed, five noted an interval of one to six weeks between initiation of antipsychotic drugs and detection of liver function test abnormalities. None of the included studies reported severe or fatal hepatic injury.

For the atypical antipsychotic quetiapine, elevations in ALT and AST occurred in about 5% and 3% of patients, respectively, in clinical trials of the drug as monotherapy for schizophrenia or bipolar mania.[4] These elevations were usually transient, occurring within the first three weeks of treatment initiation and subsiding with continued treatment.

There are rare published reports, however, of serious and even fatal hepatotoxicity induced by quetiapine. One 59-year-old woman developed fulminant hepatic failure (FHF) six weeks after she began taking quetiapine in addition to carbidopa/levodopa for Parkinson disease. She reported nausea, vomiting, poor appetite, and abdominal pain and required a six-week hospitalization, with multidrug treatment that continued after discharge. Liver biopsy identified acute hepatitis with confluent bridging necrosis, a sign that the liver injury was drug-induced. The authors concluded that, because drug-induced hepatotoxicity is the most common cause of FHF in many parts of the world, clinicians should evaluate a patient's medications for a potential cause.[5]

In another case report, elevated liver enzymes were identified one month after a 58-year-old woman taking several other medications began treatment with quetiapine (100 mg/d). She developed liver failure and died after a three-week hospitalization. The authors concluded that liver failure was caused by an idiosyncratic reaction to a relatively low dose of quetiapine. This case supports the advisability of close monitoring of liver enzyme levels during quetiapine treatment.[6]

Naharci et al reported a case of a 77-year-old woman treated with quetiapine (12.5 mg bid for nine days). She developed acute hepatic failure leading to multi-organ system failure and died eight days later. Liver failure was attributed to an idiosyncratic reaction to low-dose quetiapine. The authors concluded that liver function monitoring is essential with quetiapine administration, especially in elderly or fragile patients.[7]

The initial recommended dosage of quetiapine for elderly patients (defined as age 65 or older) is 50 mg/d, with the dose increased in increments of 50 mg/d, based on clinical response and tolerability. In clinical trials, the mean plasma clearance of quetiapine was reduced by 30% to 50% in the elderly, so dos-

ing adjustments may be necessary in this age-group.[4] Gareri et al recommended that atypical antipsychotics be prescribed for elderly patients for the shortest necessary duration and at the lowest effective dose.[8]

For hepatically impaired patients, recommended initial dosing is 25 mg/d, with increases of 25 to 50 mg/d until an effective and tolerable dose is reached.[4] Further, because quetiapine is primarily metabolized via the cytochrome P450 liver enzymes CYP3A4 and CYP2D6,[9] when the clinician prescribes a potent CYP3A4 inhibitor (eg, ketoconazole) to a patient taking quetiapine, the quetiapine dosage needs to be reduced. Conversely, when prescribing a CYP3A4 inducer (eg, phenytoin), the quetiapine dosage should be adjusted upward.[4]

Even when an apparently well-tolerated, effective quetiapine dosage has been reached, clinicians and patients should remain alert to the warning signs of potentially serious events. Adverse effects of atypical antipsychotics, including quetiapine, were summarized by Gareri et al and rated on a scale ranging from *no effect* to *severe effect*.[8] The most severe adverse effects for quetiapine were hypotension and prolonged QTc interval. Weight gain was identified as a moderate effect, and sedation, gastrointestinal problems (nausea, vomiting, and constipation), and anticholinergic effects as mild. Some effects—tardive dyskinesia, seizures, and hepatic—were deemed "uncertain"; this rating suggests the need for careful monitoring of patients (who should be informed of signs and symptoms that should be reported to the clinician).[8]

Atasoy et al reviewed the records of 110 patients to assess the effect of atypical antipsychotics on liver function tests. The patients' records included both baseline liver function tests and repeat testing at six months. Forty-eight patients received quetiapine; 33 patients, olanzapine; and 29 patients, risperidone. Liver enzymes were elevated in 27.1% of the quetiapine group, 30.3% of the olanzapine group, and 27.6% of the risperidone group. In two patients taking olanzapine, liver enzyme levels reached three to four times normal but returned to normal when treatment was stopped. The authors concluded that baseline liver enzyme studies should be done prior to initiation of treatment with atypical antipsychotics, as well as periodically thereafter, especially for patients with preexisting hepatic disorders, those being treated with other potentially hepatotoxic drugs, or those who exhibit signs or symptoms of hepatic impairment.[10]

TABLE 2
Selected Test Results at Five-Week Follow Up

Study	Result (normal range)
Alkaline phosphatase (ALP)	280 (38-126) U/L
Alanine aminotransferase (ALT)	94 (17-63) U/L
Aspartate aminotransferase (AST)	58 (0-37) U/L
A1C	6.2% (< 6.5%)
Hepatitis panel	Negative
Lactate dehydrogenase (LDH)	196 (98-192) U/L
Ultrasound, liver	Normal

PATIENT OUTCOME

Gladys's ALT and AST levels were mildly elevated. One of the more common causes for this pattern is medication. In addition, her ALP level of more than twice the upper limit of normal further pointed to a viral, alcohol-related, or drug toxicity cause. Since her hepatitis panel was negative and she did not use alcohol, it was determined that elevated liver enzymes were related to the recent addition of quetiapine, which was discontinued. In addition, in light of Gladys's hypotension (which is also a potential adverse effect of quetiapine[8]), her dose of lisinopril/hydrochlorothiazide was decreased by half.

One week later, liver enzyme levels were returning to normal. Gladys, however, began having more difficulty sleeping and more trouble remaining focused and getting things done, despite taking methylphenidate. In place of quetiapine, risperidone (0.5 mg at bedtime) was initiated. At first, Gladys was concerned with her continuing dry mouth symptoms, but when she skipped doses of risperidone, she noticed that she functioned less well. Further, her liver enzyme levels were being closely monitored and were normal. With this reassurance, Gladys remained adherent to risperidone for mood stabilization.

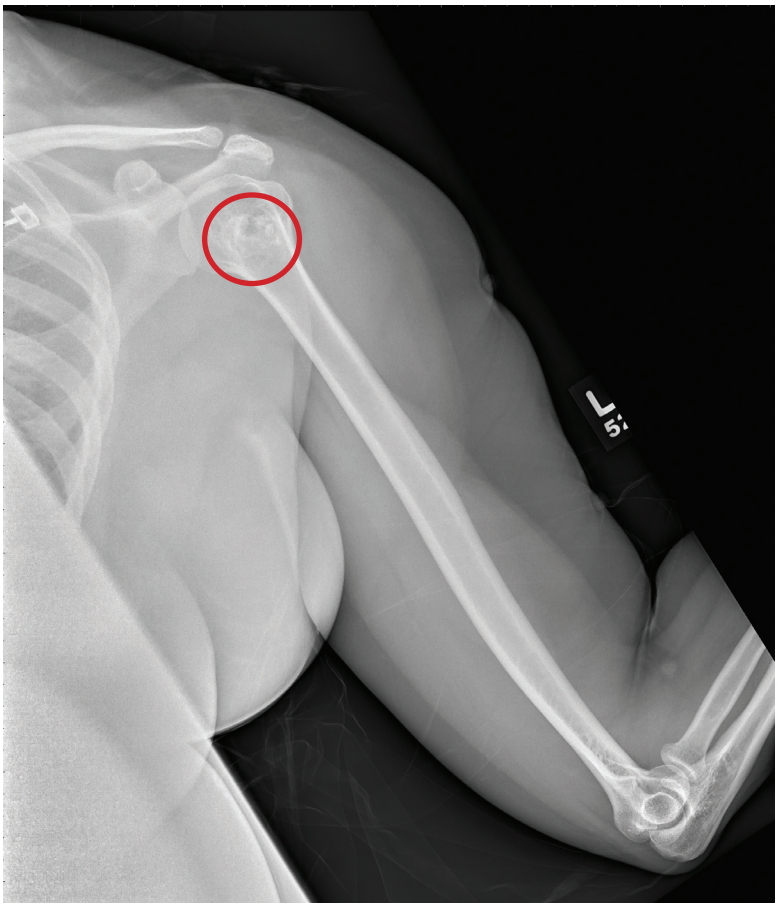
CONCLUSION

Atypical antipsychotic drugs such as quetiapine can cause elevated liver enzyme levels, especially in the elderly, patients with hepatic impairment, or patients on polypharmacotherapy. Rarely, quetiapine

>> *continued from page 15*

ANSWER

The radiograph shows no evidence of a fracture. However, there is a 2-cm focal sclerotic area noted within the juncture of the humeral neck and head. This finding could represent an enchondroma, a bone cyst, or a bone infarct. Additional imaging, including MRI and bone scan, is warranted, as is orthopedic evaluation. This finding is likely incidental, as the patient's clinical exam is suggestive of a cervical radiculitis referable to the herniated disc in her neck. **CR**



has been reported to cause serious hepatotoxicity and even death. Patients taking these drugs should be informed of possible symptoms of liver toxicity, including fatigue, nausea, vomiting, abdominal pain, and change in color of urine or stools. Particularly in more vulnerable patients, liver enzyme levels should be monitored carefully to confirm the continued safety of antipsychotic treatment. **CR**

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