How to modify psychotropic therapy for patients who have liver dysfunction

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Series Editor

Police bring Ms. R, age 35, to the psychiatric ER after they find her asleep in a park. She is awake but drowsy, and states that she has a history of bipolar disorder. She claims that she had been stable on valproic acid (VPA), 1,500 mg/d, bupropion XL, 300 mg/d, quetiapine, 400 mg/d, and trazodone, 100 mg/d, until 2 weeks ago, when her best friend died and she stopped taking her medications all together. The previous evening, feeling "alone, hopeless, and sad," she attempted suicide by ingesting a handful of VPA and clonazepam, obtained from a friend, and 2 liters of vodka. She complains of nausea, vomiting, and abdominal pain. Elevated laboratory chemistries included aspartate aminotransferase (AST), 220 U/L; alanine aminotransferase (ALT), 182 U/L; alkaline phosphatase (AP), 75 U/L; γ-glutamyltransferase (GGT), 104 U/L; total bilirubin, 1.4 mg/dL; and an elevated VPA serum concentration of 152 µg/mL.

Drug-induced hepatotoxicity accounts for approximately 50% of acute liver failure cases, and almost 10% of liver transplants in some facilities.[1] The incidence of drug-induced hepatotoxicity is between 0.001% and 0.1% in patients on standard medication doses.[2] Drug-induced hepatotoxicity is characterized by:

- abnormalities in laboratory parameters (hepatocellular, cholestatic, or mixed)
- mechanisms of toxicity (direct, immune-mediated, idiosyncratic, mitochondrial toxicity)
- liver biopsy histology (steatosis, sinusoidal obstruction syndrome).[3]

Liver function test results of hepatocellular injury are characterized by ALT elevation and minimal AP elevation, whereas cholestatic injury manifests as high AP. ***Table 1***[3] categorizes psychotropics based on type of liver injury and how each injury manifest in liver function tests. Delayed idiosyncratic reactions occur after taking the drug, whereas direct toxicities are dose-dependent and more predictable. By definition, a clinically significant hepatotoxicity is associated with an ALT >3 times the upper limit of normal.[3]

Practice points

- **Hepatotoxicity with psychotropic agents is uncommon** with standard dosing.
- The risk of drug-induced liver injury can be greater with **concomitant administration of multiple medications that are potentially hepatotoxic**.
- Upon initiation of a hepatotoxic agent, **patients should be cautioned about the risks and counseled** to recognize signs and symptoms of liver dysfunction.
- For patients recovering from hepatic injury or with liver dysfunction, **close monitoring of liver function tests and appropriate dosing of potentially hepatotoxic agents** are warranted.

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Table 1

Classification of drug-induced liver injury and associated psychotropics

Pattern of liver injury	Psychotropic agent
Acute	
Hepatocellular (ALT >3 × upper limit of normal)	Bupropion Fluoxetine Nefazodone[a] Paroxetine Risperidone Sertraline Trazodone Valproic acid
Cholestatic (AP >2 × upper limit of normal, ALT/AP <2)	Chlorpromazine Phenothiazines Tricyclics
Mixed (↑AP and ALT)	Amitriptyline Carbamazepine Phenobarbital Phenytoin
Chronic	
Microvesicular steatosis	Valproic acid

[a]Brand discontinued in the United States

ALT: alanine aminotransferase; AP: alkaline phosphatase

Source: Adapted from Reference 3

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Among mood stabilizers, carbamazepine and valproic acid are associated with the highest incidence of hepatoxicity

VPA-induced liver injury occurs in approximately 1 in 37,000 persons taking the drug.[4] Patients at an increased risk of VPA-induced liver injury include:

- children
- patients with mitochondrial enzyme deficiencies
- Reye's syndrome
- Friedreich's ataxia
- polypharmacy patients
- patients with a sibling who has experienced VPA toxicity.[4]

Benign enzyme elevations occur in approximately 20% of patients taking VPA.[5] In Ms. R's case, concomitant VPA, clonazepam, and alcohol may have led to elevations in ALT, AST, and GGT. Her nausea, vomiting, and abdominal pain are consistent with hepatic dysfunction.

Carnitine is effective in increasing survival of patients with VPA-induced hepatotoxicity.[4] Because Ms. R is symptomatic, discontinuing VPA and administering IV L-carnitine is warranted.[5] L-carnitine can be initiated at 100 mg/kg as an IV bolus, followed by 50 mg/kg as an IV infusion every 8 hours, with a maximum dosage of 3,000 mg.[6] Patients may require several days of therapy based on symptoms. L-carnitine should be continued until a patient shows clinical improvement, such as decreases in ALT and AST.

Ms. R experienced a VPA-induced hepatotoxic reaction. However, continuous monitoring is appropriate for all patients who are prescribed any potentially hepatotoxic psychotropic, especially after hepatic injuries resolve. This includes mood stabilizers, antipsychotics, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors, especially when given concomitantly with other hepatotoxic agents.

Table 2 (***page 48***) lists dosing recommendations for commonly used psychotropics in patients with hepatic impairment. Among mood stabilizers, carbamazepine and VPA are associated with the highest incidence of hepatotoxicity.[2] A follow-up study of more than 1,000,000 VPA prescriptions found 29 cases of fatal hepatotoxicity in a 7-year period.[7] Although there are case

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SSRIs are relatively safe; among SSRIs, paroxetine is most frequently associated with hepatoxicity

Table 2

Dosage modifications of psychotropics in hepatic impairment

Class and drug	Dosage modification in hepatic impairment
ANTIDEPRESSANTS	
Amitriptyline	Use with caution. Use lower initial dosage and caution in titration
Bupropion	Severe cirrhosis: do not exceed 75 mg/d IR, 100 mg/d or 150 mg SR every other day, 150 mg XL every other day Reduce dosage or less frequent dosing in mild-to-moderate impairment
Citalopram	Do not exceed 20 mg/d
Desvenlafaxine	Do not exceed 100 mg/d
Duloxetine	Do not use with any degree of hepatic impairment
Escitalopram	Do not exceed 10 mg/d
Fluoxetine	Reduce dosage or use less frequent dosing in impairment
Nefazodone	Discontinue in hepatocellular injury or liver function tests >3 × the upper limit of normal
Nortriptyline	Initiate with caution in hepatic impairment
Paroxetine	Initiate: 10 mg/d (12.5 mg/d CR); do not exceed 40 mg/d (50 mg/d CR)
Sertraline	Reduce dosage or less frequent dosing in hepatic impairment
Trazodone	Dosage adjustment required based on severity of impairment
Venlafaxine	Dosage should be reduced by 50%; greater dosage reduction in patients with cirrhosis
MOOD STABILIZERS	
Carbamazepine	Not recommended in decompensated liver failure. Reduce dosage in stable hepatic disease. If hepatic damage occurs during treatment, consider discontinuation
Lamotrigine	Reduced dose by 25% moderate to severe hepatic impairment without ascites. Reduce dose by 50% in severe impairment with ascites
Oxcarbazepine	Mild or moderate: No dosage adjustment. Severe: Caution in use. Do not use XR
Topiramate	No guidelines available. Use with caution in hepatically impaired
Valproic acid	Clearance might be reduced. Guidelines on adjustment not available. Avoid use in active hepatic impairment
SECOND-GENERATION ANTIPSYCHOTICS	
Aripiprazole	No guidelines available. No dosage adjustment seems necessary
Asenapine	No adjustment for mild or moderate impairment. Avoid in severe hepatic impairment
Clozapine	Discontinue if symptoms of hepatic impairment develop during treatment
Iloperidone	Avoid use with any degree of impairment
Lurasidone	No adjustment for mild impairment. Moderate impairment: Initiate 20 mg/d, do not exceed 80 mg/d. Severe impairment: Initiate 20 mg/d, do not exceed 40 mg/d
Olanzapine	Lower initial dosage and careful titration
Quetiapine	IR: Initiate 25 mg, titrate by 25 to 50 mg/d; XR: initiate 50 mg, titrate by 50 mg/d
Risperidone	Initiate 0.5 mg twice a day, increase up to 0.5 mg twice a day. Increases >1.5 mg twice a day should only be done weekly
Ziprasidone	No dose adjustment recommended
FIRST-GENERATION ANTIPSYCHOTICS	
Fluphenazine	Phenothiazines are contraindicated with significant hepatic impairment
Haloperidol	Specific guidelines not available. Use with caution
Molindone	Specific guidelines not available. Use with caution. Lower dosage or avoid use
Perphenazine	Phenothiazines are contraindicated with significant hepatic impairment
Thiothixene	Specific guidelines not available. Discontinue if jaundice develops
Trifluoperazine	Phenothiazines are contraindicated with significant hepatic impairment

Source: Dosage modification suggestions adapted from Clinical Pharmacology. Tampa, FL: Gold Standard, Inc.; 2013. www.clinicalpharmacology.com

CR: controlled release; IR: immediate release; SR: sustained release; XR: extended release

reports of hepatotoxicity with oxcarbazepine, it may have a better liver safety profile than carbamazepine.[2] Hepatotoxicity with lamotrigine is rare, although fatal cases have been reported.[5]

When initiating an antipsychotic, a temporary, benign increase in liver enzymes can be expected, but typically discontinuation is unnecessary.[2] Phenothiazines in particular can cause increases in liver enzymes in 20% of patients.[2] Hepatotoxicity with benzodiazepines is infrequent, with a few cases of cholestatic injury reported with diazepam, chlordiazepoxide, and flurazepam.[2]

SSRIs are relatively safe; incidents of hepatic injury are rare. Among SSRIs, paroxetine is most frequently associated with hepatotoxicity. Abnormal liver function tests have been observed with fluoxetine (0.5% of long-term recipients) and other SSRIs.[1,2,4]

Among antidepressants with dual serotonergic action, nefazodone carries a black-box warning for hepatotoxicity and is used rarely, whereas trazodone is not regarded as hepatotoxic.[2] Antidepressants with dual norepinephrine and serotonin reuptake inhibitor properties carry a higher risk of liver injury, especially duloxetine. Hepatocellular, cholestatic, and mixed types of hepatotoxicity are associated with duloxetine-induced hepatotoxicity.[2]

Monitoring recommendations

Before prescribing potentially hepatotoxic medications, order baseline liver function tests. During therapy, periodic liver function monitoring is recommended. Elevated transaminase concentrations (>3 × the upper limit of normal), bilirubin (>2 × the upper limit of normal), and prolonged prothrombin times are indicators of hepatic injury.[2] Caution should be taken to prevent polypharmacy with multiple hepatotoxic medications and over-the-counter use of hepatotoxic drugs and supplements.

When choosing a psychotropic, take into account patient-specific factors, such as underlying liver disease and alcohol consumption. Patients on potentially hepatotoxic medications should be counseled to recognize and report symptoms of liver dysfunction, including nausea, vomiting, jaundice, and lower-extremity edema.[2] If liver injury occurs, modify therapy with the potential offending agent and check liver function periodically.

Related Resources

- Bleibel W, Kim S, D'Silva K, et al. Drug-induced liver injury: review article. Dig Dis Sci. 2007;52(10):2463-2471.
- U.S. National Library of Medicine. LiverTox. National Institute of Health. www.livertox.nih.gov.

Drug Brand Names

Amitriptyline • Elavil
Aripiprazole • Abilify
Asenapine • Saphris
Bupropion XL • Wellbutrin XL
Citalopram • Celexa
Carbamazepine • Tegretol
Chlordiazepoxide • Librium
Chlorpromazine • Thorazine
Clonazepam • Klonopin
Clozapine • Clozaril
Desvenlafaxine • Pristiq
Diazepam • Valium
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluphenazine • Prolixin
Flurazepam • Dalmane
Haloperidol • Haldol
Iloperidone • Fanapt
Lamotrigine • Lamictal
Levocarnitine • L-carnitine
Lurasidone • Latuda
Molindone • Moban
Nefazodone • Serzone
Nortriptyline • Pamelor
Olanzapine • Zyprexa
Oxcarbazepine • Trileptal
Paroxetine • Paxil
Perphenazine • Trilafon
Phenobarbital • Luminal
Phenytoin • Dilantin
Quetiapine • Seroquel
Risperidone • Risperdal
Sertraline • Zoloft
Thiothixene • Navane
Trazodone • Desyrel
Trifluoperazine • Stelazine
Topiramate • Topamax
Valproic acid • Depakote
Venlafaxine • Effexor
Ziprasidone • Geodon

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When choosing a psychotropic, take into account patient-specific factors, such as underlying liver disease and alcohol consumption

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