‘I’m sober, Doctor, really’: Best biomarkers for underreported alcohol use

When and how to use highly specific combinations to assess withdrawal risk

Hospitalized patients who are not truthful about their alcohol consumption may be at risk for an unplanned withdrawal. Self-reports of alcohol use—such as CAGE and the Alcohol Use Disorders Identification Test (AUDIT)—are valid, inexpensive, and noninvasive, but patients easily can feign results. Biochemical measures are more objective, and combinations of markers are an effective tool to detect recent heavy drinking in the 10% to 25% of patients who underreport alcohol use.

Biochemical measures can detect acute alcohol intoxication and recent prolonged drinking. Because marker levels return to normal after long-term abstinence, ongoing monitoring can help detect a relapse before a patient admits to it.

This article presents 3 cases in which biochemical markers helped prevent alcohol withdrawal in patients who denied alcohol abuse. We discuss why we ordered biochemical tests and which combinations provided highly sensitive results.

CASE 1
Depression and substance abuse
Ms. C, age 39, presents with bleeding gums due to excessive warfarin, which she takes prophylactically for a history of deep vein thrombosis. She is seen by the psychiatric consultation service for depression—which she says she has experienced since “the day I was born”—and substance abuse that includes a history binge drinking. Ms. C says she has stopped drinking and remained abstinent for the past year because she is fearful of further damaging her kidneys.

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She also denies psychosis. She does not have a history or symptoms of hepatobiliary or hematologic disease.

**Challenge.** Despite Ms. C’s self-reported 1 year of sobriety, her history of binge drinking and depression calls for evaluating her alcohol withdrawal risk. Laboratory markers of alcohol abuse are the only means to assess her recent drinking behavior.

**Discussion.** Lab results include serum albumin of 3.4 g/dL, total bilirubin of 0.3 mg/dL, total protein of 6.3 g/dL, aspartate aminotransferase (AST) of 13 U/L, alanine aminotransferase (ALT) of 19 U/L, alkaline phosphatase of 136 U/L, and blood ammonia level of 37 μg/dL. Gamma-glutamyl transferase (GGT) is elevated at 104 U/L (normal range for women: 0 to 45 U/L). Mean corpuscular volume (MCV) is elevated at 101 fL (normal range 80 to 100 fL).

The combination of elevated MCV and GGT has a 95% sensitivity for alcohol abuse. GGT levels become elevated after 24 hours to 2 weeks of heavy alcohol consumption and return to normal within 2 to 6 weeks of abstinence, which allows them to detect binge drinking. MCV takes 6 to 8 weeks of heavy drinking—we define as consuming ≥40 grams of alcohol/day—to become elevated and returns to normal within 3 months of abstinence.

These data provide evidence that Ms. C recently consumed substantial amounts of alcohol. As a result, we start her on alcohol withdrawal precautions (AWP).

**Markers of alcohol abuse**

Biochemical markers commonly used to detect alcohol abuse (*Table 1, page 19*) include:

- blood alcohol level (BAL)
- MCV
- liver function tests (LFTs) such as ALT, AST, and GGT
- carbohydrate deficient transferrin (CDT).

**BAL** can document acute alcohol intoxication, but its use is limited because alcohol has a 4-hour half-life and an elimination rate of 7 grams/hour—equivalent to 1 drink/hour. (A “drink” typically is defined as a 12-ounce bottle of beer or wine cooler, a 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled spirits.) Therefore, BAL will identify as false negatives alcohol-dependent patients who abstain from alcohol within 24 hours of testing.

**MCV** is an index of the average volume of erythrocytes. Macrocytosis occurs when the volume exceeds 100 fL. Elevated MCV is the most typical morphologic abnormality associated with excessive alcohol consumption and macrocytosis—sometimes without associated anemia—is often evident in persons with alcoholism. MCV elevates after 6 weeks of alcohol misuse and may remain elevated for up to 3 months after a person has stopped drinking.

Because patients with disorders unrelated to alcohol use can have elevated MCV, alone it is not a useful screening marker for alcohol abuse. Additionally, because macrocytosis can persist under strictly controlled alcohol abstinence, MCV is not a reliable clinical indicator of relapse.

**LFTs** measure enzymes and proteins. ALT, AST, and GGT are the most relevant for detecting heavy drinking. An AST:ALT ratio >2:1 supports a suspicion of alcohol abuse. More than 90% of patients with an AST:ALT ratio of 2:1 have alcoholic liver disease. This increases to more than 96% if the ratio is 3:1.

GGT is an enzyme concentrated in the liver, bile ducts, and kidneys; normal range is 0 to 45 U/L (for females) or 53 U/L (for males). GGT levels >30 U/L correlate with alcohol consumption of >4 drinks per day. GGT has a half-life of 14 to 26 days and remains elevated for 4 to 6 weeks after drinking cessation, which make it useful for monitoring abstinence in treatment programs. Sensitivity ranges from 37% to 85% and specificity is as high as 93% in...
By the numbers: Biomarkers of excessive alcohol consumption

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>CDT</th>
<th>GGT</th>
<th>AST</th>
<th>ALT</th>
<th>MCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood test normal range</td>
<td>&lt;60 mg/L</td>
<td>Women: 0 to 45 U/L</td>
<td>10 to 34 U/L</td>
<td>8 to 37 U/L</td>
<td>80 to 100 fL</td>
</tr>
<tr>
<td>Blood test abnormal range</td>
<td>&gt;1.3% of total transferrin concentration</td>
<td>Levels rarely exceed 500 U/L</td>
<td>Levels rarely exceed 300 U/L</td>
<td>&gt;100 fL</td>
<td></td>
</tr>
<tr>
<td>Time to elevation</td>
<td>2 to 3 weeks</td>
<td>24 hours to 2 weeks</td>
<td>3 to 7 days</td>
<td>3 to 7 days</td>
<td>After 6 weeks</td>
</tr>
<tr>
<td>Time to descent to normal levels</td>
<td>2 to 4 weeks of abstinence</td>
<td>2 to 6 weeks of abstinence</td>
<td>Half-life 12 to 24 hours</td>
<td>Half-life 37 to 57 hours</td>
<td>3 months</td>
</tr>
<tr>
<td>Dose-response of alcohol</td>
<td>60 g/d</td>
<td>80 to 200 g/d</td>
<td>&gt;40 g/d</td>
<td>&gt;40 g/d</td>
<td>&gt;40 g/d</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>55% to 90%</td>
<td>37% to 85%</td>
<td>AST:ALT ratio &gt;2:1 has a 70% sensitivity and 92% to 100% specificity for alcoholic-induced liver disease</td>
<td>20% to 70%</td>
<td></td>
</tr>
<tr>
<td>Relapse sensitivity</td>
<td>55% to 76%</td>
<td>50%</td>
<td>AST:ALT ratio &gt;2:1 has a 70% sensitivity and 92% to 100% specificity for alcoholic-induced liver disease</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>92% to 97%</td>
<td>18% to 93%</td>
<td>AST:ALT ratio &gt;2:1 has a 70% sensitivity and 92% to 100% specificity for alcoholic-induced liver disease</td>
<td>64% to 66%</td>
<td></td>
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<tr>
<td>Positive predictive value</td>
<td>46% to 75%</td>
<td>41%</td>
<td>AST:ALT ratio &gt;2:1 has a 70% sensitivity and 92% to 100% specificity for alcoholic-induced liver disease</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>72% to 98%</td>
<td>69% to 92%</td>
<td>AST:ALT ratio &gt;2:1 has a 70% sensitivity and 92% to 100% specificity for alcoholic-induced liver disease</td>
<td>67%</td>
<td></td>
</tr>
</tbody>
</table>

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CDT: carbohydrate deficient transferrin; GGT: gamma-glutamyl transferase; MCV: mean corpuscular volume

Source: For reference citations, see this article on CurrentPsychiatry.com

Clinical Point
Gamma-glutamyl transferase levels >30 U/L reflect alcohol consumption of >4 drinks per day

nonmedical populations. Although non-alcoholic liver disease can elevate GGT in persons who do not abuse alcohol, 50% to 72% of GGT elevations can be explained by excessive alcohol consumption.

CDT is a newer biomarker used to monitor alcohol consumption. The most accurate way to express CDT level is as a percentage of total transferrin concentration. This method accounts for individual variations in transferrin levels, thus minimizing false positives. In persons who consume >4 or 5 drinks per day for 2 weeks or more, CDT is >1.3% of total transferrin. Unfortunately, because it is expensive and requires sophisticated test methodology, CDT testing is not available at most hospitals.

Combinations improve detection
Each biochemical measure has strengths and weaknesses as a marker for determining patients’ alcohol consumption (Table 2, page 20). CDT and GGT show the highest sensitivity for heavy drinking, and CDT has a higher specificity than GGT (Table 3, page 21). Relapse to alcohol use after abstinence may be best identified by a simultaneous 30% increase in CDT and GGT.

Because GGT has a longer half-life than CDT, its diagnostic efficiency in detecting alcohol relapse may not develop until 4 weeks after alcohol detoxification, whereas CDT may become clinically useful for detecting relapse as early as 1 week after detoxification.
**Table 2**

Biomarkers of alcohol use: Strengths and weaknesses

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tbody>
<tr>
<td>CDT</td>
<td>High specificity for alcohol use; few factors cause false positives</td>
<td>Low sensitivity; more valuable to confirm than exclude heavy drinking</td>
</tr>
<tr>
<td></td>
<td>High sensitivity in distinguishing alcoholics from social drinkers</td>
<td>Cost (average $30/assay) and low availability of testing</td>
</tr>
<tr>
<td></td>
<td>Marker of relapse and abstinence from drinking</td>
<td>Likely less sensitive for women and younger patients compared with men</td>
</tr>
<tr>
<td></td>
<td>Confirmatory test for patients suspected of alcohol abuse</td>
<td>Poor screening tool for alcohol use in general population</td>
</tr>
<tr>
<td>GGT</td>
<td>Elevations precede alcohol-induced liver damage</td>
<td>Can be falsely elevated by liver and biliary disease, smoking, obesity, and medications that</td>
</tr>
<tr>
<td></td>
<td>High sensitivity in patients with suspected alcohol abuse</td>
<td>induce microsomal enzymes</td>
</tr>
<tr>
<td></td>
<td>Effective marker for patients suspected of binge drinking</td>
<td>Low sensitivity makes it a poor screening tool in general population</td>
</tr>
<tr>
<td></td>
<td>Inexpensive (&lt;$10)</td>
<td>Poor marker of relapse</td>
</tr>
<tr>
<td>AST/ALT &gt;2:1</td>
<td>Highly sensitive and specific for alcohol-induced liver damage</td>
<td>Enzyme elevations can be detected only after periods of heavy drinking</td>
</tr>
<tr>
<td></td>
<td>E elevations secondary to liver damage at the hepatocellular level (after</td>
<td></td>
</tr>
<tr>
<td></td>
<td>alcoholic changes)</td>
<td></td>
</tr>
<tr>
<td>MCV</td>
<td>Accuracy similar in male and female patients</td>
<td>Poor biomarker for relapse</td>
</tr>
<tr>
<td></td>
<td>Elevations in suspected cases of alcohol use indicate chronicity of drinking</td>
<td>False positives caused by liver disease, hemolysis, bleeding disorders, anemia, folate</td>
</tr>
<tr>
<td></td>
<td>Routine laboratory test</td>
<td>deficiency, and medications that reduce folate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low sensitivity and specificity for alcohol use make it a poor screening tool for alcohol</td>
</tr>
</tbody>
</table>

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CDT: carbohydrate deficient transferrin; GGT: gamma-glutamyl transferase; MCV: mean corpuscular volume

There is evidence that combining tests can improve alcohol use detection. For example, Dolman et al found that the ability of the AUDIT questionnaire to correctly predict which patients would experience alcohol withdrawal increases when it is used in combination with biochemical markers. Specifically, the positive predictive value of an AUDIT score ≥8 increased from 17% to 47% when found in combination with ≥2 abnormal biochemical marker levels; the study looked at GGT, ALT, AST, and MCV. Sensitivity was 94% and specificity was 98%.

Similarly, combinations of biochemical markers—especially CDT and GGT—have improved detection of alcohol use and subsequent risk of withdrawal. Table 4 provides a summary of studies that evaluated using combinations of biochemical markers.  

**Consider patients’ comorbidities**

Patients at risk for underreporting alcohol use include those with unemployment histories, previous alcohol treatment, and higher scores on the Alcohol Dependence Scale (18.5, SD=8.1). Interpret biochemical testing results in the context of a patient’s overall clinical picture.

The following 2 case patients denied or underreported recent alcohol use but we determined they were at high risk for an alcohol disorder because of their medical and/or psychiatric histories. Analysis of biochemical markers helped assess the risk of alcohol withdrawal.

**CASE 2**

**Altered mental status**

Family members bring Mr. N, age 44, to the hospital because of his odd behavior. He presents with paranoid delusions and an
inappropriate elated mood. His medical history includes acquired immune deficiency syndrome (AIDS). After cerebrospinal fluid analysis, computed tomography of the head, electroencephalogram, and metabolic work-up are within normal limits, the patient is diagnosed with human immunodeficiency virus (HIV) mania and is admitted.

On admission, Mr. N denies alcohol use. A blood alcohol/urine toxicity screen is negative. One day after admission, Mr. M develops elevated blood pressure and tachycardia and reports headache and nausea.

**Challenge.** Gathering a valid history of Mr. N’s alcohol use is difficult because of his acutely altered mental status and manic-like state. We use laboratory data to assess his risk of alcohol withdrawal. His liver function tests include an AST of 33 U/L, ALT of 30 U/L, and an alkaline phosphatase of 94 U/L. MCV is normal at 90 fL. Interestingly, the GGT level is elevated almost 4 times normal at 164 U/L.

**Discussion.** Although Mr. N denied alcohol use and presented with a negative BAL, laboratory data support alcohol dependence. His GGT was elevated well beyond normal limits, without evidence of hepatobiliary disease. GGT has a sensitivity as high as 85%\(^\text{12}\) and limited specificity for alcohol abuse. Be-
cause of his high probability of recent alcohol consumption, we place Mr. N on AWP.

We postulate that our patient’s autonomic instability, headache, and nausea are related to alcohol withdrawal. We are aware that delirium occurs frequently in patients with HIV infection, and although Mr. N’s medical workup is negative, HIV infection can produce an acute encephalopathy that could resemble our patient’s clinical picture.  

Mr. N’s autonomic instability, headache, and nausea abated after treatment for alcohol withdrawal.

**CASE 3**  
**Suicide attempt?**

Mr. S, age 28, presents to the trauma service with a self-inflicted gunshot wound to the face. He reports feeling depressed for the last year but denies a history of psychotic symptoms or heroin withdrawal symptoms. He also denies recent or past alcohol abuse and does not have a history of biliary tract disease or megaloblastic anemia. His mother tells us Mr. S has had a history of depression since childhood.

**Challenge.** Based on Mr. S’s apparent suicide attempt and history, we feel he is at high risk for alcohol abuse. We use laboratory markers to assess the likelihood of alcohol consumption and possibly decrease his risk of alcohol withdrawal.

**Discussion.** Mr. S’s lab data show an MCV of 91 fL, AST of 95 U/L, alanine ALT of 156 U/L, and alkaline phosphatase of 160 U/L. GGT was elevated at 122 U/L.

Although Mr. S’s MCV is within the normal range, his GGT is elevated, and the combination of an elevated GGT and MCV has a 95% sensitivity for the diagnosis of alcohol abuse. We place Mr. S on alcohol withdrawal precautions and discuss with him the potential life-threatening complications of alcohol withdrawal. Confronted with this information and the possible implication of his elevated LFTs, the patient admits his alcohol history—which consists of drinking 12 beers/day for at least the past 2 years. He admits this despite exhibiting no signs or symptoms of alcohol withdrawal.

**References**


**Bottom Line**

Because CDT—the most accurate biomarker—is not available at most hospitals, we recommend using combinations of other measures to detect unreported recent alcohol consumption. If GGT and MCV are elevated, GGT is elevated and AST:ALT is >2:1, or MCV is elevated and AST:ALT is >2:1, consider initiating alcohol withdrawal precautions.
Multiple Sclerosis (MS), Aspirin, and Warfarin—Serotonin release by platelets plays an important role in hemostasis. Observational studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interact with serotonin receptors and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Anticoagulant effects, including increased bleeding, have been reported when SSRI s and SNRs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. Ethanol—A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, with all OTC-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. Potential for other Drugs to Affect Desvenlafaxine—Inhibitors of CYP3A4 (atorvastatin, clarithromycin, diltiazem, itraconazole, ketoconazole, nefazodone, nelfinavir, protease inhibitors, quinidine, ritonavir, tetracycline, and verapamil) have been shown to increase the exposure to desvenlafaxine. This effect may lead to increased risk of adverse reactions associated with desvenlafaxine. Conversely, use of Pristiq with potent CYP3A4 inducers (rifampin, rifabutin, St. John’s Wort) may result in lower concentrations of CYP3A4 inhibitors; this effect may lead to decreased risk of adverse reactions associated with desvenlafaxine. This effect may be further mitigated if desvenlafaxine is coadministered with CYP3A4 inducers. Elderly—Pristiq metabolism is reduced in elderly individuals. In a study of 24 elderly patients, elderly patients had lower plasma concentrations of desvenlafaxine compared to young patients. Pregnancy—Pristiq is not a substrate or an inhibitor of the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. Electrocoagulation Therapy—There are no clinical data establishing the risks and benefits of electrocoagulation therapy combined with Pristiq treatment.

MME IN SPECIFIC POPULATIONS—Pregnancy—Patients should be advised to notify their physician if they become pregnant or intend to become pregnant. Pregnancy Category C. Children—The safety and effectiveness of Pristiq are unknown in children. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. Nursing Mothers—Desvenlafaxine is an inhibitor of CYP2D6, a hepatic enzyme. It should be noted that in some cases, the clinical picture is consistent with serotonin syndrome (hypertension and incontinence). During treatment with Pristiq during the third trimester, the physician should consider the potential risks and benefits of treatment (see Dosage and Administration (2.3). Labor and Delivery—The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. Medication/Drug Interactions—Serotonin syndrome has been reported with the use of MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) in combination with Pristiq. Therefore, patients should be monitored closely for concomitant use of serotonergic agents (e.g., pravastatin) with desvenlafaxine.

Overview—In a study of 24 elderly patients, elderly patients had lower plasma concentrations of desvenlafaxine compared to young patients. Elderly patients may be more sensitive to the effects of Pristiq. The potential for drug interactions with Pristiq was demonstrated in a study of healthy volunteers. The pharmacokinetics of Pristiq were not significantly different between healthy young volunteers and elderly volunteers. However, the exposure to Pristiq was higher in elderly patients compared to young patients.

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Related Resources

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