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LEARNING OBJECTIVES

Upon completion of this article, the reader will be able to:

1. Identify five biomarkers for measuring alcohol consumption.
2. Describe laboratory procedures for each of the biomarkers.
3. Compare the diagnostic performance of CDT, EDAC, WBAA, EtG, and FAEE.
4. Describe the clinical benefit related to each of the alcohol biomarkers.

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State of the art: contemporary biomarkers of alcohol consumption

By Pamela Bean, PhD, MBA

The new century is experiencing an expansive boost in the area of alcohol-abuse diagnosis. New laboratory tools are emerging that show better performance than traditional biomarkers for the detection and monitoring of excessive drinking. Blood alcohol levels, while accurate for identifying acute drinking, do not provide information about long-term alcohol use and are helpful only within narrow time frames. The ineffectiveness of mean corpuscular volume, or MCV; gamma-glutamyl transferase (GGT); and other liver-enzyme tests in screening for excessive alcohol consumption in medical patients has been recognized for many years, despite the wide use of these tests in medical practice. Sensitivity and/or specificity rates are far too low to propose their systematic use as screening tests in unselected medical patients. These new biomarkers are more specific and have longer half-lives than traditional biomarkers. They are also able to detect different drinking behaviors, such as binges and sustained heavy drinking.

There are indirect and direct biomarkers to detect alcohol use. Indirect biomarkers reflect the effects of alcohol in the body. GGT is a classical example of an indirect biomarker. Direct markers are ethanol itself and all the products of its metabolism. A typical example of this class of biomarkers is ethanol concentrations in the body.

The most widely used indirect biomarkers in the United States are carbohydrate-deficient transferrin (CDT) and the early detection of alcohol consumption (EDAC) test. Three direct biomarkers are also available in different stages of development: whole-blood-associated acetaldehyde (WBAA), ethyl glucuronide (EtG), and fatty acid ethyl esters (FAEE). This article summarizes the technology behind these five biomarkers and compares their diagnostic performance and clinical benefit.

Biomarker #1: CDT

CDT was discovered in Europe in the late 1970s, but it was not until the early 1990s that the first commercial CDT test became available in the United States.¹ Heavy alcohol consumption, defined as more than 60 grams of ethanol (five beers, five glasses of wine, or four mixed drinks) per day for seven to 10 consecutive days, causes hepatocytes to start producing molecules of transferrin that are deficient in carbohydrates,² hence the term carbohydrate-deficient transferrin. The mechanism for this elevation is still not understood; but, most likely, it represents the effects of both increased trimming of carbohydrates in serum and abnormal synthesis of carbohydrates by enzymes in the hepatocyte.³ CDT changes are reversible within two to three weeks of alcohol abstinence.² For the last 15 years, hundreds of studies have described the diagnostic performance of CDT.

Undoubtedly, CDT's major asset is its high specificity.

Laboratory procedures for CDT: Several CDT assays have been developed around the world, from the time-consuming isoelectric focusing procedure — considered the “gold standard” in the mid-1990s — to sophisticated in-house methods [i.e., high-performance liquid chromatography (HPLC) and gas chromatography followed by mass spectrometry], and from the pioneer ion exchange chromatography procedures that separate CDT in minicolumns to recent direct enzyme immunoassays that use monoclonal antibodies against CDT.

CDT received approval as a test from the U.S. Food and Drug Administration (FDA) in 1999 with a kit called %CDT Turbidimetric Immunoassay.⁴ This year, the FDA approved a second CDT kit — the CAPILLARYS CDT test — which uses capillary electrophoresis and represents the latest breakthrough in CDT testing. This test is more automated than previous CDT tests; it has better capacity to identify false-positives; and it is the largest volume test being used in the United States today.⁵

Diagnostic performance of CDT: Several hundred publications in the last decade have helped our understanding of the diagnostic performance of CDT in several populations. Undoubtedly, CDT's major asset is its high specificity. Hypertension, asthma, diabetes, abnormal lipid metabolism, depression, and disorders of the digestive tract do not influence the specificity of the CDT test; neither do the accompanying prescribed drugs.⁶ There are a few nonalcohol-related medical conditions that will render a false-positive CDT result: genetic D variants of transferrin, the carbohydrate-deficient glycoprotein syndromes, chronic viral hepatitis, and end-stage liver disease.⁷

The sensitivity of the CDT test in detecting heavy drinkers depends on several parameters: amount of alcohol consumed, extent of the drinking behavior, time of sample collection after cessation of drinking, age, and gender. For instance, CDT is a

good tool for detecting chronic heavy drinkers, but it has low sensitivity when detecting binge drinkers. Even though a wide range of sensitivities (39% to 94%) is reported in various populations, CDT performs best in middle-age Caucasian males, and it shows better sensitivity in males than in females.⁸ Its low sensitivity in females has been explained by changes in both estrogen and iron status.⁹ Currently, the best option to detect heavy-drinking females is to use a combination of different tests. Indeed, the combined use of GGT and CDT in women increases the sensitivity to detect alcohol consumption from 40% to 72%.⁸ A large multisite study also shows that when these two markers were combined, sensitivity was increased for males and females.¹⁰

In general, the use of CDT to screen the general population for heavy drinking has shown less than optimal results. In other words, CDT determinations are more valuable to confirm rather than to exclude heavy drinking. A recent study in primary care suggests that brief intervention, when combined with feedback on CDT levels, can reduce alcohol use in diabetes and hypertension patients.¹¹ Abnormal high density lipoprotein (HDL) cholesterol concentrations should also alert clinicians to investigate a patient's recent pattern of alcohol consumption because in actively drinking males HDL and CDT are highly correlated.¹²

Benefits of the CDT test in clinical practice: The CDT test has been used successfully in three main areas: 1) confirming a suspicion of alcohol abuse in insurance applicants, 2) monitoring abstinence and relapses in patients undergoing treatment for alcohol dependence, and 3) traffic medicine.

To confirm a suspicion of heavy drinking, one-third of national insurance companies use CDT as a reflex test. Reflex testing is effective in detecting heavy drinkers because it is only done when there is already a significant suspicion of alcohol abuse. A comprehensive study¹³ in over 50,000 insurance applicants showed best performance when CDT was used as a reflex test from an increased HDL result. This study also showed that a significant number of heavy drinkers with elevated GGT levels will have normal CDT results, suggesting better confirmation rates when reflexing to CDT from an elevated HDL than from an elevated GGT. More recently, a few insurance companies have begun using the EDAC test as a screen before reflexing to CDT.

Monitoring abstinence and relapses requires measuring CDT over time to record the changes in %CDT between follow-up periods. For instance, a 30% decrease from the CDT value measured at the start of alcohol treatment is indicative of abstinence. In contrast, a 30% increase from the CDT value measured after three weeks of abstinence is indicative of relapse. Many studies describe a positive treatment outcome supported by the general reduction of CDT during the treatment period, especially when used in conjunction with GGT. In fact, the most recent multisite study¹⁰ showed that CDT and GGT both decreased during four weeks of abstinence, but CDT appeared marginally better than GGT at indicating relapse in men (but not in women). Similarly, CDT has proven useful to monitor relapses in patients who have undergone orthotopic liver transplantation due to alcoholic cirrhosis.¹⁴

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A strongly developing area in Europe, traffic medicine, consists of using the CDT test and other biomarkers to monitor the drinking of convicted drunken drivers. Seven countries in Europe use biomarkers routinely as part of the clinical evaluation for drunk drivers and to assess if the person is abstaining. For example, in Switzerland, Italy, and Austria, repeat offenders are sent to therapy where biological markers, including CDT, are measured every quarter for an entire year to monitor alcohol abstinence. After one year, if treatment is successful and biomarkers are kept in check, the driver's license is reinstated.



Biomarker #2: EDAC

The use of routine tests panels for the diagnosis of heavy drinking started in the 1980s when several statistical methods were used to analyze a variety of routine blood-chemistry panels.¹⁵ Most of these methods rendered highly accurate sensitivity and specificity rates; but, despite some early promise, computing costs at that time made this type of statistical analysis impractical for mainstream use. It was not until 1991 that a similar method emerged when Dr. James Harasymiw developed a linear discriminant function equation to detect heavy drinkers in different clinical settings. He obtained alcohol-consumption data and examined blood chemistries from close to 2,000 heavy drinkers and light drinkers recruited from multiple sites in the United States. His analysis was more refined than previous statistical methods because he separated subjects based on ethnicity, gender, and age.¹⁶ His method — known as the early detection of alcohol consumption test — is currently being used to screen, diagnose, and monitor heavy drinking.

The EDAC test detects heavy drinkers through the use of standard panels of routine laboratory tests.

Technical description of the EDAC test: The EDAC test detects heavy drinkers through the use of standard panels of routine laboratory tests. Two main panels have been used: the preferred panel, which contains 16 routine chemistry and hematology analytes chosen by stepwise analysis¹⁷ and the insurance-industry panel, which contains 12 routine tests, mainly chemistry analytes.¹⁸ All the laboratory tests used to calculate the EDAC are FDA-approved and reimbursement for testing can be obtained by using a specific CPT code.

To calculate the EDAC, the results of these laboratory tests are first entered into a spreadsheet, and then a simple statistical analysis is performed. This analysis is a statistical model of predictions, which uses the routine laboratory tests to construct a customized “fingerprint” for each subject.^{16,17} This “fingerprint” is a representation of how closely the pattern of routine laboratory tests obtained from any given subject resembles stereotype “fingerprints” previously developed from either light drinkers or heavy drinkers. The probability that an individual's “fingerprint” corresponds to that of a heavy

drinker is referred to as P-positive. Values above 50% suggest that the routine test profile of the individual resembles the stereotype of a current heavy drinker and values at or below 50% P-positive suggest light drinking. In general, the higher the P-positive, the higher the probability the individual has been drinking.

Diagnostic performance of the EDAC test: The sensitivity and specificity rates of the EDAC have been described in several publications.¹⁶⁻¹⁹ Sensitivity ranges from 66% to 88% in populations of heavy drinkers, and the specificity fluctuates around 85% to 98%, depending on the age and gender of the subject being tested. The EDAC identifies binge drinking as well as a more steady, daily consumption of alcohol; most males consuming at least two ounces of alcohol per day (one ounce equals two standard drinks) and women consuming at least 1.5 ounces of alcohol per day can be identified after two weeks of drinking. Optimal performance is found when testing is done within the first five days of a drinking episode. The EDAC, however, can also often detect heavy drinkers for up to 10 days — and some individuals for more than a month — after cessation of drinking. Older chronic drinking males are detected with the highest sensitivity rate (87%), whereas young females are detected with the lowest sensitivity rate (80%).

Benefits of the EDAC test in clinical practice: The EDAC has been used in three main areas: 1) detection of at-risk and heavy drinking, 2) screening for alcohol abuse in insurance applicants, and 3) monitoring abstinence and relapses in patients undergoing treatment for alcohol abuse or dependence.

A pioneer study¹⁹ determined the performance of the EDAC alone or combined with the CDT test to detect heavy drinking in a large population of males. When used alone, the EDAC showed a sensitivity rate of 88% and 98% specificity, whereas the CDT test showed a sensitivity rate of 58% at a corresponding 96% specificity. When the EDAC was used as a screen and the CDT was used only to confirm a positive EDAC, the combination eliminated all false-positives. This study indicated that the EDAC and CDT tests react independently to alcohol intake, and they can be combined for maximum diagnostic accuracy.

A recent report describes the use of the EDAC as a tool to screen nearly 6,000 insurance applicants for heavy drinking and compares the results to those obtained with liver enzymes.¹⁸ Those applicants who screened positive by either the traditional liver enzymes or with the newer EDAC approach were submitted to confirmatory testing using the CDT test. The results showed that more than twice (14%) as many applicants screened positive by the traditional method compared to the EDAC approach (6%). More important, the results also showed that there was a fivefold increase in the percentage (15%) of positive EDAC tests confirmed with the CDT test compared to the traditional approach (3%). These results implied that the EDAC test is more specific than the liver-enzymes tests, and also suggest that the use of the EDAC combined with the CDT test represent an optimal strategy to identify heavy drinking in insurance applicants. The strength of the EDAC test resides in its capacity to weigh the contribution of several routine tests, avoiding the selection bias that occurs

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when screening is based solely on a single abnormal test. This new EDAC-CDT combination has been shown to render enhanced identification, improved risk selection, and significant costs savings compared to the traditional approach.

Several hundred patients undergoing treatment for alcohol dependence have been monitored in the United States and Canada using the EDAC test alone or in combination with other biomarkers. The newest report²⁰ describes several case studies illustrating the use of the EDAC in three different scenarios: 1) to detect full-blown relapse episodes, 2) to monitor long-term abstinence during outpatient treatment, and 3) to recognize a slip early enough to avoid a more severe drinking episode. In both these reports, the key feature for treatment providers was the fact that the EDAC helped them to verify patient self-reporting and to improve treatment.



Biomarker #3: WBAA

Acetaldehyde is the first degradation product of alcohol metabolism. After alcohol ingestion, acetaldehyde stays free in plasma as a short-lived compound and binds to hemoglobin to form stable protein-acetaldehyde adducts. The combination of free and protein-bound acetaldehyde is referred to as whole-blood-associated acetaldehyde. Healthy volunteers ingesting moderate amounts of alcohol show free acetaldehyde concentrations that peak 30 minutes after the last drink with levels returning to baseline by 3.5 hours. The hemoglobin-associated acetaldehyde remains elevated for approximately a month.²¹

Human studies have demonstrated that following ethanol ingestion, acetaldehyde concentrations peak in blood in parallel with ethanol. Thus, an isolated elevated level of whole-blood acetaldehyde might be expected prior to an elevation in the other markers that reflect tissue damage from ethanol exposure. It is also widely hypothesized that WBAA measurement has the potential of being an integrating marker of alcohol abuse that sums up the extent of exposure to alcohol over a long time frame, such as several weeks. These combined studies suggest that WBAA is a marker of both acute and chronic drinking. In fact, measurements of increased acetaldehyde-adduct formation have been reported since the late 1980s to distinguish between drinkers and nondrinkers.

The use of biomarkers to detect and monitor alcohol consumption is an important and expanding part of medical practice.

WBAA is measured on a specimen of whole blood preserved in EDTA; serum, plasma, and tissue samples can be analyzed as well. The only high-performance liquid chromatography procedure to measure whole-blood acetaldehyde in the United States is available exclusively through Primus Corp. (Kansas City, MO). The assay relies on the reaction of free or the liberation of bound acetaldehyde in the presence of heat to

form a fluorophore that can be separated from other reacted aliphatic aldehydes on a carbon column.²² The total run time is four minutes, and the analytical sensitivity is in the picomole range; inter- and intra-assay precision is less than 3.5%. The main challenge for this test is its potential to produce false-positives due to the formation of acetaldehyde in blood after sample collection. Ethanol conversion to acetaldehyde in the red blood cell has been shown to occur in the presence of oxy-hemoglobin acting as an alcohol dehydrogenase.²³ This means that precautions are necessary for those individuals who have ingested significant amounts of alcohol in the eight-to-12-hour period prior to obtaining the specimen. When an extremely high value is obtained in the laboratory, the specimen should be tested again the following day and the tests' results compared for reproducibility.

The WBAA test has been used successfully in several areas: 1) to confirm a suspicion of heavy drinkers in insurance applicants¹³ and 2) to document differences in response by genotype in Asian-American subjects given an alcohol challenge.²⁴ In addition, the results of a large study estimating ethanol consumption by university students attending a student-health facility show that men had higher absolute values for WBAA than women. Significantly greater numbers of women (74%) than men (44%), however, had WBAA levels above the 99th percentile for teetotalers.²⁵ Overall, measures of acetaldehyde-protein adducts provide a potential means by which drinking behavior might be quantified in a manner analogous to the use of glycosylated hemoglobin assays in diabetes mellitus.



Biomarker #4: EtG

Almost 98% of ingested alcohol is eliminated through the liver in an oxidation process that involves its conversion to acetaldehyde and acetic acid; most of the rest is eliminated through the urine, sweat, or breath. A small fraction (0.5%) is conjugated with glucuronic acid to form a nonvolatile, water-soluble metabolite called ethyl glucuronate. Formation of EtG is dependent on the presence of circulating ethanol, which peaks approximately three hours after the peak in ethanol concentration.²⁶ Since EtG shows much longer elimination times than ethanol itself, a positive EtG result provides a strong indication of recent alcohol consumption, even when the ethanol concentration is no longer measurable in the body.²⁷ In fact, ethyl glucuronide may be present in urine samples for up to five days after heavy drinking. EtG has also been measured in serum, body tissues, and hair.

Serum and urine ethyl glucuronide have been isolated by liquid-liquid extraction and recently by solid-phase extraction techniques.²⁸ The metabolite has typically been quantified by gas chromatography-mass spectrometry (GC-MS) as well as by liquid chromatography/mass spectrometry-mass spectrometry (LC/MS-MS); limits of detection range between 0.03 mg/L to 0.05 mg/L. There is also a more recent enzyme immunoassay (ELISA), which uses polyclonal antibodies for determination of EtG in serum and urine.²⁹ Specificity for this ELISA is 92%

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for serum and 77% for urine; sensitivity is 91% for serum and 76% for urine.

Several publications over the past decade have compared EtG concentrations in the urine of alcoholics with no alcoholic controls. The most recent study³⁰ described its diagnostic performance in more than 400 patients and used a receiver operating characteristic curve analysis to distinguish between non-drinkers and individuals sober for more than four days versus individuals drinking in the recent four days. Using a cutoff of 0.145 mg/L, sensitivity was 84% and specificity 68%. For those with a self-reported sobriety of less than 24 hours, sensitivity was 91%, and specificity was 77%. Using regression analysis, this study shows that age, gender, marijuana use, kidney disease, and total grams of alcohol consumed 30 days before sample collection are the variables that most significantly influenced EtG levels. Another recent report warns that urinary-tract infections may lead to false-negative EtG results.³¹ Regarding sample storage, when urine is stored at 4°C in airtight tubes, EtG concentrations remain relatively constant, but storage of ventilated vials at room temperature for five weeks results in an average of 37% increase in EtG.³²

In clinical practice, EtG is currently being used to identify alcohol use in impaired health professionals.³³ Physicians Health Programs in the United States are using this test in three primary ways: 1) for 'for-cause' testing, when there is credible suspicion of alcohol use, 2) to confirm a positive urine alcohol test when alcohol use is denied, and 3) to monitor for relapses to alcohol during follow-up. The use of EtG alone or as a complement with self-report is expected to lead to significant improvements in treatment outcome.



Biomarker #5: FAEE

Ethanol is metabolized via oxidative and nonoxidative pathways. While the predominant oxidative pathway results in the formation of acetaldehyde, one of the nonoxidative pathways results in the production of fatty acid ethyl esters. The enzymatic formation of FAEE after alcohol consumption was first discovered in 1981; and, since then, research has shown the presence of FAEE in many biological tissues and fluids, including blood, various post-mortem specimens, meconium (for the determination of fetal alcohol exposure), and hair. In serum and blood, FAEE can be detected up to 24 hours after drinking. Esters, however, are not stable in blood samples due to continued enzyme activity but are incorporated into hair and can be analyzed in this medium even after several months. In fact, the detection of four esters in hair has been reported to differentiate between alcoholics and teetotalers with a high degree of accuracy.³⁴ Using a cutoff of 0.46 ng/mg, sensitivity was 94% at 90% specificity. This pioneering procedure, however, was time-consuming and involved extensive solvent extraction, followed by headspace gas chromatography and electron impact mass spectrometry. A newer and faster procedure was recently developed to detect and monitor alcohol consumption using a more efficient and rapid extraction for a much wider range of FAEEs.

Analysis of FAEE concentrations in adipose tissue is also useful in determining alcohol intake. In fact, since the estimated half-life of FAEEs in adipose tissue (16 hours) is significantly greater than that of alcohol itself (four hours), the presence of measurable concentrations of FAEEs in adipose tissue represents a valuable marker for previous alcohol use.³⁵ Interestingly, the composition of FAEEs is tissue-specific with different fatty acids present in FAEEs from blood, liver, pancreas, and adipose tissues. The levels of a particular fatty acid also vary according to the frequency of alcohol consumed. For example, levels of ethyl oleate are higher in chronic alcoholics versus binge drinkers, thus providing a marker that could be used to differentiate distinct patterns of alcohol abuse.³⁶

Conclusions

The use of biomarkers to detect and monitor alcohol consumption is an important and expanding part of medical practice. Indirect markers, such as CDT and the EDAC, have been studied more extensively and are well established as indicators of heavy alcohol consumption. These two biomarkers — when used in combination — show improved diagnostic accuracy compared to either one used alone. Direct markers are in the earlier stages of development and show promise because they provide additional information on different patterns of drinking. Laboratorians could play an important role in this field by learning how to use and combine these laboratory tests for optimal clinical benefit. □

Pamela Bean, PhD, MBA, is executive director of Research at Rogers Memorial Hospital in Oconomowoc, WI, and main partner at Millennium Strategies in Madison, WI.

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OTC and Rx drugs require rapid screen in overdose

By Robin Bramson

Acetaminophen [paracetamol or n-acetyl-p-aminophenol (APAP)] — a common over-the-counter (OTC) analgesic — is found in more than 100 common OTC prescription products. Additionally, in 2003, more than 144 million prescriptions were written in the United States for other drugs containing acetaminophen.

When used according to labeling instructions, acetaminophen has an excellent safety profile; however, acetaminophen toxicity may occur after intentional overdose or acute ingestion of approximately 150 mg to 250 mg of acetaminophen per kilogram of body weight — the equivalent of 15 to 28 extra-strength tablets for a 155-pound person.

In the United States, acetaminophen overdose is estimated to represent 5%, or 275,000 of the 5.2 million total toxic exposures annually, and nearly 10%, or 275,000 of 2.9 million of all toxic pharmaceutical exposures annually. Such overdoses, which can lead to hepatotoxicity (liver damage), account for more than 60,000 hospital visits every year, and over 100,000 calls per year to the U.S. Poison Control Centers.

Clinical course of acetaminophen toxicity is very different from poisoning with other drugs (i.e., aspirin). Symptoms of hepatotoxicity, such as nausea, vomiting, and abdominal pain, may not appear until more than 24 hours post ingestion, but liver damage — and even death — may occur if the antidote n-acetylcysteine (or NAC) is not administered within eight hours after ingestion. Acute overdose, whether intentional or unintentional, requires rapid diagnosis.

Acetaminophen-overdose patients may be classified as 1) suicidal/intentional or 2) accidental/unintentional. Most suicidal patients present within four hours of ingestion and, therefore, receive the NAC treatment in a timely manner. The group that is labeled as accidental or unintentional overdoses usually present for treatment much later — after the onset of hepatotoxic symptoms — leading to poorer outcomes for these patients. In the absence of specific symptoms, rapid turnaround time of APAP-screening tests can quickly rule out suspected APAP overdose.

The 2003 NACB Laboratory Medicine Practice Guidelines recommend that all emergency department patients who present with intentional drug ingestion and chronic overuse secondary to chronic pain should be screened with a quantitative serum or plasma acetaminophen. The guidelines go on to state that if the results of the majority of samples tested were negative (by urine qualitative screen), the need and costs for performing quantitative serum or plasma testing would be diminished.¹

“Checking for the presence of acetaminophen is the standard of care in all patients who intentionally overdose,” says Aaron Schneir, MD, assistant professor, University of California, San Diego, School of Medicine, Division of Emergency Medicine and Clinical Toxicologist. “Having a rapid screening method to test for the presence of acetaminophen has the potential to shorten the length of time a patient is in the emergency department.”

Timely, accurate diagnosis can mean the difference between patient admission and discharge, between relief of symptoms and prolonged suffering, between early intervention and missed therapeutic opportunities and, in the gravest instances, between life and death. □

Robin Bramson is product manager, Qualitative Products, for Biosite, San Diego, CA (www.biosite.com), which manufactures Triage Drugs of Abuse and Triage TOX Drug Screen with Acetaminophen (APAP); the latter detects acetaminophen in urine in 30 minutes after ingestion of an adult therapeutic dosage of extra-strength acetaminophen tablet.

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