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Novel Objective Biomarkers of Alcohol Use: Potential Diagnostic and Treatment Management Tools in Dual Diagnosis Care

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Abstract

Alcohol use disorders are highly prevalent conditions that generate a large fraction of the total public health burden. These disorders are concentrated in mentally ill populations, in which reliability of self-reporting of alcohol consumption may be especially compromised. The application of objective biomarkers for alcohol use may therefore play an important role in these patients. This article provides a description and comparative overview of traditional versus novel biomarkers of alcohol consumption. Greater professional familiarity with and use of novel biomarkers as diagnostic and treatment management tools may enhance clinical standards and research on alcohol use in patients with a dual diagnosis.

Keywords

Alcohol biomarker; dual diagnosis; alcohol abuse; alcohol dependence; objective measure

Introduction

Alcohol abuse and dependence are globally prevalent disorders that span various sociodemographic groups and produce a broad range of secondary injury and disease (Alvarez, Olson, Jason, Davis, & Ferrari, 2004; Domino et al., 2005; Li, 2008; Roeloffs, Wells, Ziedonis, Tang, & Unutzer, 2002). In the United States alone, alcohol use disorders are associated with 100,000 deaths a year and incur \$185 billion in health care and other costs (Sommers, Savage, Wray, & Dyehouse, 2003). Twenty to thirty percent of all hospital admissions may be alcohol-related (Niemela, 2007). Morbidity and mortality consist of, but are not limited to, suicide (Wilcox, Conner, & Caine, 2004), violence (Chermack & Blow, 2002), child abuse/neglect (Harris, Lieberman, & Marans, 2007), drownings (Mitic & Greschner, 2002), house fires (Barillo & Goode, 1996), heart disease (Spies et al., 2001), hepatic dysfunction (Grando-Lemaire, Kazemi, & Trinchet, 2005), gastrointestinal neoplasms (Seitz & Meier, 2007), fetal alcohol syndrome (Sokol, Delaney-Black, & Nordstrom, 2003), peripheral neuropathy (Zambelis, Karandreas, Tzavellas, Kokotis, & Liappas, 2005), dementia (Hulse, Lautenschlager, Tait, & Almeida, 2005), and pancreatitis (Nakamura et al., 2003).

Despite alcohol use disorders producing public health consequences similar to major medical diseases such as diabetes, objective tests for diagnosis and clinical management of alcoholism have yet to become a standard of care as have objective tests for other medical diseases.

Although alcohol itself can be readily measured via breath analysis, the time window of detection is limited to hours within drinking and thus provides information about acute levels of intoxication. Alcohol detection itself provides no indication about patterns of alcohol use spanning days, weeks, or months, which are temporal windows more directly related to the diagnosis of alcohol addiction. The relative nonspecificity of other traditional alcohol biomarkers, the reluctance of some clinicians to “drug test” their patients for fear of complicating the therapeutic alliance, and the conventional reliance on self-reporting may restrain interest in the development and adoption of novel alcohol biomarkers. Certainly, self-report questionnaires, such as the Alcohol Use Disorders Identification Test, the Michigan Alcohol Screening Test, and the CAGE (Cut down, Annoyed, Guilty, Eye Opener), carry the advantages of being relatively rapidly administered, noninvasive, and inexpensive. However, such measures may be easily feigned and/or rely on coherent thought process, intact insight, and overall mental status (Allen & Litten, 2003). Since minimization and denial are widely recognized as typical features of alcoholism and other addictive disorders (Alling et al., 2005), achieving greater clinical accuracy in tracking alcohol use patterns in various settings is largely an unmet need. Examples include outpatient detoxification and abstinence clinics, liver transplant programs, and research studies in which subjects are reimbursed for participation and may overreport positive results (Erim et al., 2007; Schmidt et al., 1997; Schwan et al., 2004).

Alcohol use disorders occur at rates greatly exceeding those in the general population across many psychiatric disorders, including schizophrenia, bipolar disorder, antisocial personality disorder, major depressive disorder, and panic disorder. Substantial proportions of the entire population with alcoholism have concurrent mental disorders (Helzer, Burnam, & McEvoy, 1991). Lifetime prevalence of alcohol abuse or dependence is 34% among patients with schizophrenia (Regier et al., 1990). Up to 75% of combat veterans with lifetime post-traumatic stress disorder have met criteria for lifetime alcohol abuse or dependence (Jacobsen, Southwick, & Kosten, 2001). The US National Comorbidity Survey found that 51.4% of respondents with a lifetime alcohol or drug use disorder met criteria for at least one lifetime mental disorder, while 50.9% of respondents with a lifetime mental disorder had a history of alcohol or drug abuse or dependence (Kessler et al., 1996; Kessler, 2004). The National Epidemiological Survey on Alcohol and Related Conditions found significant associations between alcohol use disorders and any mood disorder (odds ratio = 2.4) and any anxiety disorder (odds ratio = 2.3; Grant et al., 2004; Hasin, Stinson, Ogburn, & Grant, 2007).

Increased objectivity offered by one or more of the emerging novel alcohol biomarkers when used in combination with self-reporting (Wurst et al., 2008) could represent an important part of improving diagnosis and treatment response monitoring in dual diagnosis patients. Inaccuracies in self-reporting due to minimization and denial in non-mentally ill alcoholic patients may be further exacerbated by a range of factors prevalent in mental illness, such as with cognitive deficits and impaired insight in schizophrenia (Agelink, Ullrich, Lemmer, Dirkes-Kersting, & Zeit, 1999), deceitfulness in patients with antisocial personality disorder (Goldstein et al., 2007; Pihl, 2007), or the quite rational fear of losing mental health/disability benefits if a co-occurring addiction is diagnosed. In a recent study of 486 admitted psychiatric patients, 37% to 56% underreported alcohol use as evaluated by novel alcohol biomarkers used alone or in combination with traditional ones (de Beaurepaire et al., 2007).

The goal of this review article is to describe and compare a number of traditional and leading novel alcohol biomarkers, some of which may have important utility in the care of dual diagnosis patients with alcohol use disorders. Greater familiarity with and use of these tests among clinicians and researchers serving dual diagnosis populations may drive improvements in diagnosis, clinical treatment monitoring, and experimental treatment efficacy testing.

Categories and Characteristics of Alcohol Biomarkers

Objective alcohol biomarkers may be broadly divided into *indirect* and *direct* biomarkers (Substance Abuse and Mental Health Services Administration, 2006). *Indirect* biomarkers detect the effects of alcohol on organ systems or body chemistry. Most of the traditional biomarkers fall under this category, including those that examine effects on blood (mean corpuscular volume [MCV]) and the liver (gamma-glutamyltransferase [GGT]), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). The novel indirect biomarkers generally examine more fine structural changes in biochemistry detected in blood serum and include carbohydrate-deficient transferrin (CDT), total serum sialic acid (TSA), 5-hydroxytryptophol (5-HTOL), N-acetyl-beta-hexosaminidase (Beta-Hex), plasma sialic acid index of apolipoprotein J (SIJ), and salsolinol. *Direct* biomarkers detect alcohol itself and/or the products of alcohol metabolism. Alcohol itself may be regarded as the only traditional direct biomarker, whereas novel direct biomarkers include acetaldehyde, acetic acid, fatty acid ethyl ester (FAEE), ethyl glucuronide (EtG), ethyl sulfate (EtS), and phosphatidylethanol (PEth).

A more detailed description of each of these 10 indirect and 7 direct biomarkers is provided in Table 1. The indirect markers Beta-Hex (Javors & Johnson, 2003), SIJ (Javors & Johnson, 2003), and salsolinol (Haber, Jahn, Ehrenreich, & Melzig, 2002) and the direct markers EtS (Substance Abuse and Mental Health Services Administration, 2006) and PEth (Substance Abuse and Mental Health Services Administration, 2006) will not be covered further in this review, as they represent the most experimental of the novel biomarkers, and more work is needed for their characterization. For the remaining 7 indirect and 5 direct biomarkers, there are now sufficient data to provide initial comparisons, in terms of the following performance characteristics or test conditions:

1. Detection period from time of alcohol abstinence
2. Intensity/pattern of alcohol use detected
3. Sources of false-positives/-negatives
4. Hepatic impairment
5. Demographics (age, sex, ethnicity)
6. Cost and availability

In the following sections, we review the clinical utility of the 7 indirect and 5 direct biomarkers. We then provide a concluding discussion, considering which of these biomarkers used alone or in combination may be optimal in dual diagnosis care.

Detection Period From Time of Alcohol Abstinence

Table 2 provides a general summary of the detection period of the indirect and direct biomarkers from time of alcohol abstinence. The indirect measures require longer periods (days to weeks) to normalize compared to the direct measures (hours to days), as somatic reactions to the presence of alcohol change more slowly than alcohol itself is metabolized.

Among traditional indirect biomarkers, MCV is the slowest to normalize, requiring 2 to 4 months (Niemela, 2007) and occasionally even longer if other causes of macrocytic change associated with alcohol use are not addressed upon abstinence (Peterson, 2004). Normalization of GGT can vary between and within individuals according to the phase in drinking history, ranging between 1 and 4 weeks (Conigrave, Davies, Haber, & Whitfield, 2003; Niemela, 2007; Peterson, 2004). AST/ALT changes are evident between 2 and 3 weeks (Niemela, 2007). The novel indirect biomarkers offer comparable or shorter ranges. TSA values may show resolution over time frames similar to the liver function tests (GGT, AST, ALT; Javors

& Johnson, 2003), ranging between 2 and 5 weeks (Niemela, 2007). 5-HTOL detects alcohol use for up to 24 hours (Beck & Helander, 2003; Niemela, 2007; Peterson 2004). CDT changes are reversible in 2 to 3 weeks from the time of alcohol abstinence (Bean, 2005), with a half-life of 15 days (Allen, Litten, Fertig, & Sillanaukee, 2001; Neumann & Spies, 2003; Niemela, 2007). CDT may be responsive to detecting brief relapses within longer stretches of abstinence. Relapse to 2 days of heavy drinking with a 2-week abstinence period before testing can be detected about 60% of the time by a 30% increase in CDT over a patient's abstinent value (Alling et al., 2005).

Among the direct biomarkers, alcohol itself is well known to offer unsurpassed specificity. However, it has a variable but severely limited time frame of detection from 2 to 14 hours, depending on dose, intake and elimination rate, and previous drinking history (e.g., tolerance; Neumann & Spies, 2003; Niemela, 2007; Sommers et al., 2003; Swift, 2003). Novel direct markers attempt to improve on this time frame. While acetic acid offers little to no advantage here (Sarkola, Iles, Kohlenberg-Mueller, & Eriksson, 2002; Swift, 2003), acetaldehyde offers improvements in its protein-bound forms called acetaldehyde adducts. These adducts can be present for days after alcohol has been eliminated (Swift, 2003). In the setting of abstinence after chronic heavy alcohol use, free and protein-bound acetaldehyde, called whole-blood acetaldehyde (WBAA), may provide even longer detection coverage due to hemoglobin-bound acetaldehyde accumulating in erythrocytes over a 120-day average life-span (Peterson, 2004). FAEs have been detected in serum for 24 to 99 hours, with 99 hours being in heavy drinkers (Borucki et al., 2007). Improving on FAEs, EtG offers some flexibility in being detectable in both blood and urine, albeit with differing detection time frames. About 0.02% to 0.06% of the dose of consumed alcohol is recovered as EtG in the urine, which can be detected starting a few hours after alcohol is consumed and for up to 5 days (Das, Dhanya, & Vasudevan, 2008; Wurst, Skipper, & Weinmann, 2003; Wurst et al., 2005). EtG can be detected in blood for up to 36 hours (Peterson, 2004; Wurst et al., 2005) and peaks about 3 hours after the peak in alcohol concentration (Bean, 2005). Via mechanisms that are poorly understood, EtG reaches higher concentrations in urine than in blood, rendering urine assays the more sensitive and longer-lasting measure of EtG (Hoiseth et al., 2007).

Intensity/Pattern of Alcohol Use Detected

Table 3 summarizes aspects of how the indirect and direct biomarkers may indicate intensities and patterns of alcohol use. From among the indirect biomarkers, the traditional ones are relatively limited by lack of sensitivity to either nonheavy chronic patterns of drinking or brief periods of relapse. MCV elevations require prolonged heavy intake of up to 60 g (~6 drinks) per day for a month (Neumann & Spies, 2003). MCV does not change in phase with short-term progress in abstinence (Conigrave et al., 2003) or with acute episodes of heavy drinking (Sommers et al., 2003). GGT offers some improvement on these parameters. While it is increased more readily by sustained excessive rather than episodic drinking (Hannuksela, Liisanantti, Nissinen, & Savolainen, 2007; Sommers et al., 2003), a reduction (but not normalization) in GGT may be apparent after the first week of abstinence, followed by a rise with resumption of sustained heavy drinking in alcohol-dependent patients (Conigrave et al., 2003). Both AST and ALT follow similar attributes but may be even less responsive to stopping and starting drinking relative to GGT (Conigrave et al., 2003; Substance Abuse and Mental Health Services Administration, 2006; Sommers et al., 2003).

The novel indirect biomarker TSA is increased in alcohol-dependent patients compared to social drinkers and may provide more information about broader ranges of alcohol consumed. However, TSA is less useful for detecting early relapse, as it takes longer than GGT and other novel biomarkers to decrease during abstinence (Javors & Johnson, 2003; Peterson, 2004). Although 5-HTOL offers relatively high responsiveness to recent relapse (Beck & Helander,

2003; Niemela, 2007), low amounts of alcohol use an evening prior to testing may still not result in an elevated 5-HTOL level the following morning (Beck & Helander, 2003).

In contrast to the other traditional and novel indirect biomarkers, CDT may offer some of the best utility in detecting the pattern and intensity of alcohol use. CDT measures the regular intake of 50 to 80 g of alcohol (5 to 7 standard drinks) per day for at least 1 to 3 weeks (Niemela, 2007). A 30% decrease from the CDT value measured at the start of treatment indicates abstinence, and a 30% increase from the CDT value measured after 3 weeks of abstinence indicates relapse (Bean, 2005). Such sensitivity to changes in drinking pattern contribute to CDT being more sensitive than GGT in detecting relapse during detoxification (Hannuksela et al., 2007). CDT may provide utility in distinguishing patients with alcohol dependence from patients with recent high alcohol use not occurring in the setting of dependence (Neumann & Spies, 2003; Niemela, 2007). CDT appears to increase gradually with chronic low levels of alcohol use in patients with a history of alcohol abuse (Niemela, 2007) due to a sensitization-like effect (Allen et al., 2001).

Among the direct biomarkers, current alcohol levels, when compared to level of clinical intoxication, may be used to deduce tolerance (Niemela, 2007; Sommers et al., 2003). Because acetic acid concentration lacks correlation with alcohol concentration (Swift, 2003) and has a severely limited detection window as alcohol, its utility in detecting intensity of use may be even more limited than that of alcohol itself. WBAA detects both acute and chronic drinking (Bean, 2005) and may show windows of detection that are sustained longer after abstinence (up to weeks), depending on the occurrence of intervening heavy drinking episodes (Sommers et al., 2003). Pronounced individual variability in the amount of acetaldehyde adducts may render serial WBAA tests especially important for its clinical utility (Swift, 2003). FAEs appear to be more reliable for chronic than for acute alcohol abuse (Kaphalia, Cai, Khan, Okorodudu, & Ansari, 2004). Like acetic acid, FAEs do not correlate with the amount of alcohol use and only determine whether heavy drinking occurred (Swift, 2003). EtG pairs sensitivity to relatively low levels of alcohol use, with an ability to detect use days later. EtG becomes positive with recent use of as little as 10 g (<1 beer; Wurst et al., 2003) and can potentially distinguish social drinkers (nondrinkers, light drinkers) from harmful drinkers (heavy drinkers, those currently needing treatment) if alcohol use was in the last 24 hours (Wurst, Wiesbeck, Metzger, & Weinmann, 2004). From among all the direct biomarkers, EtG may provide the best assay for detection of relapse more than 1 day prior to clinical assessment (Hoiseth et al., 2008; Peterson, 2004; Reuben, 2007).

Sources of False-Positives/-Negatives

Table 4 summarizes many of the major sources of nonhepatic false-positives/-negatives for the indirect and direct biomarkers. In general, the traditional indirect biomarkers suffer from being vulnerable to a wide variety of not uncommon conditions that can significantly alter their values independent of alcohol consumption. For example, MCV can be increased by folate or B₁₂ deficiency, bleeding, hemoglobinopathies, hypothyroidism (Niemela, 2007), hyperglycemia, and bone marrow disorders (Conigrave et al., 2003; Das et al., 2008). Valproic acid (Abbott Laboratories, 2006; Hauser, Seidl, Freilinger, Male, & Herkner, 1996) and smoking can cause a slight increase in MCV, whereas MCV is inversely associated with coffee intake (Conigrave et al., 2003).

The liver function tests are similarly impacted by a wide variety of conditions outside the range of hepatic disease. For instance, GGT may be increased by pancreatitis, prostate disease (Peterson, 2004), hypertriglyceridemia, diabetes, obesity (Conigrave et al., 2003), renal disease, smoking (Hannuksela et al., 2007; Sommers et al., 2003), and medications such as phenytoin, NSAIDs, (Conigrave et al., 2003), venlafaxine (Phillips, Digmann, & Beck, 2006), oral contraceptives, barbiturates, and anticoagulants (Hannuksela et al., 2007; Sommers

et al., 2003). AST and ALT can change with obesity, weight gain, coffee intake (Conigrave et al., 2003), and medications such as antibiotics, statins, NSAIDs (Conigrave et al., 2003), anticoagulants (Sommers et al., 2003), valproic acid (Abbott Laboratories, 2006), bupropion (Hu, Tiyyagura, Kanel, & Redeker, 2000), venlafaxine (Phillips et al., 2006), tacrine (Gracon et al., 1998), naltrexone (Barr Laboratories, 2003), atomoxetine (Eli Lilly and Company, 2008), and atypical antipsychotics (olanzapine, risperidone, quetiapine; Atasoy et al., 2007; Erdogan et al., 2008). Even strenuous exercise and various muscle disorders may increase AST (Conigrave et al., 2003).

From among the novel indirect biomarkers, common medical conditions may impact TSA the most. These include lung and cervical cancer, cardiovascular/hypertensive disease, diabetes, and obesity (Javors & Johnson, 2003; Sillanaukee, Ponnio, & Jaaskelainen, 1999). Although further clinical experience is needed before definitive statements can be made about 5-HTOL and CDT, these biomarkers thus far appear to show the least vulnerability. 5-HTOL is increased by disulfiram and dietary intake of serotonin (Beck & Helander, 2003). Increased CDT may be due to iron deficiency, carbohydrate-deficient glycoprotein syndrome, genetic D variants of transferrin (Bean, 2005; Das et al., 2008; Substance Abuse and Mental Health Services Administration, 2006), and possibly use of enzyme-inducing antiepileptics (Brathen, Bjerve, Brodtkorb, Helde, & Bovim, 2001), while decreases may occur due to use of oral contraceptives (Cook 2003) and angiotensin II receptor blockers (Mundt, Kraus, & Fleming, 2004). There appears to be a small but significant inverse relationship between body mass index and CDT (Anton, 2001). To “normalize” differences in total transferrin levels across people and/or co-occurring medical conditions, CDT can be measured in serum as the percentage of total transferrin that is carbohydrate-deficient rather than as the absolute amount of CDT (e.g., % CDT; Substance Abuse and Mental Health Services Administration, 2006). Examination of specific glycoforms of CDT (e.g., the disialotransferrin glycoform) may offer further selectivity of CDT testing free of non-alcohol-related confounds (Bergstrom & Helander, 2008).

Direct biomarkers, compared to the indirect ones, are relatively free of medical confounds. However, if tested using highly sensitive assays or under other special conditions, false-positives or -negatives can still arise. For instance, low concentrations of alcohol can be found in the blood of completely abstinent patients due to fermentation of carbohydrates in the colon (Sommers et al., 2003). Administration of 4-methylpyrazole, used to treat ethylene glycol intoxication, can reduce alcohol-induced acetic acid levels (Sarkola et al., 2002). False-positive WBAA may be due to the formation of acetaldehyde in the blood sample itself after sample collection (Bean, 2005). Free fatty acid levels increase during fasting, and restricting fat intake may lead to detectable levels in serum (Bisaga, Laposata, Xie, & Evans, 2005). False-positive EtG may be due to incidental alcohol exposure such as alcohol in food, over-the-counter cough syrup, communion wine, and mouthwash. Detection cutoffs of EtG below 500 $\mu\text{g/L}$ may render such confounds unlikely (Skipper et al., 2004). Renal disease decreases urine EtG levels, possibly due to a decreased ability to reuptake glucuronides in early phases of excretion. Urinary tract infections may also lead to false-negative EtG results (Helander, Olsson, & Dahl, 2007; Helander & Dahl, 2005). Marijuana use has been associated with higher urine EtG levels, although this could be due to a higher overall intake of alcohol in marijuana users (Wurst, Wiesbeck, et al., 2004). To make urine EtG values inter- and intra-individually comparable, EtG can be standardized by expressing it as a ratio to creatinine (Wurst et al., 2003).

Hepatic Impairment

Table 5 summarizes many effects of hepatic impairment on the indirect and direct biomarkers. The high incidence of subclinical or frank liver disease in alcoholic patients is widely recognized as a major limitation in the utility of traditional indirect biomarkers in detecting

ongoing patterns of alcohol consumption. Levels of GGT, AST, and ALT on liver function tests can all be abnormally elevated in acute hepatitis due to many causes. Chronic progressive cirrhosis due to any cause can produce abnormally low values of GGT, AST, ALT, and MCV, often accompanied by reductions in albumin and elevated bilirubin (Conigrave et al., 2003; Hock et al., 2005; Torezan-Filho, Alves, Neto, Fernandes, & Strauss, 2004). Coadministration of several psychiatric medications not uncommonly used in dual diagnosis alcoholic populations, such as valproic acid, quetiapine, and atomoxetine, can also limit interpretation of AST and ALT. This is especially pertinent in the presence of low-grade hepatic disease (Abbott Laboratories, 2006; AstraZeneca Pharmaceuticals, 2008; Eli Lilly and Company, 2008).

Compared to the traditional indirect biomarkers, the novel indirect biomarkers appear less vulnerable to underlying liver impairment. TSA appears to be less dependent on liver function in the assessment of alcohol use disorders (Romppanen et al., 2002) and may be of value when effects of hepatic disease and alcohol drinking need to be differentiated (Anttila et al., 2005). Similarly, CDT shows greater specificity to alcohol consumption in both acute hepatitis and mild to moderate cirrhosis, compared to MCV and GGT (Hannuksela et al., 2007; Hock et al., 2005). However, in advanced stages of cirrhosis or hepatocarcinoma, CDT values may be also abnormally elevated independent of alcohol use (Bean, 2005; Behrens, Worner, Braly, Schaffner, & Lieber, 1988; Fleming, Anton, & Spies, 2004; Miller et al., 2006; Substance Abuse and Mental Health Services Administration, 2006). More evidence is needed for determining the effect of hepatic disease on 5-HTOL (Rosman & Lieber, 1994).

In general, the direct biomarkers are also less susceptible to inaccuracy due to liver disease than are the traditional indirect biomarkers. However, since the liver plays a role in metabolizing alcohol, some effects may be anticipated. Blood alcohol concentrations are not themselves distinguishable between an alcoholic hepatitis group and a control group (Zorzano, Ruiz del Arbol, & Herrera, 1989). Nondrinking patients with nonalcoholic hepatic disease and abstinent alcoholics with cirrhosis have increased concentrations of erythrocyte acetaldehyde and acetaldehyde adducts (Rosman & Lieber, 1994). EtG is perhaps the superior performer, as cirrhosis of the liver has no significant effect on EtG levels (Wurst, Wiesbeck, et al., 2004). More evidence is needed to determine the effect of hepatic disease on acetic acid and FAEs (Swift, 2003).

Demographics (Age, Sex, Ethnicity)

Age, sex, and ethnicity all contribute to individual variation in baseline or alcohol-related expression of the various alcohol biomarkers. However, preliminary findings indicate that in many cases, the novel biomarkers may offer greater resistance to these sources of variation and better utility as initial diagnostic tests regarding general population reference ranges.

As suggested in Table 6, patient age can impact all of the traditional biomarkers, while some of the novel tests may offer better age independence. MCV, GGT, AST, and ALT may all be unreliable as diagnostic tests in patients younger than 30 and in the elderly, due to normative age-related changes in serum concentrations (Conigrave et al., 2003; Niemela, 2007). The novel indirect biomarker TSA also varies with age (Javors & Johnson, 2003), but further studies are needed to determine whether this is as distinct as with the traditional biomarkers. 5-HTOL is apparently not influenced by age (Helander & Eriksson, 2002), but further studies are needed. Although CDT appears to have a higher sensitivity and specificity in young men aged 20 to 40 (83% and 87%, respectively) than in older men and women (Sommers et al., 2003), the “% CDT” test does not appear to be age-dependent (Fleming et al., 2004).

As a group, the direct biomarkers may be less susceptible to age-related change. Due to the decrease in body water with aging (Meier & Seitz, 2008), the elderly become intoxicated and

reach higher peak alcohol levels more quickly than the young. Further research is needed to determine age effects on acetaldehyde and acetic acid (Swift, 2003). A correlation between FAEE and age has not yet been found (Wurst, Alexson, et al., 2004). Preliminary evidence suggests that increased age may increase EtG levels (Wurst, Wiesbeck, et al., 2004).

Effects of sex vary considerably among the biomarkers (Table 7). All of the traditional indirect biomarkers are susceptible to sex effects. While the sensitivity of MCV in predicting heavy alcohol use is higher in women, its specificity may be greater in men (Sommers et al., 2003). Men are more likely to show an increased GGT in response to heavy drinking (Conigrave et al., 2003; Hannuksela et al., 2007). Women are likely to have a lower GGT, possibly due to suppression of GGT from estrogen and progesterone (Sommers et al., 2003). Men have a wider range in ALT than women, especially in older subgroups (Elinav et al., 2005; Sommers et al., 2003), but a similar association has not been found with AST (Elinav et al., 2005).

The novel indirect biomarkers may show fewer sex differences. Neither TSA (Ponnio et al., 1999) nor 5-HTOL appears to be influenced by sex (Beck & Helander, 2003; Helander & Eriksson, 2002), but further studies are needed. In contrast, sex-based differences in CDT values at baseline or in response to drinking have been documented. Women with heavy menstrual bleeding have increased erythropoiesis, decreased iron stores, and higher transferrin production, leading to higher CDT values compared to postmenopausal women (Cook, 2003; Sommers et al., 2003). Premenopausal women may naturally produce more absolute CDT (Neumann & Spies, 2003) but show a milder CDT change in response to heavy alcohol use compared to men (Niemela, 2007). Sex-based differences in CDT may be ameliorated if percentage of CDT is assayed instead of CDT alone, although further studies are needed to confirm this possibility (Anton, 2001; Fleming et al., 2004).

Few studies have documented sex differences in the direct biomarkers. Blood alcohol concentrations elevate more quickly in women compared to men, perhaps due to reduced gastric antral activity of alcohol dehydrogenase and a host of other sex-specific factors (Sommers et al., 2003). Women also show higher rates of alcohol elimination than men, perhaps due to increased relative liver volume in women (Swift, 2003). These trends could produce sex differences in either acetaldehyde or acetic acid production that lessen at postmenopausal ages, although more studies are needed (Halvorson, Noffsinger, & Peterson, 1993). Variable results have been found with FAEEs (Kaphalia et al., 2004; Soderberg et al., 1999). Men appear to have decreased EtG levels, possibly reflecting differential expression of UDP-glucuronyltransferase (Wurst, Wiesbeck, et al., 2004).

Similar to sex, studies describing the effects of ethnicity on alcohol biomarkers are limited. However, evidence suggests that the traditional indirect biomarkers are the most susceptible to ethnicity-related effects, while the novel indirect and direct markers may be the least (Table 8). For instance, MCV values can vary among African American, Latin American, European, and Asian groups, potentially involving complex interactions between ethnicity and sex or ethnicity and age (Isaacs, Altman, & Valman, 1986; Saxena & Wong, 1990). GGT, AST, and ALT can range higher in South Asian, African, or Hispanic groups than in European groups (Conigrave et al., 2003; Sommers et al., 2003). The novel indirect biomarker TSA may show 20% to 30% greater values in Northern European groups than in Japanese groups (Lindberg, Iso, Rastam, Lundblad, & Folsom, 1997). 5-HTOL does not appear to be influenced by ethnicity (Beck & Helander, 2003). CDT does not appear to differ significantly among African American, Puerto Rican, Korean, or South Asian groups (Behrens et al., 1988; Kim et al., 2007; Wickramasinghe, Corridan, Izaguirre, Hasan, & Marjot, 1995). An epidemiologic study of 1,400 Australian adults that examined the frequency of false-positive CDT variants reported a frequency of 1% false-positive of the CDTest test (a method that measures asialotransferrin, monosialotransferrin, and disialotransferrin) due to genetic variants (Whitfield et al., 1998).

Data characterizing the effects of ethnicity on the direct biomarkers are lacking. However, given well-characterized differences in alcohol metabolism involving genotypes of alcohol dehydrogenase and aldehyde dehydrogenase-2 that vary in frequency across different ethnic groups, differences in alcohol-induced levels of acetaldehyde and/or acetic acid may be expected across ethnic groups (Ramchandani, Bosron, & Li, 2001). No studies have examined the effects of ethnicity on FAEEs. Ethnicity appears to have no significant effect on EtG (Wurst, Wiesbeck, et al., 2004).

Cost and Availability

Table 9 lists the availability and cost comparison of alcohol biomarkers compiled from 3 different types of hospitals located in the downtown area of a major Midwestern city in the United States, Indianapolis, Indiana (Indiana University, 2007; VA Hospital, 2007; Wishard Hospital, 2007). CDT, acetaldehyde, and EtG were the only novel biomarkers consistently available across these hospital systems. In all likelihood, this is representative of their general availability across the United States. While the traditional biomarkers are consistently less expensive than the available novel biomarkers, more widespread use of the novel biomarkers may just be enough to close these cost gaps in the market over time.

Discussion

Denial and minimization of alcohol use in patients with alcohol use disorders limit the utility of self-report measures of alcohol use. The additional presence of a co-morbid psychiatric disorder may further limit the reliability of self-reporting. The application of objective biomarkers for alcohol use may play an important role in dual diagnosis patients.

The authors have found these objective biomarkers useful in their own clinical practices. For example, a 75-year-old male veteran with mild cognitive impairment and hepatitis C was asked about his alcohol intake at his initial outpatient psychiatric evaluation. He was unable to quantify his alcohol use, and relying on self-report alone was questionable. Differential diagnoses for his cognitive impairment were major depressive disorder, alcohol dependence, alcohol-induced mood disorder, and alcohol-induced persisting amnesic disorder. MCV (99; range, 80–94), AST (203; range, 0–41), ALT (151; range, 0–45), and GGT (134; range, 6–65) were elevated. Although he had no cirrhosis, CDT assessment was ordered given the hepatic impairment, with a result of 3.1% (range, 0.0%–2.6%). With the additional use of CDT testing, we more confidently opened up a discussion about his alcohol use and what alcohol treatment services were available if he chose to seek treatment. The objective measure in this case was important for the patient to understand alcohol's physiologic impact in his body and for us to understand his recent pattern of drinking.

Across the 6 performance characteristics and test conditions by which these biomarkers were compared, the novel indirect biomarker CDT and the novel direct biomarker EtG appear to hold the greatest promise for all-around utility. Given their complementary strengths as shorter-versus longer-term alcohol detection assays, their differential abilities to indicate overall patterns of use versus recent relapses, and their distinct indirect versus direct detection methods, these assays used in combination could provide unprecedented informative power in characterizing multiple aspects of recent alcohol use. In particular, both may be used as a means to cancel out inter-individual variability and as a method for monitoring trajectories of recovery during intensive abstinence treatment. Combinations of novel biomarkers used over multiple time points in patients could represent a significant advance in dual diagnosis care, similar to how glucose and hemoglobin A_{1c} monitoring represent standard of care for patients with diabetes.

Conclusions

This article has reviewed a number of traditional and novel objective alcohol biomarkers that might serve as important tools in diagnosing and monitoring the treatment response of alcohol use disorders in dual diagnosis patient populations. Greater clinical and research experience with novel biomarkers is needed. Future directions for research include exploring which biomarker assessments (alone or in combination) may be advantageous or disadvantageous for specific subtypes of dual diagnosis patients and effects of psychotropic medications on the more novel alcohol biomarkers.

References

- Abbott Laboratories. Divalproex sodium delayed-release prescribing information. 2006. Retrieved June 25, 2008 from <http://www.rxabbott.com/pdf/depakote.pdf>
- Agelink MW, Ullrich H, Lemmer W, Dirkes-Kersting A, Zeit T. Screening for concomitant alcohol abuse in schizophrenia: Clinical significance of the Munich Alcoholism Test and laboratory tests. *European Addiction Research* 1999;5(2):82–87. [PubMed: 10394038]
- Allen JP, Litten RZ. Recommendations on use of biomarkers in alcoholism treatment trials. *Alcoholism: Clinical and Experimental Research* 2003;27:1667–1670.
- Allen JP, Litten RZ, Fertig JB, Sillanaukee P. Carbohydrate-deficient transferrin: An aid to early recognition of alcohol relapse. *American Journal on Addictions* 2001;10(supplement):24–28. [PubMed: 11268818]
- Alling C, Chick JD, Anton R, Mayfield RD, Salaspuro M, Helander A, et al. Revealing alcohol abuse: To ask or to test? *Alcoholism: Clinical and Experimental Research* 2005;29:1257–1263.
- Alvarez J, Olson BD, Jason LA, Davis MI, Ferrari JR. Heterogeneity among Latinas and Latinos entering substance abuse treatment: Findings from a national database. *Journal of Substance Abuse Treatment* 2004;26:277–284. [PubMed: 15182892]
- Anton RF. Carbohydrate-deficient transferrin for detection and monitoring of sustained heavy drinking. What have we learned? Where do we go from here? *Alcohol* 2001;25:185–188. [PubMed: 11839464]
- Anttila P, Jarvi K, Latvala J, Romppanen J, Punnonen K, Niemela O. Biomarkers of alcohol consumption in patients classified according to the degree of liver disease severity. *Scandinavian Journal of Clinical and Laboratory Investigation* 2005;65:141–151. [PubMed: 16025837]
- AstraZeneca Pharmaceuticals. Seroquel prescribing information. 2008. Retrieved June 25, 2008 from <http://www1.astrazeneca-us.com/pi/Seroquel.pdf>
- Atasoy N, Erdogan A, Yalug I, Ozturk U, Konuk N, Atik L, et al. A review of liver function tests during treatment with atypical antipsychotic drugs: A chart review study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2007;31:1255–1260. [PubMed: 17600607]
- Barillo DJ, Goode R. Substance abuse in victims of fire. *Journal of Burn Care & Rehabilitation* 1996;17:71–76. [PubMed: 8808362]
- Barr Laboratories. Naltrexone prescribing information. 2008. Retrieved August 16, 2008 from <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=4682>
- Bean P. State of the art contemporary biomarkers of alcohol consumption. *Medical Laboratory Observer* 2005;37(11):10–17. [PubMed: 16374991]
- Beck O, Helander A. 5-Hydroxytryptophol as a marker for recent alcohol intake. *Addiction* 2003;98(supplement 2):63–72. [PubMed: 14984243]
- Behrens UJ, Worner TM, Braly LF, Schaffner F, Lieber CS. Carbohydrate-deficient transferrin, a marker for chronic alcohol consumption in different ethnic populations. *Alcoholism: Clinical and Experimental Research* 1988;12:427–432.
- Bergstrom JP, Helander A. Clinical characteristics of carbohydrate-deficient transferrin (% disialotransferrin) measured by HPLC: Sensitivity, specificity, gender effects, and relationship with other alcohol biomarkers. *Alcohol and Alcoholism* 2008;43:436–441. [PubMed: 18411243]
- Bisaga A, Laposata M, Xie S, Evans SM. Comparison of serum fatty acid ethyl esters and urinary 5-hydroxytryptophol as biochemical markers of recent ethanol consumption. *Alcohol and Alcoholism* 2005;40:214–218. [PubMed: 15797884]

- Borucki K, Dierkes J, Wartberg J, Westphal S, Genz A, Luley C. In heavy drinkers, fatty acid ethyl esters remain elevated for up to 99 hours. *Alcoholism: Clinical and Experimental Research* 2007;31:423–427.
- Brathen G, Bjerve KS, Brodtkorb E, Helde G, Bovim G. Detection of alcohol abuse in neurological patients: Variables of clinical relevance to the accuracy of the % CDT-TIA and CDTest methods. *Alcoholism: Clinical and Experimental Research* 2001;25:46–53.
- Chermack ST, Blow FC. Violence among individuals in substance abuse treatment; The role of alcohol and cocaine consumption. *Drug and Alcohol Dependence* 2002;66:29–37. [PubMed: 11850133]
- Conigrave KM, Davies P, Haber P, Whitfield JB. Traditional markers of excessive alcohol use. *Addiction* 2003;98(supplement 2):31–43. [PubMed: 14984240]
- Cook JD. Biochemical markers of alcohol use in pregnant women. *Clinical Biochemistry* 2003;36:9–19. [PubMed: 12554054]
- Das SK, Dhanya L, Vasudevan DM. Biomarkers of alcoholism: An updated review. *Scandinavian Journal of Clinical and Laboratory Investigation* 2008;68(2):81–92. [PubMed: 17852805]
- de Beaurepaire R, Lukasiewicz M, Beauverie P, Castera S, Dagorne O, Espaze R, et al. Comparison of self-reports and biological measures for alcohol, tobacco, and illicit drugs consumption in psychiatric inpatients. *European Psychiatry* 2007;22:540–548. [PubMed: 17596918]
- Domino KB, Hornbein TF, Polissar NL, Renner G, Johnson J, Alberti S, et al. Risk factors for relapse in health care professionals with substance use disorders. *The Journal of the American Medical Association* 2005;293:1453–1460.
- Eli Lilly and Company. Strattera prescribing information. 2008. Retrieved June 25, 2008 from <http://pi.lilly.com/us/strattera-pi.pdf>
- Elinav E, Ben-Dov IZ, Ackerman E, Kiderman A, Glikberg F, Shapira Y, et al. Correlation between serum alanine aminotransferase activity and age: An inverted U curve pattern. *The American Journal of Gastroenterology* 2005;100:2201–2204. [PubMed: 16181369]
- Erdogan A, Atasoy N, Akkurt H, Ozturk D, Karaahmet E, Yalug I, et al. Risperidone and liver function tests in children and adolescents: A short-term prospective study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2008;32:849–857. [PubMed: 18258348]
- Erim Y, Boucher M, Dahmen U, Beck O, Broelsch CE, Helander A. Urinary ethyl glucuronide testing detects alcohol consumption in alcoholic liver disease patients awaiting liver transplantation. *Liver Transplantation* 2007;13:757–761. [PubMed: 17457868]
- Fleming MF, Anton RF, Spies CD. A review of genetic, biological, pharmacological, and clinical factors that affect carbohydrate-deficient transferrin levels. *Alcoholism: Clinical and Experimental Research* 2004;28:1347–1355.
- Goldstein RB, Dawson DA, Saha TD, Ruan WJ, Compton WM, Grant BF. Antisocial behavioral syndromes and DSM-IV alcohol use disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Alcoholism: Clinical and Experimental Research* 2007;31:814–828.
- Gracon SI, Knapp MJ, Berghoff WG, Pierce M, Dejong R, Lobbestael SJ, et al. Safety of tacrine: Clinical trials, treatment IND, and postmarketing experience. *Alzheimer Disease and Associated Disorders* 1998;12:93–101. [PubMed: 9651138]
- Grando-Lemaire V, Kazemi F, Trinchet JC. Predictive factors for progression to cirrhosis in chronic liver diseases. *La Revue Du Praticien* 2005;55:1533–1538. [PubMed: 16255294]
- Grant BF, Stinson FS, Dawson DA, Chou SP, Dufour MC, Compton W, et al. Prevalence and co-occurrence of substance use disorders and independent mood disorders and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* 2004;61:807–816. [PubMed: 15289279]
- Haber H, Jahn H, Ehrenreich H, Melzig MF. Assay of salsolinol in peripheral blood mononuclear cells of alcoholics and healthy subjects by gas chromatography-mass spectrometry. *Addiction Biology* 2002;7:403–407. [PubMed: 14578016]
- Halvorson MR, Noffsinger JK, Peterson CM. Studies of whole blood-associated acetaldehyde levels in teetotalers. *Alcohol* 1993;10:409–413. [PubMed: 8216889]
- Hannuksela ML, Liisanantti MK, Nissinen AE, Savolainen MJ. Biochemical markers of alcoholism. *Clinical Chemistry and Laboratory Medicine* 2007;45:953–961. [PubMed: 17579567]

- Harris WW, Lieberman AF, Marans S. In the best interests of society. *Journal of Child Psychology and Psychiatry* 2007;48:392–411. [PubMed: 17355403]
- Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry* 2007;64:830–842. [PubMed: 17606817]
- Hauser E, Seidl R, Freilinger M, Male C, Herkner K. Hematologic manifestations and impaired liver synthetic function during valproate monotherapy. *Brain and Development* 1996;18:105–109. [PubMed: 8733899]
- Helander A, Dahl H. Urinary tract infection: A risk factor for false-negative urinary ethyl glucuronide but not ethyl sulfate in the detection of recent alcohol consumption. *Clinical Chemistry* 2005;51:1728–1730. [PubMed: 16120954]
- Helander A, Eriksson CJ. Laboratory tests for acute alcohol consumption: Results of the WHO/ISBRA Study on State and Trait Markers of Alcohol Use and Dependence. *Alcoholism: Clinical and Experimental Research* 2002;26:1070–1077.
- Helander A, Olsson I, Dahl H. Postcollection synthesis of ethyl glucuronide by bacteria in urine may cause false identification of alcohol consumption. *Clinical Chemistry* 2007;53:1855–1857. [PubMed: 17717128]
- Helzer, JE.; Burnam, A.; McEvoy, LT. Alcohol abuse and dependence. In: Pokins, LN.; Regier, DA., editors. *Psychiatric disorders in America: The Epidemiologic Catchment Area Study*. New York: The Free Press; 1991.
- Hock B, Schwarz M, Domke I, Grunert VP, Wuertemberger M, Schiemann U, et al. Validity of carbohydrate-deficient transferrin (% CDT), gamma-glutamyltransferase (gamma-GT) and mean corpuscular erythrocyte volume (MCV) as biomarkers for chronic alcohol abuse: a study in patients with alcohol dependence and liver disorders of non-alcoholic and alcoholic origin. *Addiction* 2005;100:1477–1486. [PubMed: 16185209]
- Hoiseth G, Bernard JP, Karinen R, Johnsen L, Helander A, Christophersen AS, et al. A pharmacokinetic study of ethyl glucuronide in blood and urine: Applications to forensic toxicology. *Forensic Science International* 2007;172:119–124. [PubMed: 17306943]
- Hoiseth G, Bernard JP, Stephanson N, Normann PT, Christophersen AS, Morland J, et al. Comparison between the urinary alcohol markers EtG, EtS, and GTOL/5-HIAA in a controlled drinking experiment. *Alcohol and Alcoholism* 2008;43:187–191. [PubMed: 18230699]
- Hu KQ, Tiyyagura L, Kanel G, Redeker AG. Acute hepatitis induced by bupropion. *Digestive Diseases and Sciences* 2000;45:1872–1873. [PubMed: 11052334]
- Hulse GK, Lautenschlager NT, Tait RJ, Almeida OP. Dementia associated with alcohol and other drug use. *International Psychogeriatrics* 2005;17:S109–S127. [PubMed: 16240487]
- Indiana University. Personal communication. Financial office–Indiana University Hospital; Indianapolis, IN: 2007 Jul 6.
- Isaacs D, Altman DG, Valman HB. Racial differences in red cell indices. *Journal of Clinical Pathology* 1986;39:105–109. [PubMed: 3950023]
- Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: A review of the literature. *American Journal of Psychiatry* 2001;158:1184–1190. [PubMed: 11481147]
- Javors MA, Johnson BA. Current status of carbohydrate deficient transferrin, total serum sialic acid, sialic acid index of apolipoprotein J and serum beta-hexosaminidase as markers for alcohol consumption. *Addiction* 2003;98(supplement 2):45–50. [PubMed: 14984241]
- Kaphalia BS, Cai P, Khan MF, Okorodudu AO, Ansari GA. Fatty acid ethyl esters: Markers of alcohol abuse and alcoholism. *Alcohol* 2004;34:151–158. [PubMed: 15902908]
- Kessler RC. The epidemiology of dual diagnosis. *Biological Psychiatry* 2004;56:730–737. [PubMed: 15556117]
- Kessler RC, Nelsom CB, McGonagle KA, Edlund MJ, Frank RG, Leaf PJ. The epidemiology of co-occurring addictive and mental disorders: Implications for prevention and service utilization. *American Journal of Orthopsychiatry* 1996;66:17–31. [PubMed: 8720638]

- Kim SM, Kim JS, Kim KM, Pack HJ, Lee DH, Kim SS, et al. Carbohydrate-deficient transferrin as a marker of heavy drinking in Korean males. *Journal of Korean Medical Science* 2007;22:652–655. [PubMed: 17728504]
- Li TK. Quantifying the risk for alcohol-use and alcohol-attributable health disorders: Present findings and future research needs. *Journal of Gastroenterology and Hepatology* 2008;23:S2–S8. [PubMed: 18336658]
- Lindberg G, Iso H, Rastam L, Lundblad A, Folsom AR. Serum sialic acid and its correlates in community samples from Akita, Japan and Minneapolis, USA. *International Journal of Epidemiology* 1997;26:58–63. [PubMed: 9126503]
- Meier P, Seitz HK. Age, alcohol metabolism and liver disease. *Current Opinion in Clinical Nutrition and Metabolic Care* 2008;11(1):21–26. [PubMed: 18090653]
- Miller PM, Spies C, Neumann T, Javors MA, Hoyumpa AM, Roache J, et al. Alcohol biomarker screening in medical and surgical settings. *Alcoholism: Clinical and Experimental Research* 2006;30:185–193.
- Mitic W, Greschner J. Alcohol's role in the deaths of BC children and youth. *Canadian Journal of Public Health* 2002;93:173–175.
- Mundt MP, Kraus CK, Fleming MF. Potential drug interactions with the percent carbohydrate-deficient transferrin (% CDT) test, a new alcohol biomarker. *Pharmacotherapy* 2004;24:831–837. [PubMed: 15303446]
- Nakamura Y, Ishikawa A, Sekiguchi S, Kuroda M, Imazeki H, Higuchi S. Spirits and gastrectomy increase risk for chronic pancreatitis in Japanese male alcoholics. *Pancreas* 2003;26:e27–e31. [PubMed: 12604924]
- Neumann T, Spies C. Use of biomarkers for alcohol use disorders in clinical practice. *Addiction* 2003;98 (supplement 2):81–91. [PubMed: 14984245]
- Niemela O. Biomarkers in alcoholism. *Clinica Chimica Acta* 2007;377(1-2):39–49.
- Peterson K. Biomarkers for alcohol use and abuse: A summary. *Alcohol Research & Health* 2004;28(1): 30–37. [PubMed: 19006989]
- Phillips BB, Digmann RR, Beck MG. Hepatitis associated with low-dose venlafaxine for postmenopausal vasomotor symptoms. *The Annals of Pharmacotherapy* 2006;40:323–327. [PubMed: 16418323]
- Pihl RO. Personality disorders, behavioral disinhibition, and addiction: A commentary. *Biological Psychiatry* 2007;62:551–552. [PubMed: 17765452]
- Ponnio M, Alho H, Nikkari ST, Olsson U, Rydberg U, Sillanauke P. Serum sialic acid in a random sample of the general population. *Clinical Chemistry* 1999;45:1842–1849. [PubMed: 10508132]
- Ramchandani VA, Bosron WF, Li TK. Research advances in ethanol metabolism. *Pathologie-Biologie (Paris)* 2001;49:676–682.
- Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. *Journal of the American Medical Association* 1990;264:2511–2518. [PubMed: 2232018]
- Reuben A. Alcohol and the liver. *Current Opinion in Gastroenterology* 2007;23:283–291. [PubMed: 17414844]
- Roeloffs CA, Wells KB, Ziedonis D, Tang L, Unutzer J. Problem substance use among depressed patients in managed primary care. *Psychosomatics* 2002;43:405–412. [PubMed: 12297610]
- Romppanen J, Punnonen K, Anttila P, Jakobsson T, Blake J, Niemela O. Serum sialic acid as a marker of alcohol consumption: Effect of liver disease and heavy drinking. *Alcoholism: Clinical and Experimental Research* 2002;26:1234–1238.
- Rosman AS, Lieber CS. Diagnostic utility of laboratory tests in alcoholic liver disease. *Clinical Chemistry* 1994;40:1641–1651. [PubMed: 8045023]
- Sarkola T, Iles MR, Kohlenberg-Mueller K, Eriksson CJ. Ethanol, acetaldehyde, acetate, and lactate levels after alcohol intake in white men and women: Effect of 4-methylpyrazole. *Alcoholism: Clinical and Experimental Research* 2002;26:239–245.
- Saxena S, Wong ET. Heterogeneity of common hematologic parameters among racial, ethnic, and gender subgroups. *Archives of Pathology and Laboratory Medicine* 1990;114:715–719. [PubMed: 2363629]

- Schmidt LG, Schmidt K, Dufeu P, Ohse A, Rommelspacher H, Muller C. Superiority of carbohydrate-deficient transferrin to gamma-glutamyltransferase in detecting relapse in alcoholism. *The American Journal of Psychiatry* 1997;154:75–80. [PubMed: 8988962]
- Schwan R, Albuissou E, Malet L, Loiseaux MN, Reynaud M, Schellenberg F, et al. The use of biological laboratory markers in the diagnosis of alcohol misuse: An evidence-based approach. *Drug and Alcohol Dependence* 2004;74:273–279. [PubMed: 15194205]
- Seitz HK, Meier P. The role of acetaldehyde in upper digestive tract cancer in alcoholics. *Translational Research* 2007;149:293–297. [PubMed: 17543846]
- Sillanauke P, Ponnio M, Jaaskelainen IP. Occurrence of sialic acids in healthy humans and different disorders. *European Journal of Clinical Investigation* 1999;29:413–425. [PubMed: 10354198]
- Skipper GE, Weinmann W, Thierauf A, Schaefer P, Wiesbeck G, Allen JP, et al. Ethyl glucuronide: A biomarker to identify alcohol use by health professionals recovering from substance use disorders. *Alcohol and Alcoholism* 2004;39:445–449. [PubMed: 15289206]
- Soderberg BL, Sicinska ET, Blodgett E, Cluette-Brown JE, Suter PM, Schuppisser T, et al. Preanalytical variables affecting the quantification of fatty acid ethyl esters in plasma and serum samples. *Clinical Chemistry* 1999;45:2183–2190. [PubMed: 10585351]
- Sokol RJ, Delaney-Black V, Nordstrom B. Fetal alcohol spectrum disorder. *The Journal of the American Medical Association* 2003;290:2996–2999.
- Sommers MS, Savage C, Wray J, Dyehouse JM. Laboratory measures of alcohol (ethanol) consumption: Strategies to assess drinking patterns with biochemical measures. *Biological Research for Nursing* 2003;4:203–217. [PubMed: 12585784]
- Spies CD, Sander M, Stangl K, Fernandez-Sola J, Preedy VR, Rubin E, et al. Effects of alcohol on the heart. *Current Opinion in Critical Care* 2001;7:337–343. [PubMed: 11805530]
- Substance Abuse and Mental Health Services Administration. Rockville, MD: Author; 2006. The role of biomarkers in the treatment of alcohol use disorders. Retrieved June 25, 2008 from http://www.kap.samhsa.gov/products/manuals/advisory/pdfs/0609_biomarkers.pdf
- Swift R. Direct measurement of alcohol and its metabolites. *Addiction* 2003;98(supplement 2):73–80. [PubMed: 14984244]
- Torezan-Filho MA, Alves VA, Neto CA, Fernandes HS, Strauss E. Clinical significance of elevated alanine aminotransferase in blood donors: A follow-up study. *Liver International* 2004;24:575–581. [PubMed: 15566507]
- VA Hospital. Personal Communication. Financial office–Veterans' Affairs Hospital; Indianapolis, IN: 2007 Jul 11.
- Whitfield JB, Fletcher LM, Murphy TL, Powell LW, Halliday J, Heath AC, et al. Smoking, obesity, and hypertension alter the dose-response curve and test sensitivity of carbohydrate-deficient transferrin as a marker of alcohol intake. *Clinical Chemistry* 1998;44:2480–2489. [PubMed: 9836715]
- Wickramasinghe SN, Corridan B, Izaguirre J, Hasan R, Marjot DH. Ethnic differences in the biological consequences of alcohol abuse: A comparison between south Asian and European males. *Alcohol and Alcoholism* 1995;30:675–680. [PubMed: 8554653]
- Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: An empirical review of cohort studies. *Drug and Alcohol Dependence* 2004;76:S11–S19. [PubMed: 15555812]
- Wishard Hospital. Personal Communication. Financial office–Wishard Memorial Hospital; Indianapolis, IN: 2007 Jul 10.
- Wurst FM, Alexson S, Wolfersdorf M, Bechtel G, Forster S, Alling C, et al. Concentration of fatty acid ethyl esters in hair of alcoholics: Comparison to other biological state markers and self reported-ethanol intake. *Alcohol and Alcoholism* 2004;39:33–38. [PubMed: 14691072]
- Wurst FM, Alling C, Aradottir S, Pragst F, Allen JP, Weinmann W, et al. Emerging biomarkers: new directions and clinical applications. *Alcoholism: Clinical and Experimental Research* 2005;29:465–473.
- Wurst FM, Kelso E, Weinmann W, Pragst F, Yegles M, Sundstrom Poromaa I. Measurement of direct ethanol metabolites suggests higher rate of alcohol use among pregnant women than found with the AUDIT—a pilot study in a population-based sample of Swedish women. *American Journal of Obstetrics and Gynecology* 2008;198:407–405. [PubMed: 18221928]

- Wurst FM, Skipper GE, Weinmann W. Ethyl glucuronide—the direct ethanol metabolite on the threshold from science to routine use. *Addiction* 2003;98(supplement 2):51–61. [PubMed: 14984242]
- Wurst FM, Wiesbeck GA, Metzger JW, Weinmann W. On sensitivity, specificity, and the influence of various parameters on ethyl glucuronide levels in urine—results from the WHO/ISBRA study. *Alcoholism: Clinical and Experimental Research* 2004;28:1220–1228.
- Zambelis T, Karandreas N, Tzavellas E, Kokotis P, Liappas J. Large and small fiber neuropathy in chronic alcohol-dependent subjects. *Journal of the Peripheral Nervous System* 2005;10:375–381. [PubMed: 16279987]
- Zorzano A, Ruiz del Arbol L, Herrera E. Effect of liver disorders on ethanol elimination and alcohol and aldehyde dehydrogenase activities in liver and erythrocytes. *Clinical Science (London)* 1989;76:51–57.

TABLE 1

Alcohol Biomarkers

Indirect Biomarker	Description
MCV	Mean volume of the red blood cell.
GGT	Glycoprotein enzyme on cell membrane of tissues, such as liver, kidney, brain, spleen, and pancreas; found in serum.
AST	Hepatocellular enzyme involved in amino acid metabolism; found in serum.
ALT	Hepatocellular enzyme involved in amino acid metabolism; found in serum.
CDT	Desialylated transferrin variant appearing in serum.
TSA	Total amount of sialic acid in the serum.
5-HTOL	Minor metabolite of serotonin; body excretes via urine.
Beta-Hex	Lysosomal hydrolase that exists in most cell types; metabolism of carbohydrates and gangliosides in liver cells.
SIJ	Glycoprotein found in needed complexes, such as lipoproteins, that are responsible for transporting lipids in the blood.
Salsolinol	Formed when dopamine reacts either with alcohol's byproduct acetaldehyde or with pyruvate; found in blood, urine, or brain tissue.
Direct Biomarker	Description
Acetaldehyde	Alcohol dehydrogenase converts ethanol to acetaldehyde; measured in blood; acetaldehyde that is bound to tissue proteins, called acetaldehyde adducts, found in essentially all perfused tissues.
Acetic acid	Major final product of ethanol metabolism; found in blood.
FAEE	Formed by reaction of ethanol with free fatty acids in blood and tissues; found in blood, hair, and meconium fluid.
EtG	Minor nonoxidative metabolite of alcohol that forms in the liver when alcohol reacts with glucuronic acid in the presence of membrane-bound mitochondrial uridine diphosphate glucuronyl transferase; found in blood, urine, hair, bone marrow, bile, muscle, and fat.
EtS	Formed from ethanol through sulfotransferase; excreted in urine.
PEth	Formed from ethanol through phosphatidylolation action of enzyme phospholipase D; found in blood.
Alcohol-ethanol	Found in blood, urine, saliva, vitreous fluid, and sweat.

TABLE 2**Detection Period From Time of Alcohol Abstinence**

Indirect Biomarker: Collection Method	Time Frame
MCV: blood	Normalizes in 2–4 months
GGT: blood	1–4 weeks
AST: blood	2–3 weeks
ALT: blood	2–3 weeks
TSA: blood	2–5 weeks
5-HTOL: urine	Up to 24 hours
CDT: blood	2–4 weeks
Direct Biomarker: Collection Method	Time Frame
Alcohol: blood	Half-life 2–14 hours
Acetaldehyde: blood	Adducts persist for days after alcohol is eliminated
Acetic acid: blood	Few hours
FAEE: blood	24–99 hours
EtG: urine, blood	Up to 5 days in urine, 36 hours in blood

TABLE 3**Intensity/Pattern of Use of Alcohol Biomarkers**

Indirect Biomarker: Collection Method	Intensity/Pattern of Use
MCV: blood	Chronic heavy drinking; response slow to abstinence/relapse.
GGT: blood	Sustained excessive drinking; affected more by intensity than frequency.
AST: blood	Chronic or heavy drinking.
ALT: blood	Chronic or heavy drinking.
TSA: blood	Longer than CDT/GGT to decrease during abstinence; less useful in relapse; increased more in alcohol-dependent patients than in social drinkers.
5-HTOL: urine	Effective to monitor recent alcohol intake and relapse; not for low and nontoxic amounts.
CDT: blood	50–80 g of alcohol or 5–7 standard drinks per day for at least 1–3 weeks; 30% decrease indicates abstinence; 30% increase indicates relapse.
Direct Biomarker: Collection Method	Intensity/Pattern of Use
Alcohol: blood	Levels can be used to deduce tolerance; helps distinguish between acute intoxication and chronic alcohol use.
Acetaldehyde: blood	Detects acute and chronic drinking; variation in amount of adducts formed.
Acetic acid: blood	Lacks correlation to ethanol concentration.
FAEE: blood	More reliable for chronic than acute abuse.
EtG: urine	Minor amounts of alcohol use; potentially distinguish social drinkers from harmful drinkers; detects relapse.

TABLE 4

Sources of False-Positives/-Negatives for Alcohol Biomarkers

Indirect Biomarker: Collection Method	False +/False –
MCV: blood	Increased with folate/B ₁₂ deficiency, bleeding, hemoglobinopathies, hypothyroidism, valproic acid use, hyperglycemia, bone marrow disorders, or smoking. Inversely associated with coffee intake.
GGT: blood	Increased with pancreatitis, prostate disease, hypertriglyceridemia, diabetes, phenytoin use, NSAID use, obesity, renal disease, oral contraceptive use, barbiturate use, venlafaxine use, anticoagulant use, or smoking.
AST: blood	Increased with use of antibiotics, valproic acid, statins, NSAIDs, anticoagulants, bupropion, venlafaxine, tacrine, naltrexone, atomoxetine, and atypical antipsychotics; obesity; strenuous exercise; or muscle disorders. Inversely associated with coffee intake.
ALT: blood	Increased with use of antibiotics, valproic acid, statins, NSAIDs, anticoagulants, bupropion, venlafaxine, tacrine, naltrexone, atomoxetine, and atypical antipsychotics or obesity. Inversely associated with coffee intake.
TSA: blood	Increased with lung/cervical cancer, cardiovascular disease, or diabetes.
5-HTOL: urine	Increased with disulfiram use and dietary intake of serotonin.
CDT: blood	Increased with iron deficiency, carbohydrate-deficient glycoprotein syndrome, genetic D variants of transferrin, or possibly use of enzyme-inducing antiepileptics. Decreased in women using oral contraceptives. Inversely associated with body mass index. Lower % CDT with angiotensin II receptor blockers.
Direct Biomarker: Collection Method	False +/False –
Alcohol: blood	In abstinent patients, low concentrations of alcohol due to fermentation in colon.
Acetaldehyde: blood	False-positive due to formation of acetaldehyde in blood after sample collection.
Acetic acid: blood	Alcohol-induced increase in acetate levels partially inhibited by 4-methylpyrazole, a selective inhibitor of alcohol dehydrogenase.
FAEE: blood	Free fatty acid levels rise during fasting; restriction of fat intake may lead to detectable levels in serum.
EtG: urine	Increased with kidney disease, alcohol in food, cough syrup, communion wine, or mouthwash. False-negative with urinary tract infection.

TABLE 5**Effects of Hepatic Impairment on Alcohol Biomarkers**

Indirect Biomarker: Collection Method	Hepatic Impairment
MCV: blood	Specificity lower in hepatitis and non-alcohol-dependent cirrhosis.
GGT: blood	Specificity lower in hepatitis and non-alcohol-dependent cirrhosis; lower in hepatic failure.
AST: blood	Lower in hepatic failure.
ALT: blood	Lower in hepatic failure; increased in nonalcoholic steatohepatitis and hemochromatosis.
TSA: blood	Less dependent on hepatic status in assessment of alcohol use disorders; higher sensitivity if without hepatic disease than with hepatic disease.
5-HTOL: urine	More evidence is needed.
CDT: blood	Very severe hepatic damage may elevate levels in absence of heavy alcohol use; caution if cirrhosis reaches Child-Pugh class of C; % CDT elevated in primary biliary cirrhosis and hepatocarcinoma; fulminant hepatitis C may cause false-positive; more specific than GGT in hepatic disease.
Direct Biomarker: Collection Method	Hepatic Impairment
Alcohol: blood	Blood alcohol concentration indistinguishable between alcoholic hepatitis group and controls in one study.
Acetaldehyde: blood	Abstinent alcoholics with cirrhosis and nondrinking patients with nonalcoholic hepatic disease have increased concentrations.
Acetic acid: blood	More evidence is needed.
FAEE: blood	More evidence is needed.
EtG: urine	Cirrhosis of liver has no significant effect on levels.

TABLE 6**Effects of Age on Alcohol Biomarkers**

Indirect Biomarker: Collection Method	Age Effect
MCV: blood	Less sensitive in patients younger than 30 and in the elderly.
GGT: blood	Limited value in patients younger than 30 and older than 60.
AST: blood	Relatively insensitive to alcohol use in patients younger than 30 and older than 70.
ALT: blood	Relatively insensitive to alcohol use in patients younger than age 30 and older than 70.
TSA: blood	Reportedly varies with age, but more research is needed.
5-HTOL: urine	Reportedly does not vary with age, but more research is needed.
CDT: blood	Higher sensitivity and specificity in young men aged 20–40 compared to older men and women; % CDT test does not appear to be age-dependent.
Direct Biomarker: Collection Method	Age Effect
Alcohol: blood	Elderly become intoxicated and reach higher peak levels more quickly than the young.
Acetaldehyde: blood	More research is needed.
Acetic acid: blood	More research is needed.
FAEE: blood	Correlation with age not found, but more research is needed.
EtG: urine	Increased age may increase levels.

TABLE 7

Effects of Sex on Alcohol Biomarkers

Indirect Biomarker: Collection Method	Sex Effect
MCV: blood	Women more likely to show elevation; sensitivity to predict heavy alcohol use higher in women; specificity to predict heavy alcohol use higher in men.
GGT: blood	Men more likely to show elevation; lower in women due to suppression of enzyme activity by estrogen and progesterone; higher after menopause.
AST: blood	No association noted.
ALT: blood	Men have wider range, especially in older subgroups.
TSA: blood	Not influenced by sex, but more research is needed.
5-HTOL: urine	Not influenced by sex, but more research is needed.
CDT: blood	More sensitive to frequency of alcohol use in men and to intensity of alcohol use in women; higher levels before menopause may be due to blood loss during menses; may not need sex-specific normal cutoff if % CDT is used.
Direct Biomarker: Collection Method	Sex Effect
Alcohol: blood	Blood concentrations elevate quicker in women.
Acetaldehyde: blood	Metabolism in women may decrease with age.
Acetic acid: blood	More research is needed.
FAEE: blood	Variable results found.
EtG: urine	Men have decreased levels.

TABLE 8

Effects of Ethnicity on Alcohol Biomarkers

Indirect Biomarker: Collection Method	Ethnicity Effect
MCV: blood	Among African Americans and Latin Americans, women have lower values; values in Asian children lower than in European children.
GGT: blood	May be more likely elevated in South Asians, Africans, Mexicans, or Brazilians.
AST: blood	May be more likely elevated in South Asians, Africans, Mexicans, or Brazilians.
ALT: blood	May be more likely elevated in South Asians, Africans, Mexicans, or Brazilians; 1.5 times higher in African American men and 1.8 times higher in Hispanic than in European men; values in European men are 40% higher than in European women; values in African American women are 20% higher, and values in Hispanic women are 40% higher in than European women.
TSA: blood	Japanese studies report levels in the range of 50–58 mg/dL, while German, U.K., and Swedish studies report levels in the range of 60–65 mg/dL in healthy subjects.
5-HTOL: urine	Reportedly not influenced by ethnicity, but more research is needed.
CDT: blood	Valid in African Americans, Puerto Ricans, Caucasians, and Koreans; similar in South Asians and Europeans; 1% false-positive rate on CDTect (total CDT levels) due to genetic variants.
Direct Biomarker: Collection Method	Ethnicity Effect
Alcohol: blood	Asians have a functional polymorphism of ALDH2 that encodes a low-activity form of mitochondrial ALDH2 enzyme.
Acetaldehyde: blood	Asians have a functional polymorphism of ALDH2 that encodes a low-activity form of mitochondrial ALDH2 enzyme.
Acetic acid: blood	Asians have a functional polymorphism of ALDH2 that encodes a low-activity form of mitochondrial ALDH2 enzyme.
FAEE: blood	More research is needed.
EtG: urine	No significant effect.

TABLE 9**Cost of Alcohol Biomarkers in 3 Hospital Settings**

Indirect Biomarker: Collection Method	University Hospital (Indiana University 2007)	VA Hospital (VA Hospital 2007)	Public County Hospital (Wishard Hospital 2007)
MCV: * blood	\$71.50	\$55.25	\$50.00
GGT: blood	\$24.25	\$52.18	\$45.00
AST: blood	\$17.75	\$36.84	\$26.00
ALT: blood	\$18.75	\$38.37	\$26.00
TSA: blood	**	**	**
5-HTOL: urine	**	**	**
CDT: blood	\$406.00	\$128.93	\$169.28
Direct Biomarker: Collection Method	University Hospital (Indiana University 2007)	VA Hospital (VA Hospital 2007)	Public County Hospital (Wishard Hospital 2007)
Alcohol: blood	\$98.00	\$76.74	\$105.00
Acetaldehyde: blood	\$91.00	\$89.02	\$76.00
Acetic acid: blood	**	**	**
FAEE: blood	**	**	**
EtG: urine	\$126.00	\$98.23	\$106.00

Note.

* As part of complete blood count with differential and platelets

** Unavailable: these tests were not part of this hospital's capability at the time of publication. *