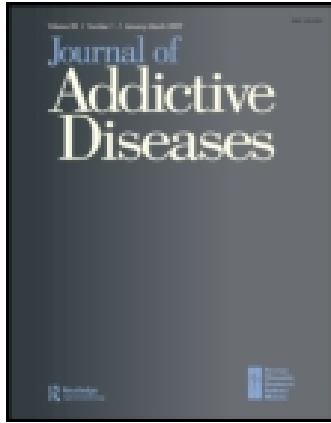


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R. Gregory Lande DO^a & Barbara Marin PhD^b

^a Department of Psychiatry, Walter Reed Army Medical Center, Silver Spring, MD

^b Army Substance Abuse Program, Walter Reed Army Medical Center, Washington, DC

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Biomarker Characteristics of Alcohol Use in the U.S. Army

R. Gregory Lande, DO
Barbara Marin, PhD

ABSTRACT. The objective of this study was to collect data providing information about the biomarker characteristics of alcohol use among a sample of military personnel in the U.S. Army. Military personnel enrolled in the Army Substance Abuse Program at the Walter Reed Army Medical Center in Washington, DC, received a comprehensive assessment that included a panel of direct and indirect biomarkers. A total of 80 records were reviewed to assess biomarker results. Higher Alcohol Use Disorders Identification Test scores correlated with higher gamma glutamyltransferase levels. All subjects tested negative on the initial breathalyzer. All subjects completed an initial ethyl glucuronide and approximately one-third received a positive report. A second positive ethyl glucuronide did correlate with a positive third and fourth result. Military personnel deployed to an area of combat operations reported tobacco use more frequently than military personnel not assigned to an area of combat operations. A broad range of assessment tools, including traditional interviews, standardized questionnaires, indirect, and direct biomarkers, provide clinicians the techniques to screen alcohol use disorders. Direct biomarkers are a valuable assessment tool but must be integrated with the other components of the diagnostic evaluation.

KEYWORDS. Alcohol, screening, biomarkers, tobacco

INTRODUCTION

The Army Substance Abuse Program (ASAP) is a manpower conservation program established to support the Army's readiness mission, providing outpatient substance abuse treatment services for beneficiaries of the military healthcare system. Largely dedicated to serving returning soldiers since the outset of the Iraqi conflict in 2003, the ASAP at Walter Reed Army Medical Center, as with other ASAP clinics throughout the world, has the potential to serve retirees, family members, and civilian employees as resources permit. Regardless of the population

served, the program is structured and staffed in accordance with Department of Army regulatory guidance, providing comprehensive assessment procedures that inform the development of accurate diagnostic impressions. These, in turn, guide the individualization of treatment activities. Whether individuals self-refer or are referred through command, medical, or legal channels, the evaluation process and treatment options are consistently applied and compliance is enhanced through close communication with the service member's command.

A thorough and accurate initial substance use assessment is the cornerstone of effective

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R. Gregory Lande is affiliated with the Department of Psychiatry, Walter Reed Army Medical Center, Silver Spring, MD.

Barbara Marin is Clinical Director, Army Substance Abuse Program, Walter Reed Army Medical Center, Washington, DC.

Address correspondence to: R. Gregory Lande, DO, Clinical Consultant, Department of Psychiatry, Walter Reed Army Medical Center, 13826 Bison Court, Silver Spring, MD 20906 (E-mail: rglande@pol.net).

treatment. With this in mind, the ASAP at the Walter Reed Army Medical Center undertakes a comprehensive assessment for all patients referred to the program. Each new patient receives a detailed clinical evaluation conducted by a licensed addiction counselor. Counselors augment the initial clinical interview through the use of both direct and indirect biomarkers. The indirect biomarkers include gamma glutamyltransferase (GGT), aspartate aminotransferase (AST), alanine amino-transferase (AST), and erythrocyte mean cell volume (MCV). These biomarkers are well established in clinical practice. Both objective and subjective measures are used to complete a thorough biopsychosocial history in the context of monitored abstinence for a period of at least 2 weeks. A variety of laboratory tests are employed, including AST, GGT, MCV, and total cholesterol. Abstinence from alcohol is assessed through daily breath testing and unannounced urinalysis for ethyl glucuronide (EtG). The Alcohol Use Disorders Identification Test (AUDIT) is used to augment the patient's self-report in building this history. Biomarker tests and abstinence monitoring continue at varying intervals throughout the course of treatment.

The indirect biomarkers of alcohol use have varying degrees of sensitivity, specificity, and detection windows. As a screen for alcohol dependence, GGT, AST, and ALT have moderate sensitivity and moderate specificity, with MCV scoring low on sensitivity but higher on specificity.^{1,2} The reported sensitivity of GGT for detecting alcohol abuse can range from 40% to 60%, with specificity as high as 80%.³ In another report, the authors reported a sensitivity of 42% and a specificity of 76% for GGT and a sensitivity of 24% and a specificity of 96% for MCV in detecting alcohol abuse.⁴ Continued high elevations of GGT over time correlate with an increased number of drinking episodes.⁵

GGT levels increase with consumption levels around 4 drinks a day for 1 or 2 months and typically return to normal levels after about a month of abstinence.⁶ Less is known about the relationship between alcohol levels and MCV, although it still takes 1 or 2 months for red cell morphology to reflect consumption excesses.⁶ High MCV values persist for months under conditions

of abstinence.⁷ Again, precise drinking patterns associated with AST and ALT elevations are unclear, but once elevations occur they persist for several weeks.⁷

Several clinical conditions conspire to reduce the effectiveness of the indirect biomarkers. Liver disease affects the GGT sensitivity whereas other medical conditions, such as diabetes, pancreatitis, a high carbohydrate diet, and various medications, affect the specificity.⁸ The same factors affecting GGT can also affect AST and ALT.¹ The screening utility of MCV is adversely impacted by folate deficiency, various hematologic disorders, and medications that reduce folate.¹

Screening questionnaires, particularly when used as part of a comprehensive assessment, increase the identification of alcohol use disorders. The AUDIT is a simple, self-administered 10-item questionnaire. Scores of eight or higher suggest an alcohol use disorder.⁹ The AUDIT, using a score of 8 or more, can achieve both high sensitivity and specificity in screening alcohol use disorders.¹⁰ For purposes of identifying patients who may experience alcohol withdrawal, researchers reported a positive predictive value of 47.1% when an AUDIT score of 8 or more was combined with two abnormal biomarkers.¹¹ All self administered clinical assessments, including the AUDIT, fundamentally rely on the test taker's frank and full disclosure. The AUDIT can be a useful component in the comprehensive assessment of alcohol use disorders but solely by itself would be inadequate.

Direct measures of alcohol consumption include blood alcohol tests, breathalyzers, and a variety of new biomarkers. Both blood alcohol and the breathalyzer have short windows of detection with metabolism often complete within 10 hours.¹² The new direct biomarkers offer certain clinical advantages, when combined with a comprehensive assessment, in screening alcohol use disorders and in monitoring abstinence. In particular, the new biomarkers offer a longer window of detection and, as in the case of EtG, permit quantification through a urine specimen.

The human body metabolizes the vast majority of alcohol, in the range of 90% to 95%, through an oxidative process involving liver enzymes.¹³ Researchers in 1952 reported that a

small fraction of alcohol is metabolized through nonoxidative pathways and excreted in the urine as ethyl glucuronide.¹⁴ For three decades, the medical and scientific communities paid scant attention to EtG. A group of researchers revived the interest in EtG through a study examining the potential value of this direct alcohol biomarker as a tool in detecting relapse.¹³ This research group reported detectable amounts of EtG 80 hours after alcohol consumption. Subsequent studies published by several researchers have further defined basic characteristics of EtG.

Small quantities of alcohol, as little as seven grams, can be detected through EtG analysis 6 hours after consumption.¹⁵ Researchers examined the effect of water dilution on EtG levels.¹⁶ Voluntary water consumption 3 hours after alcohol use produced a drop in the urinary values of both EtG and creatinine. The study authors suggested that one method of compensating for water dilution might be through an EtG–creatinine ratio. In another study, a comprehensive literature review examining test data from more than 4,000 specimens led to the authors' endorsement of EtG as a useful screening tool for detecting relapse.¹⁷ Another favorable characteristic of EtG is the apparent lack of the metabolite accumulating after multiple episodes of drinking.¹⁸ Multiple urine specimens with increasing levels of EtG actually seem to point toward recent drinking as opposed to any accumulation.¹⁹

EtG is a normal byproduct of alcohol metabolism which raises concerns unique to this class of direct biomarkers. Any source of alcohol, intentionally or accidentally consumed, produces EtG. Two studies examined the effect of gargling with mouthwash on EtG levels.²⁰ The authors reported that gargling mouthwash containing 12% alcohol resulted in positive EtG levels but none exceeded 345 ng/mL. A false negative EtG might result in the presence of bacteria laden urine. The presence of bacteria promotes glucuronidase which degrades EtG.²¹

Even as researchers learn more about the characteristics of EtG, its value as a direct biomarker with an 80-hour detection window has led to few clinical applications. Perhaps the first major clinical role for EtG evolved as part of a state medical board's physician monitoring program. Physicians enrolled in the monitoring pro-

gram all had a substance use disorder and, as a condition of maintaining a medical practice, agreed to remain alcohol free. To ensure compliance, the state medical board required the submission of observed urine specimens to test for the presence of EtG.²² To address the risk of accidental alcohol exposure, various programs adopted an informed consent agreement reminiscent of similar warnings accompanying the use of disulfiram.^{23,24}

Recognizing both the promise and potential pitfalls of EtG, a federal advisory noted that EtG "may have a supportive role in therapeutic interventions in an environment where breath or blood alcohol tests are used. . . . However, until further research has been conducted, the high sensitivity of the EtG . . . does not permit the distinction between alcohol exposure and alcohol consumption at lower levels of possible biomarker detection."¹

METHODS

This study reviewed 80 records of patients in an effort to explore the screening test results from a sample of individuals enrolled in the Walter Reed Army Substance Abuse Program. The entire sample consisted of active duty military personnel consecutively enrolled in the ASAP at the Walter Reed Army Medical Center during an approximate 6-month period. The Institutional Review Board at the Walter Reed Army Medical Center approved the study as an exempt protocol. Data were analyzed using SPSS version 14 (SPSS, Inc., Chicago, IL).

RESULTS

Records reviewed included 65 (81%) men and 15 (19%) women. Mean age of the subjects was 29 years, with a range of 18 to 53 years. Approximately 10% ($n = 9$) of the subjects were officers, the remainder were enlisted military personnel. Slightly more than one-third of the sample ($n = 31$) reported deployment to an area of combat operations. Another one-third ($n = 25$) of the sample reported active tobacco

use. The most commonly identified substance use disorders included alcohol abuse ($n = 41$, 51.25%) and alcohol dependence ($n = 28$, 35%). Among other substances, 11 subjects met criteria for a cannabis use disorder ($n = 80$, 13.75%) and 7 met diagnostic criteria for a cocaine use disorder ($n = 80$, 8.75%).

All subjects completed an AUDIT ($n = 80$, 8.52 ± 8). Slightly fewer than half ($n = 33$, 41.25%) scored an eight or above on the AUDIT. All subjects tested negative on the initial breathalyzer. The indirect biomarkers were available from 79 records. The reference range for GGT was 15 to 73 u/L, with the mean among the study subjects falling roughly in the middle ($n = 79$, 41.58 ± 83). The reference range for AST is 15 to 59 u/L, with the mean among the study subjects again falling roughly in the middle ($n = 79$, 30.30 ± 26). The reference range for MCV is 79.5 to 96.8 fl, with the mean among the study subjects falling near the middle ($n = 79$, 88.43 ± 10.18).

Aside from the negative breathalyzers, the only other direct biomarker routinely used in the ASAP at the Walter Reed Army Medical Center is EtG. National Medical Services performs the EtG analysis using liquid chromatography/tandem mass spectrometry with a 3-day turnaround time and reports the results in ng/mL. All subjects completed an initial EtG, among which approximately one-third received a positive report ($n = 25$, 31.25%). Positive EtGs ranged from 260 ng/mL to 290,000 ng/mL. Subjects enrolled in the ASAP provided an EtG specimen approximately once a week. Among a sample of 45 second specimen EtGs, approximately one-fifth tested positive ($n = 8$, 17.78%). Of the 8-second specimen positive samples, most ($n = 6$, 75%) came from subjects with an initial positive screen for EtG. Among a sample of 38 third specimen EtGs, less than one-fifth ($n = 6$, 15.79%) tested positive. Among a sample of the 6 third specimen positive samples, most ($n = 5$, 83%) came from subjects with a previous positive screen for EtG. Among a sample of 25 fourth specimen EtGs, nearly all tested negative ($n = 23$, 92%). Once again, the two positives came from subjects with a previous positive screen for EtG. Among a sample of 19 fifth specimen EtGs, only one tested positive and this was from

a subject with prior positives ($n = 1$, 5.26%). Through the course of the entire study, subjects contributed 232 EtG specimens, producing an aggregate positive rate of nearly one-fifth ($n = 43$, 18.53%).

Further data analysis produced several findings. A positive initial screening EtG did not significantly correlate with a second positive result. A second positive EtG did correlate with a positive third and fourth result. Higher AUDIT scores correlated with higher GGT levels (Pearson's $\rho = .308$; $n = 79$; $P = .01$, two-tailed). Older ages also correlated with higher GGT levels (Pearson's $\rho = .312$; $n = 79$; $P = .01$, two-tailed). This sample revealed no significant correlations between elevated EtG levels, MCV, or GGT. As might be expected, older ages also correlated with higher cholesterol levels (Pearson's $\rho = .374$; $n = 78$; $P = .01$, two-tailed). Military personnel deployed to an area of combat operations reported tobacco use more frequently than military personnel not assigned to an area of combat operations $\chi^2(1, n = 77) = 4.74$, $P < .05$.

DISCUSSION

The ASAP at the Walter Reed Army Medical Center is the military's version of an employee assistance program. One major goal of an employee assistance program is the careful management of the boundary between individual treatment needs and the maintenance of a safe, productive workplace. In today's modern army, sophisticated weaponry, a lethal battlefield, and continuous operations require soldiers be physically and mentally fit. Soldiers returning home from an area of combat operations typically readjust to their non-war environment over a period of weeks or months with minimal sequelae. Substance use disorders can impair cognition and, in the chaos of war, increase the likelihood of a bad outcome. In a similar fashion, substance use disorders can impair the normal process of reintegration after the soldier returns home and may impair recovery from the physical or psychological aftermath of combat. These scenarios provide clinical justification for a comprehensive and aggressive program to identify and manage substance use disorders in the military.

As previously noted, whether individuals self-refer or are referred through command, medical, or legal channels, the evaluation process and treatment options are consistently applied and compliance is enhanced through close communication with the service member's command. This approach maximizes adherence to carefully crafted treatment plans built from joint discussions between the service members, ASAP counselor, and unit commander.

In the assessment and treatment of service members, substance use screening tools for abstinence monitoring are important components in delivering safe, effective care. The ASAP at the Walter Reed Army Medical Center relies on a battery of clinical assessments, incorporating both subjective and objective tools in a comprehensive effort to understand and manage substance use disorders. This study examined some of those efforts, most notably the biomarker characteristics exhibited by a typical sample of 80 military personnel enrolled in the ASAP.

In some settings in the military, particularly in remote assignments, access to routine laboratory studies might be limited. For that reason, it was encouraging that higher AUDIT scores correlated with higher GGT levels. The AUDIT is a simple instrument to administer and can, based on the findings in this study, be used independent of laboratory studies to screen for potential liver enzyme elevation. Another important finding with clinical application involved the higher levels of tobacco use reported by military personnel returning from an area of combat operations. Aside from the obvious physical and health implications, the higher rate of tobacco use among combat veterans may be an expression of anxiety, perhaps resulting from delayed onset or as yet unresolved traumatic experiences. Previous studies have reported increased tobacco use following a traumatic incident.²⁵⁻²⁷

The results from this study highlighted the value of direct biomarkers, particularly EtG, in both screening and abstinence monitoring. When combined with other elements of an assessment, EtG can reveal alcohol use not detected by other means. EtG's 80-hour detection window is particularly helpful in identifying binge drinking when initiated during the early part of a weekend or after holidays or other

extended absences from duty. Approximately one-third of the service members referred to the ASAP tested positive for EtG at their initial assessment. That result stands in stark contrast to the breathalyzer results, which uniformly tested negative. Although an initial positive EtG did not predict a subsequent second positive in the same individual, a second positive in the same individual predicted a third and fourth positive result. This small group probably deserves more intense clinical management.

As a new, direct clinical biomarker, EtG can play a valuable role in detecting occult alcohol use in high risk populations. Several caveats accompany the use of EtG. Any positive EtG must take into account the possibility of accidental exposure through innocuous acts such as the use of alcohol-based hand sanitizers, mouthwash, elixirs, and a myriad of other products containing alcohol. For abstinence monitoring, this may simply require a "contract" between the patient and the clinician setting forth in writing the imperative need to avoid products alcohol containing. Such a contract will bear remarkable similarity to the standard injunctions every patient receives when prescribed disulfiram. Another alternative would establish a threshold laboratory value for EtG below which all tests would be considered negative. This practice, depending on where the cut-off resides, could eliminate spurious exposure claims.

Clearly, no single test can stand alone in making important clinical or employment related decisions. A rational approach to the clinical management of alcohol use disorders in an employee assistance program setting requires a carefully crafted balance of traditional interviews, collateral data collection, the use of standardized instruments, such as the AUDIT, and a mix of direct and indirect biomarkers. This reasoned approach offers the best hope of prudently managing risk, providing evidenced based clinical care, and promoting a safe working environment.

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