Hair ethylglucuronide and blood phosphatidylethanol detection of 4 DUI driver risk factors

Paul R. Marques\(^1\) A. Scott Tippetts\(^1\) Michel Yegles\(^2\)

\(^1\)Pacific Institute for Research and Evaluation
11720 Beltsville Dr., Suite 900, Calverton, MD USA 20705

\(^2\) Laboratoire National de Santé, Toxicologie, Université du Luxembourg, 162a, av. Faïencerie, L-1511 Luxembourg

Abstract

Background
Ignition interlocks reduce recidivism while installed, a benefit lost once devices are removed. Interlock BAC test fail rates predict this post-interlock recidivism. Various alcohol biomarker types, sourced from urine, blood and hair predict interlock fail rates. Which biomarkers best predict recidivism and which would be the best components in a panel of markers to help evaluate drink-driving offenders?

Aims
The aim is to characterize risk indicators and outcomes among interlock participants. This paper focuses on new analyses comparing different marker types in prediction of 4 categories of criterion correlates or outcomes: recidivism, alcohol dependence, ordinal fail rates, maximal BAC attained during the first two interlock months.

Methods
Interlock offenders gave consent and interviews (for DSM4 diagnosis), self-report assessments (DRINC, AUDIT, TLFB) and contributed blood, hair, urine for analysis of GGT, MCV, ALT, AST, PEth-HPLC, PEth-LCMSMS, uEtG, hEtG, uETS, hFAEE, %CDT, γ%CDT. ROC analysis of interlock BAC test records and driver records yielded predictor and outcome variables.

Results
Hair EtG was the strongest predictor of baseline alcohol dependence and subsequent recidivism; it shared honors with PEth for predicting maximal recorded levels of BAC. PEth was the strongest predictor of failed BAC tests across 5 ordinal combinations of failed BAC tests, both overall and morning tests. γ%CDT was the best indirect marker. TLFB “drinks per drinking day” was the only interesting non-biomarker predictor. Hair EtG above either the 30 pg/mg cutoff (2/3 of drivers above) or the 50 pg/mg (1/3 of drivers above) is strongly associated with other self-report, diagnostic and interlock-based indicators of alcohol driving risk.

Discussion
PEth and hair EtG are the two best component alcohol biomarkers to include in a comprehensive monitoring panel for driver alcohol risk. Hair EtG overlaps little with other alcohol biomarkers in explaining variance. GGT and %CDT, while weaker, are the best indirect markers.

\(^1\) Supported by NIAAA Research Grants R01 AA014206 and R21 AA019696
Introduction

Interlock BAC test fail rates predict post-interlock recidivism. Various alcohol biomarker types, both direct and indirect sourced from urine, blood, and hair, predict interlock fail rates. This paper provides new analyses comparing different marker types in prediction of 4 criteria or outcomes: new recidivism, alcohol dependence, morning plus overall fail rates, and maximal BAC attained during the first two interlock months.

Marques et al., (2010) reported that the average levels of six different alcohol biomarkers: phosphatidylethanol (PEth), gamma glutamyltransferase (GGT), percent carbohydrate deficient transferrin (%CDT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), macrocytic volume (MCV), measured at the start and the end of a period of interlock controlled driving, were largely unchanged (at the group level) over the mean 8 intervening months. Despite recidivism reductions, and an aggregate 50% reduction in rates of failed BAC test logged on the interlock device, drinking levels held constant during the interlock period even while drinking-driving declined by 2/3 (based on recidivism data). Declining recidivism and BAC test failures during the interlock had for some years been viewed as evidence of a reduction in drinking. The biomarker data suggests that view was premature.

An estimate of drinking proclivity would be useful before a driver is released from an interlock program. The BAC test fail rates from the interlock record are one source of information, but exclusive reliance on it could easily encourage actively monitored drivers to avoid the interlock car toward the end of the required time. Alcohol biomarkers are endogenous to the individual and so cannot be easily gamed, but there are many markers to choose from. What might be the best alcohol biomarkers for estimating drinking proclivity near the end of an interlock program?

The ability to anticipate driver risk based on the pattern of interlock BAC test fail rates has led several state governments to extend interlock time for these higher risk drivers. This is sensible policy, but it leaves unanswered the question: what explains the rapid reversion to control levels of recidivism once the interlocks are removed? Having attained some degree of accommodation to drinking AND driving, why would drivers change, and what do they change?

Blood and urine alcohol biomarkers can extend the surveillance window to detect drinking for several days to weeks or more after significant consumption. Direct alcohol biomarkers (PEth, EtG, EtS, FAEE) are ethanol itself, products of minor ethanol metabolic pathways, or are produced only in the presence of alcohol; since these directly reflect alcohol exposure they have higher sensitivity and specificity than indirect markers. Indirect markers, often thought of as disease markers, include (GGT, MCV, ALT, AST, CDT); these are liver enzymes, blood products, or physiologic reactions that occur after regular high levels of alcohol exposure.

Some alcohol biomarkers can be measured in hair (due to uptake and sequester from blood in the hair follicles) and extend the detection period to several months of past alcohol consumption. Høiseth et al. (2009) noted that hEtG shows the highest sensitivity relative to traditional biomarkers with levels proportional to the alcohol consumed. Pirro et al. (2011) reported hEtG to be the most accurate biomarker for the identification of heavy drinking. Liniger et al. (2010) concluded that hEtG is the best choice for assessing fitness in suspected drinking drivers.
The Society of Hair Testing (SoHT), concluded that 30 picograms of EtG per milligram of hair, estimated to grow 1 cm/month, is consistent with abuse levels of alcohol consumption. Dufaux et al. (2012) analyzed samples from German drivers seeking to reinstate driver licenses and found that the measurement of EtG in hair, with its longer time horizon, detected 12.7% positives relative to 2.1% positives found with the measurement of EtG in urine, a 6-fold detection improvement. These are stable findings based on sample sizes of 4000 and 13,000, respectively.

Methods

Subsequent to a DUI conviction, 534 interlock offenders (87% male, age 38.6 ± 12, 64% first offenders) signed informed consent documents, sat for interviews, and provided blood, hair and urine for alcohol biomarker determinations. The project was conducted in Edmonton, Alberta, Canada, at the Guardian Interlock Center. Interlock company employees had no role in the research, and research staff had no role in the interlock business. New analyses reported here complement and extend preliminary results previously published (Marques, et al., 2010b). Key assessments included the Timeline Followback (TLFB), Alcohol Use Disorders Inventory (AUDIT), the Drinkers Inventory of Consequences (DRINC), and the DIS-C (Diagnostic Interview Schedule) for DSM-4 diagnoses of Alcohol Dependence and Alcohol Abuse.

Interlock data and biological markers

Interlock performance data were based on BAC tests during the mean 8 months of interlock program participation; the average driver contributed ≈ 2800 BAC tests. With minor exceptions, interlock BAC test data were available on all participants. Not all enrollees were willing to provide blood and other biological specimens.

12 different alcohol biomarkers, or analysis types, were measured at baseline or calculated from baseline data. Six of the alcohol biomarkers were indirect markers, the other six analyses were for direct markers. The latter include PEth measured by HPLC (high performance liquid chromatography) and a subset of those samples was also measured for PEth by LCMSMS (liquid chromatography tandem mass spectroscopy). Others include hair FAEE, urine EtG, urine EtS (ethyl sulfate), and hair EtG. Six blood source biomarkers (GGT, %CDT, PEth, AST, ALT, MCV) were available for 300 participating subjects at baseline (range 298-302). Another, gamma %CDT, was calculated as a log combination of GGT and %CDT, based on Finnish research in which gamma %CDT (γ%CDT)= [0.8 ln(GGT) + 1.3 ln(%CDT)]. Other markers, including hair EtG were added to the panel after the start of the study. 146 subjects provided hair for EtG measurement. Measurements were performed by colleagues in laboratories in the US, Germany, Luxembourg, and Sweden.

Statistical analyses

Sensitivity analyses of 4 categories of criterion variables were made by calculating A’, which represents the area under the ROC curve, ranges from 0.0 to 1.0, and summarizes sensitivity points at various specificities. Each point on the ROC curve measures a sensitivity level (on the y-axis) vs. 1-specificity (on the x-axis) that jointly produces the decision criterion as a predictor is varied. Using lower cutoff values of predictor variables results in greater sensitivity but less specificity; using higher cutoff thresholds provides greater specificity but less sensitivity.
A new fail rate variable is defined as a 5 level ordinal combination \((\text{combo5})\) of two types of BAC test failures: total fail rate and morning fail rate. \(\text{Combo5}\) reflects both overall fail rate and fails that specifically occur in the morning hours of 6-10 AM (Monday through Friday and 8 AM-12 noon Saturday and Sunday) that reflect prior night drinking. The maximal BAC levels \((\text{maxbac})\) recorded on the interlock device during the first 2 program months is analyzed as dichotomous splits; the \(A'\) values represent 5 different comparisons with increasingly higher fail maxima (BAC results above and below .05, .06, .08, .10, and .12 g/dL). These cutoffs begin as a contrast between the 67% with BAC maxima below .05 and the 33% of participants with maxima of .05 g/dL and above. The series ranges up toward a comparison of the 95% below and the top risk 5% subset with BAC maxima of .12 g/dL and above.

Also included in the ROC analyses are two dichotomous variables: new DUI events \((\text{recidivism})\) that occur after beginning the interlock study program, and program entry DSM-IV diagnoses of alcohol dependence \((\text{DSM dependence})\). 36 new DUI recidivist events among 34 participants were logged after interlock installation at a mean of 798 days, about 26 months after program entry (median 775 days, range 177-1563 days). Whether or not there was a new DUI, the duration of time following interlock installation ranged from 344 to 1602 days of data. Participant intakes proceeded continuously over 4 project years. 39% of the sample met criteria for alcohol dependence.

**Results**

The point estimates of recidivism prediction by 8 alcohol biomarkers along with pre-program prior DUI and three sensitive indicators from the TLFB interview are shown in Figure 1. Hair EtG was a substantially more sensitive predictor of recidivism \((A' = .7)\) than other test variables.

![Figure 1: Sensitivity (A') of predictors of post-installation recidivism](image)

Alcohol dependence is a valid alcohol risk factor. Figure 2 shows the point estimates associated with detection of an alcohol dependence diagnosis from the DSM-4 with all 12 biomarkers and other predictor variables. Here hEtG along with, uEtS and the TLFB measure, maximal drinks per drinking day, were all associated with entry dependence diagnoses \((A' = .67)\). However, since drinking level (max drinks) influences the dependence diagnosis, the self-report and the diagnosis are not independent. The LCMSMS PEth in Figure 2 also shows high sensitivity.
Hair ethylglucuronide and blood phosphatidylethanol detection of 4 DUI driver risk factors

Figure 2: Sensitivity (A’) of predictors of entry level of alcohol dependence

Figure 3 shows hEtG and PEth to be the most sensitive predictors of the highest BAC tests recorded during the first 2 months of interlock (A’ > .69). The chart does not show sensitivity at the highest specificity, BAC≥ .12 g/dl. At that level, hair EtG had A’ = .776, the highest found.

Figure 3: Sensitivity (A’) of predictors of mean maximal BAC tests (average .05-.12 g/dl)

The sensitivity of the predictors of the combined fail rate criterion (combo5) is not shown but the results are concordant with those reported earlier. The fail rate measures were more successfully detected by PEth (either method: A’ ≥ .72) than hEtG (A’ = .62). In that analysis, γ%CDT was also a sensitive indicator of the average of all BAC fail rates (A’ = .71).

Hair EtG levels are not strongly correlated with other alcohol biomarkers. At a sample split of 30 pg/mg (the SOHT cutoff for heavy drinking) 2/3 of the drivers are above it. At 50 pg/mg, 1/3 of drivers exceed the split. The high hEtG subsets have many other risk indicators such as TLFB self-reported consumption, dependence, and interlock-based indicators of alcohol driving risk.

Discussion

Earlier, we showed PEth was the best overall biomarker for predicting interlock BAC test failure rate, the best correlate of 9 other concurrently measured biomarkers, and the best correlate of self-report assessments about alcohol consumption and consequences in the TLFB, AUDIT, and
DRINC. In the ROC analyses here, the levels of EtG in hair were found to be a top predictor of criterion variables including: future recidivism, DSM4 alcohol dependence, and maximal BAC attained during the initial two months with an interlock. The direct markers (PEth, EtG) yielded more sensitive and specific ways to predict driver alcohol risk variables than did the indirect markers. Also, the number of prior DUI convictions, ordinarily one of the strongest indicators of driver risk, underperformed nearly all of the alcohol biomarker variables for predicting recidivism, dependence, fail rates, or maximal BACs.

Since hair EtG is not strongly correlated with the blood or urine markers concurrently studied, but still predicts driver drinking behavior, it is a good component in a panel of markers; each panel element ideally contributes unique variance. These results and our prior analyses of alcohol biomarkers suggest both hair EtG and blood PEth warrant inclusion as core parts of any alcohol biomarker panel for DUI drivers. We also know that the highest risk DUI drivers have only somewhat lower biomarker levels than do non-residential alcohol treatment patients (Marques, 2012). Few laboratories measure total PEth. However, the detection of non-zero, low levels of PEth in blood via measurement of the dominant subtype of PEth via LCMSMS (Marques et al., 2011) may make possible more widespread use of this method to enhance road safety.

References


