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Comparison of Phosphatidylethanol Results to Self-Reported Alcohol Consumption Among Young Injection Drug Users

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Abstract — **Aims:** To test the value of phosphatidylethanol (PEth) as a biomarker for alcohol consumption among injecting drug users (IDUs). **Methods:** As part of a longitudinal study of young IDUs, dried blood spots and self-reported alcohol by structured interview were collected at baseline. We compared self-reported alcohol use to detectable PEth (≥ 8 ng/ml) in the blood spots as well as the relationships between quantitative PEth results and quantity measures of alcohol consumption. **Results:** There were strong associations between PEth and self-reported categorical measures of alcohol consumption (all $P < 0.01$). There was high specificity for reporting abstaining from alcohol; 94% of those who reported not consuming alcohol in the prior month tested negative for PEth. PEth was well correlated with measures of alcohol use (e.g. with reported number of days drinking in the prior month: Spearman $r = 0.70$ ($P < 0.001$)). **Conclusions:** The positive correlation of PEth with reported alcohol consumption suggests that PEth may be a useful marker in settings where alcohol consumption is difficult to assess, or to corroborate or invalidate self-reported measures of alcohol consumption.

INTRODUCTION

Heavy alcohol consumption is known to cause and exacerbate several poor health outcomes including hypertension, liver disease, neuropsychiatric disorders, stroke, depression, pancreatitis, sexually transmitted infections and more (Miller and Anton, 2004; World Health Organization, 2013). The prevalence of heavy alcohol consumption by injecting drug users (IDUs) has been reported to range from 11 to 57% with heavy drinking defined as exceeding various thresholds (Le Marchand *et al.*, 2013). We and others (Stein *et al.*, 2000; Arasteh and Des Jarlais, 2009; Le Marchand *et al.*, 2013) have found that heavy alcohol consumption by IDUs was associated with both injection and sexual risk behaviors. Consequently, IDUs who consume large quantities of alcohol may be at increased risk for hepatitis C virus (HCV), the exacerbation of HCV-related conditions such as cirrhosis and liver cancer, HIV and other sexually transmitted diseases. Thus, interventions to reduce alcohol consumption among IDUs are needed and may have the collateral effects of decreasing the incidence and prevalence of HCV and other negative health outcomes associated with heavy drinking.

However, trials to reduce alcohol consumption and observational studies of alcohol use typically rely on self-report to measure alcohol intake (Miller and Anton, 2004). Self-report depends on the accuracy and honesty of the reporter and is potentially subject to social desirability bias and problems of recall (Stein *et al.*, 2000; Arasteh and Des Jarlais, 2009). Therefore, it may be useful to verify self-report measures with another source. Sensitive and specific biomarkers of alcohol consumption may be used to assess the validity of self-report and may additionally provide objective measures of alcohol consumption for research, monitoring, better understanding of drinking behaviors and patterns and evaluating clinical trials and treatment programs (Wurst *et al.*, 2005).

Phosphatidylethanol (PEth), an aberrant phospholipid found in cell membranes that is synthesized only in the presence of ethanol, is a sensitive and specific biomarker of alcohol consumption (Isaksson *et al.*, 2011). We found PEth

to be 88% sensitive and 89% specific among persons with HIV in Uganda for detecting any alcohol use in the prior 21 days (Hahn *et al.*, 2012), and others have found even more favorable test characteristics (97–99% sensitivity, 100% specificity) for heavy drinking in other populations (Aradottir *et al.*, 2006; Hartmann *et al.*, 2007). In comparison, while highly specific (82–100%), carbohydrate-specific transferrin (% CDT) is 39–95% sensitive for heavy drinking in the past month (Hannuksela *et al.*, 2007), and gamma-glutamyltransferase (GGT) is 34–85% sensitive and 11–95% specific for heavy drinking (Hannuksela *et al.*, 2007). Other markers have shorter windows of detection; urinary ethyl glucuronide (EtG) and ethyl sulfate (EtS) are detectable for up to 3 days (Wurst *et al.*, 2000, 2006). We therefore chose to use PEth to examine the validity of self-reported alcohol consumption over the prior month by young IDU, and we additionally characterized the relationship between quantitative PEth values and continuous measures of alcohol use among young IDUs.

METHODS

Study population and procedures

Between July 2010 and November 2011, IDUs under the age of 30 were recruited to participate in the UFO (an acronym for ‘U Find Out’) Study, a prospective cohort study examining the natural history of acute HCV infection in San Francisco. A convenience sample was recruited by street-based outreach workers, who invited potential participants to the study site using fliers, community providers and word of mouth. Eligibility criteria for participation in the baseline study visit required participants to be under age 30, to have reported injecting drugs in the prior month, to speak English and to plan to remain in the San Francisco Bay Area for at least 3 months. From 1 July 2011 onward, participants were eligible only if they reported not previously testing HCV positive, to enrich the UFO sample for HCV uninfected persons. At baseline, eligible participants gave informed consent, were interviewed by research assistants, received pre-test counseling and

were tested for HCV antibodies, and HCV RNA and dried blood spots (DBS) were collected for PEth testing.

Participants were encouraged to return for their HCV results, post-test counseling and medical and social referrals 1 week later. Participants were compensated US\$ 15 for the baseline visit and US\$ 40 when they returned for results. All study procedures were approved by the Institutional Review Board of the University of California, San Francisco.

Dried blood spot collection and laboratory testing

In order to obtain the DBS, the finger was punctured with a sterile disposable lancet and the second drop of blood was pressed onto a filter paper circle. Five spots were collected on the same card per participant. The DBS samples were allowed to dry for a minimum of 2 h and up to 3 h at room temperature prior to storage. This was considered a sufficient amount of time for the samples to dry according to the laboratory that conducted PEth testing (J. Jones, personal communication). DBS samples were stored frozen at -80°C for up to 18 months and were shipped at room temperature to the reference laboratory in December 2011.

The testing was conducted using liquid–liquid extraction of whole blood, analyzed quantitatively for PEth by a validated liquid chromatography–electrospray–tandem mass spectrometry (LC-MS/MS) method specific for PEth homologs (Jones *et al.*, 2011). The limit of detection was 2 ng/ml, the limit of quantitation was 8 ng/ml and the assay was linear up to 800 ng/ml, and the most prevalent PEth homolog (16:0/18:1) was measured. Previous studies showed that the correlation between PEth detected from whole blood versus DBS was 0.924 (Jones *et al.*, 2011). The intra-assay for concentration values of 20, 100 and 200 ng/ml ranged between 2.6 and 8.2 and the inter-assay for the same values ranged between 3.2 and 6.1 (J. Jones, personal communication). When PEth was detected, a second DBS on the same card was tested to confirm, and we used the average of the two results in our analyses. The confirmation of positive results was performed as part of the lab procedures (this lab frequently conducts drug and alcohol testing for evidentiary purposes). The Spearman correlation between the confirmatory PEth tests and the original tests was high and statistically significant ($r=0.93$, $P<0.001$) though not a 1:1 relationship as the assay was rerun on a second DBS from the same sample contributing to slight variability (J. Jones, personal communication). The coefficient of variation was 23.7%, with a slope and intercept for this linear regression of 0.80 ($P<0.001$) and -5.36 ($P=0.72$), respectively.

Baseline testing for anti-HCV was conducted using the Ortho Clinical Diagnostics, Raritan, NJ EIA-3 test, and HCV RNA testing was conducted using the discriminatory HCV transcription-mediated amplification assay component of the Procleix HIV-1/HCV assay. We considered HCV RNA positive or anti-HCV positive evidence of exposure to HCV.

Measures of self-reported alcohol consumption

Variables

Alcohol consumption was elicited using the 3-item Alcohol Use Disorders Identification Test Consumption (AUDIT-C) instrument, which produces a score from 0–12 (Bush *et al.*, 1998). The scale was modified to measure alcohol

consumption in the prior month, rather than past year, for better recall (Napper *et al.*, 2010). We created cut-off points for the AUDIT-C as follows: scores of 0–2 for women and 0–3 for men were considered an indicator of low-risk drinking, scores of 3–9 for women and 4–9 for men were considered an indicator of hazardous drinking and scores of 10–12 were considered an indicator of probable dependent drinking. The cut-offs defining hazardous drinking were based on guidelines developed by the Department of Veteran Affairs of several studies conducted in the general population (2010), and the cut-off for probable dependent drinking was found to be highly specific for alcohol dependence in family medicine patients (Rubinsky *et al.*, 2010). We previously used these cut-offs in a similar sample of young IDUs; one-third met these criteria and the results held up on analyses of the sensitivity to these cut-offs (Le Marchand *et al.*, 2013). Dichotomous measures of alcohol consumption (yes/no, in prior month) included: alcohol consumption, drinking until becoming unconscious and binge drinking defined as ever drinking six or more alcoholic drinks in one sitting. Continuous measures of alcohol consumption in the prior month included: AUDIT-C score, number of days drinking and total number of drinks consumed. In addition, we created a score representing symptoms of intoxication, with the goal of measuring alcohol consumption while avoiding known measurement issues in assessing numbers of standard drinks (Greenfield, 1998). These symptoms of intoxication questions assessed the number of days the participants became unconscious, had difficulty speaking or thinking, felt a false sense of confidence and/or they felt the mild effects of alcohol. Each day reaching each level of intoxication was given a score of 5 down to 1, corresponding with the highest to lowest level of intoxication. The scores for each person were totaled, with the highest maximum intoxication score equal to 150 (30 days reaching level 5).

Statistical analysis

For this analysis, we used baseline data. We calculated frequencies and percentages or medians and quartiles. We examined the associations between self-reported categorical measures of alcohol consumption and PEth (detectable yes/no) using Fisher's exact tests. We examined the relationship between quantitative PEth results (ng/ml) and continuous measures of self-reported alcohol consumption using scatter plots and calculated Spearman's rank correlations.

RESULTS

We screened 410 persons for the study and of them, 177 were eligible and 165 participants completed baseline study procedures. Of the 165, 1 refused DBS collection, 1 DBS was not collected in error, 22 DBS were collected but inadvertently excluded from the shipment to the lab and 4 participants over age 30 were excluded, leaving 137 for this analysis. The median age in the sample was 25.6 years [Interquartile range (IQR): 22.8–27.7] and the majority of the participants were white (75%) and male (74%) (Table 1). Almost a third (28%) had never previously been tested for HCV, and upon testing nearly half (43%) had been exposed to HCV (antibody and/or

RNA positive). The median year of injecting in the sample was 6.8 (IQR: 3.3–10.1).

Table 1. Demographic characteristics (N = 137)

	n (%)
Age median = 25.6, IQR 22.8–27.7	
<20	12 (8.8)
20–25	48 (35.0)
≥25	77 (56.2)
Race/ethnicity	
White	103 (75.2)
Non-white	34 (24.8)
Biological sex	
Male	101 (73.7)
Female	36 (26.3)
Highest grade completed	
<High school	49 (36.0)
High school degree	51 (37.5)
>High school degree	36 (26.5)
Years injecting median = 6.8, IQR 3.3–10.1	
<3 years	29 (21.2)
>3 years	108 (78.8)
HCV self-report	
Positive	25 (19.2)
Negative	50 (38.5)
Do not know	18 (13.9)
Other—indeterminate	1 (.8)
Never tested	36 (27.6)
HCV results	
Positive	58 (43.3)
Negative	76 (56.7)
HIV self-report	
Positive	4 (2.9)
Negative	97 (71.9)
Do not know	10 (7.4)
Never tested	24 (17.8)

We found strong associations between PEth and self-reported categorical measures of alcohol consumption (Table 2). Of note, there was high specificity for reporting abstaining from alcohol in the prior month. The majority (94%) of those who reported not consuming any alcohol in the prior month tested negative for PEth. In addition, the proportion with detectable PEth increased with the level of self-reported drinking. Among those who were classified as hazardous drinkers 61% tested positive, while of probable dependent drinkers, 88% tested positive for PEth.

There were statistically significant positive correlations between the continuous measures of alcohol consumption and the quantitative PEth value (ng/ml) (Figure 1). The strongest correlation was with the reported number of days drinking in the prior month and the quantitative PEth value (Figure 1; $r = 0.70, P < 0.001$).

DISCUSSION

To the best of our knowledge, this study is the first to examine the relationship between self-reported measures of alcohol consumption and PEth in young IDUs. We found a statistically significant relationship and positive correlation ($P < 0.001$) between various measures of self-reported alcohol consumption and PEth. The major findings of this study are as follows: (a) self-reported alcohol consumption (yes/no) is accurate in our sample, evidenced by 94% of the 36 participants who reported not drinking in the past 30 days were PEth negative; and (b) PEth was associated with increasing levels of alcohol consumption, as evidenced by increasing proportions positive for measures of heavier consumption and moderately strong Spearman correlations with continuous measures of alcohol consumption. Of note, a novel measure of alcohol consumption

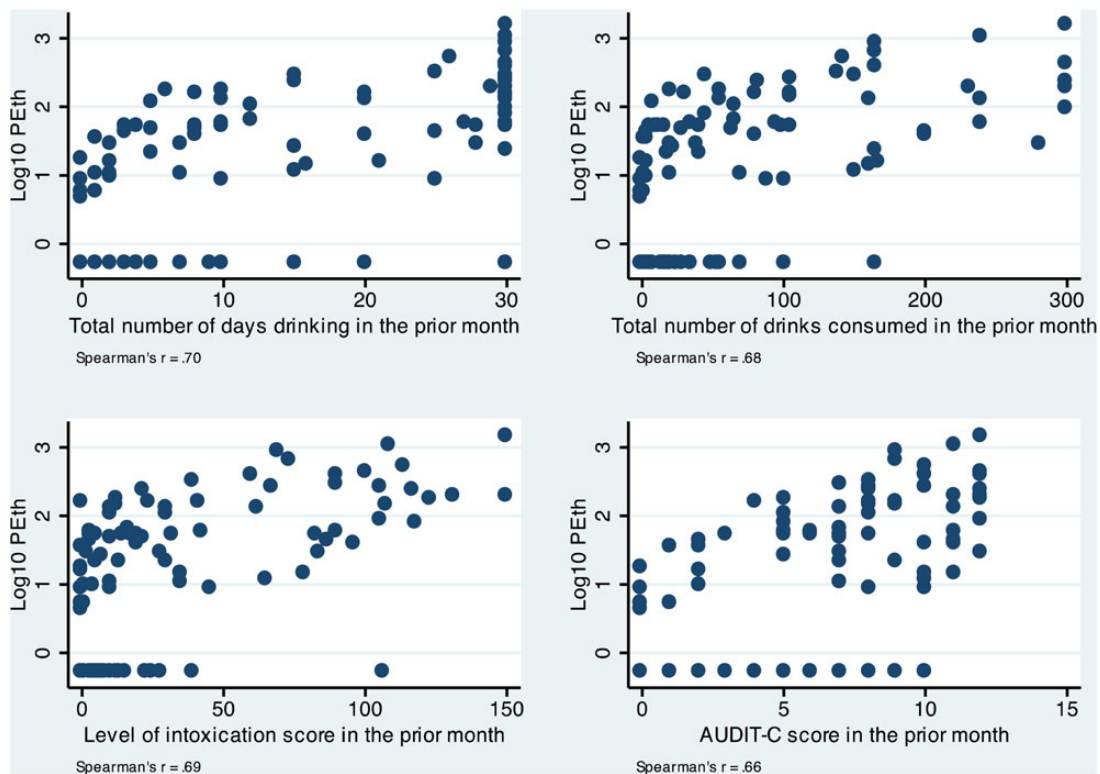


Fig. 1. Phosphatidylethanol versus measures of alcohol consumption among young IDU.

Table 2. Self-reported alcohol consumption by PEth results among young IDU in San Francisco, CA ($N = 137$)

Self-reported alcohol consumption in the prior month	n (column %)	PEth positive, n (row %)	PEth negative, n (row %)	P -value (Fisher's exact)
AUDIT-C (cut-off levels)				
Probable dependent (10–12)	26 (19.1)	23 (88.5)	3 (11.5)	<0.001
Hazardous (3–9 for women, 4–9 for men)	56 (41.2)	34 (60.7)	22 (39.3)	
Low risk (0–2 for women, 0–3 for men)	54 (39.7)	10 (18.5)	44 (81.5)	
Any alcohol consumption				
Yes	101 (73.7)	66 (65.3)	35 (34.7)	<0.001
No	36 (26.3)	2 (5.6)	34 (94.4)	
Drinking until becoming unconscious				
Yes	41 (29.9)	34 (82.9)	7 (17.1)	<0.001
No	96 (70.1)	34 (35.4)	62 (64.6)	
Binge drinking				
Yes	81 (59.6)	58 (71.6)	23 (28.4)	<0.001
No	55 (40.4)	9 (16.4)	46 (83.6)	

based on symptoms of intoxication had a high correlation with PEth. These results are consistent with previous findings that showed PEth correlations with continuous measures of alcohol consumption that ranged from 0.57 to 0.80 (Aradottir *et al.*, 2006; Hartmann *et al.*, 2007; Hahn *et al.*, 2012).

Limitations

Our study has several limitations, including a modest sample size that has limited the potential for generalizability. In addition, the literature is still mixed as to whether PEth is an indicator of any recent drinking or heavy drinking (Isaksson *et al.*, 2011). We used a conservative approach, using the limit of detection as the cut-off for PEth, as an indicator of any drinking in the last month. Therefore, some moderate drinkers were PEth positive, as seen in Table 2. A higher cut-off may have indicated more heavy drinking; however, raising the cut-off would then decrease the specificity (Stewart *et al.*, 2010). Finally, PEth is not completely sensitive, therefore we were able to obtain only a lower bound estimate on under-reported alcohol use, and some of those reporting recent alcohol consumption had undetectable levels of PEth. Thus, this is also illustrated in Figure 1, where there are undetectable PEth values for reported alcohol consumption for some subjects.

CONCLUSIONS

We conclude from these findings that there is little to no under-report of engaging in alcohol consumption by young IDU. This may not be surprising given the high level of self-report of injecting and sexual risk behaviors (Le Marchand *et al.*, 2013), which are potentially more stigmatized behaviors. This is good news for research studies collecting such data. The good correlation of PEth with levels of alcohol consumed also suggests that PEth may be a useful marker in settings where alcohol consumption is difficult to measure or in circumstances where there may be incentive for socially desirability reporting, for example alcohol treatment. PEth can be used to corroborate or invalidate self-reported measures of alcohol consumption, and combining the two may optimize their strengths. Improved alcohol detection may contribute to alcohol interventions in this population, which are greatly needed, as young IDU are at increased risk for HCV acquisition, a condition exacerbated by heavy alcohol consumption.

AUTHORS' CONTRIBUTIONS

J.A.H. and K.P. were responsible for study concept and design. A.B., J.J. and U.F.O. study field staff implemented the study and collected data. J.J., J.L.E. and J.A.H. performed data analysis and produced interpretations and findings. J.J. and J.A.H. drafted the manuscript and all authors provided critical feedback and approved the final version.

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Conflict of interest statement. All authors declare that they have no conflicts of interest.

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