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Phosphatidylethanol (PEth) in Comparison to Self-Reported Alcohol Consumption among HIV-infected Women in a Randomized Controlled Trial of Naltrexone for Reducing Hazardous Drinking

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Abstract

Background—Biomarkers can play a key role in supplementing self-report information in alcohol research. In this study, we examined phosphatidylethanol (PEth) in comparison to self-reported alcohol use over time in a randomized controlled trial.

Materials and methods—Participants were women living with HIV enrolled in a randomized placebo controlled trial of naltrexone for reducing hazardous drinking. Drinking behavior was measured using Timeline Followback (TLFB), and PEth as a biomarker using dried blood spots. Data collected at baseline, and months two and seven were analyzed. In addition to calculated Spearman's correlations, mixed effects modeling was used to evaluate the changes in self-reported drinking and PEth respectively, adjusting for body mass index.

Results—A total of 194 participants (83% black, mean age 48) were included in the analysis. PEth levels were significantly correlated with self-reported drinking via TLFB, Spearman's $r = .21$, at baseline, $r = .29$ at 2- and $r = .28$ at 7-month, respectively. No demographic or health factors, except for BMI, was associated with whether self-report was consistent with PEth. Mixed effects model indicated that self-reported drinking showed significantly greater reductions in the naltrexone treatment group than the placebo group at the 2- and 7-month visits, whereas PEth measure only showed this difference at the 7-month follow-up.

Conclusion—The magnitude of the correlation between PEth and self-reported alcohol consumption was small. Caution is needed when using either self-report or PEth as a sole outcome measure for alcohol behavior changes in clinical trials.

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Conflict of Interest

None to declare.

Keywords

Phosphatidylethanol (PEth); alcohol use; biomarker; HIV/AIDS; women

1. Introduction

Biomarkers are suggested for employment in alcohol research as objective measures of alcohol consumption (Litten and Fertig, 2003, Niemela, 2016), because of concerns with errors from self-report due to social desirability, recall bias and other factors (Livingston et al., 2016, Littlefield et al., 2017, Hahn et al., 2012b, Del Boca and Darkes, 2003). A number of biomarkers are available for use, including gamma-glutamyltransferase (GGT), Carbohydrate-Deficient Transferrin (CDT), Ethyl Glucuronide (EtG), ethyl sulfate (EtS), and Fatty Acid Ethyl Esters (FAEE)(Nanau and Neuman, 2015, Tavakoli et al., 2011). Given that a "gold standard" for alcohol use has not yet been produced, it is necessary for researchers to rely on the convergence of different measures for drinking behaviors (Miller, 2009). The agreement between multiple information sources (e.g., self-report, biomarker, observation) on alcohol use can increase researchers' confidence in data quality, enhancing the internal validity of the study (Allen et al., 2004, Miller, 2009).

Among the commonly used biomarkers, phosphatidylethanol (PEth) has gained popularity in recent years (Viel et al., 2012). PEth is a direct metabolite of alcohol that can be detected in gastrointestinal tract, kidney, lung, spleen, and blood (Isaksson et al., 2011). The membrane of red blood cells is the primary site of PEth in the body. Studies with strictly controlled conditions (e.g., patients in alcohol detoxification program) testing for total PEth using high pressure liquid chromatography with evaporative light scattering detection demonstrated high sensitivity (94.5–100%) and specificity (100%) of PEth (155ng/ml as limit of quantification) in detecting excessive drinking behaviors within a brief time period after consumption (e.g., 1 day) (Aradottir et al., 2006, Wurst et al., 2010, Hartmann et al., 2007). Subsequent observational studies using tandem mass spectrometry with liquid chromatography to detect a PEth subspecies also showed relatively high sensitivity and specificity (80–90%, cut-off values varied from 10ng/ml to 155ng/ml) of PEth (Hahn et al., 2012a, Walther et al., 2015, Francis et al., 2015), and positive correlations in moderate magnitude (ranging from 0.5–0.8) between PEth and self-reported alcohol use (e.g., AUDIT-C, number of drinks, number of days drinking) (Littlefield et al., 2017, Asiimwe et al., 2015, de Bejczy et al., 2015). Several studies also examined the correlations between PEth and self-reported alcohol use among persons living with HIV (Littlefield et al., 2017, Hahn et al., 2012b, Hahn et al., 2012a, Papas et al., 2016, Bajunirwe et al., 2014), but the results are somewhat mixed, with one recent research study showing a poor correlation between PEth and self-report among women living with HIV (Littlefield et al., 2017).

Purpose of this study

In this study, we aimed to compare PEth levels to self-reported alcohol use among HIV+ women participating in a randomized controlled trial of naltrexone for reducing hazardous drinking. The main goals included examining: (1) the consistency between PEth test result (i.e., positive or negative) and self-reported drinking status (e.g., quit hazardous drinking vs.

not quit hazardous drinking) based on Timeline Followback (TLFB)(Sobell and Sobell, 1995) interview; (2) the correlations between PEth values and self-reported drinking using TLFB interview at baseline, 2-months, and 7-months; (3) the agreement between intervention effects determined by the mixed effects modeling using self-reported drinking and PEth value as the outcome measures respectively.

2. Materials and Methods

2.1 Participants and procedures

Participants were women living with HIV who self-identified as current (i.e., in past 30 days) hazardous drinkers (>7 drinks/week or >3 drinks/occasion twice monthly) enrolled in a randomized controlled trial for alcohol treatment. More details about the trial can be found on the clinicaltrials.gov website (NCT01625091). Briefly, participants were randomized into a 7-month two-arm trial to test the efficacy of naltrexone in reducing alcohol use compared with placebo. The treatment group received 120-day Naltrexone medication (oral) while the control group received 120-day placebo, and were both followed up to 7 months. At the baseline visit, participants completed survey interviews on their drinking behaviors and demographic information. Follow-up assessments were conducted at 2- and 7-month including survey interview and biomarker sample collection.

2.2 Self-reported drinking

Number of drinks in the past 1, 2, 3, and 4 weeks—The Timeline Followback (TLFB)(Sobell and Sobell, 1995) interview was administered by trained/certified personnel to obtain self-reported alcohol use up to 90 days prior to each visit. Using a blank calendar with memory prompts (e.g., holidays) that covers the past 90 days, participants' drinking behaviors were reconstructed and calculated. The TLFB has been widely used in alcohol research to obtain information on drinking-related variables (e.g., drinks per drinking day) and shown acceptable test-retest reliability and validity (Sobell et al., 1996, Breslin et al., 2001). Considering that the elimination rate of PEth varies largely between persons (Hahn et al., 2016a), we used the total number of drinks consumed in the prior 1, 2, 3, and 4 weeks as main self-reported drinking outcomes.

Whether or not quit hazardous drinking—Participants who reported drinking fewer than 7 drinks per week and not engaging in binge drinking (defined as 4 drinks in a row for women, we used 4 drinks in one day as a proxy) in the past 4 weeks were categorized as "quit hazardous drinking", whereas those who reported drinking more than 7 drinks per week or engaging in binge drinking were categorized as "not quit hazardous drinking" at the 2- and 7-month follow-ups.

2.3 PEth analysis

A standard protocol was used to prepare dried blood spots (DBS) from participants from blood collected by venipuncture. Venous blood collection was considered less invasive than finger-prick DBS collection, and DBS were prepared because they are more stable than whole blood (Bakhireva et al., 2016). The collected samples were sent to the lab to quantify PEth. Currently, there is lack of consensus regarding the cut-off point for PEth level (Viel et

al., 2012). We have used a relatively conservative cut-off point (≥ 50 ng/ml as positive) which has been previously used as a cut-off point for unhealthy alcohol use with high sensitivity and specificity (Hahn et al., 2016b, Stewart et al., 2010), and a lower cut-off (≥ 8ng/ml, limit of quantification from the lab) as a comparison (Bajunirwe et al., 2014, Stewart et al., 2010, Fleming et al., 2017). PEth level was assessed for all participants at the baseline and two follow-ups.

2.4. Demographic variables

Demographic variables were age (in years), race/ethnicity (White, Black, Hispanic and others), marital status (single vs. in a relationship), education (less than high school, high school, college and above), employment status (employed vs. not), and body mass index (BMI). Whether or not the participant had pre-existing health conditions including liver disease/hepatitis and diabetes were also included from self-report. These variables were mainly used to describe the sample characteristics and to identify potential factors contributing to inconsistency between PEth and self-report.

2.5 Statistical analyses

The following analyses were conducted to assess to what extent the detected PEth levels were correlated with self-reported alcohol use at baseline and after treatment. Cross-tabulation between PEth and self-reported drinking status was conducted with Kappa statistics as evaluation of the overall agreement. Additional analyses were conducted to identify potential factors contributing to the inconsistency between PEth and self-report, including chi-square analysis for race-ethnicity, marital status, education, employment, liver disease/hepatitis, and diabetes, and t-test or ANOVA for age and BMI. Spearman's rank correlations were calculated to quantify the relationship between PEth levels with self-reported number of drinks. Considering that PEth may remain detectable up to 4 weeks after sobriety (Wurst et al., 2010), reported total number of drinks during different time periods (one, two, three, and four weeks prior to visit) were used in Spearman's correlation analysis.

To examine how the intervention effect estimates differed by different measures of alcohol use, we conducted mixed effects modeling analysis of the intervention effect of naltrexone, using self-reported alcohol use (i.e., number of drinks in the past week), and PEth levels as the outcome variable, respectively. A generalized linear mixed effects model (PROC Glimmix) using Poisson distribution with quasi-likelihood estimation function, which uses Gauss–Hermite quadrature as likelihood approximation to deal with overdispersion, was used to analyze reported number of drinks (as a count variable) and PEth value (continuous but can be accommodated by this model) (Morel and Neerchal, 2011), respectively. For analysis of self-reported drinking, those reporting more than 50 drinks per day on average (i.e., 350 drinks per week) were excluded (n = 4) as outliers (Helian et al., 2016). BMI was used as a covariate in the mixed effect modeling given its significant association with PEth in the current study (spearman's r ranged from -.22 to -.19 across waves).

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Carry, NC).

3. Results

3.1 Sample characteristics

The sample consisted of 194 females living with HIV with a mean age of 48 years (SD = 8.7). Among the total sample, 83% were black, 84% were single, 77% with high school or less education, and 90% not employed. Eighteen percent of the sample had liver disease (including hepatitis), and 10% had diabetes. The mean BMI of the group was 30 (SD = 8.3). The median number of weekly consumed alcoholic drinks was 43. More detailed information by randomization assignment and by PEth value at baseline is presented in Table 1.

3.2 PEth and self-reported drinking status

Table 2 presents the agreement between PEth and self-reported drinking at each wave and the Kappa statistics. At baseline, PEth was positive (≥ 50 ng/ml) among 46 (23.7%) participants, while all (100%) were self-identified as hazardous drinkers. At the 2-month follow-up, PEth was positive among 34 (32.1%) participants who reported not quitting hazardous drinking, and was negative among 65 (84.4%) participants who reported quitting hazardous drinking. At 7-month, PEth was positive among 23 (41.1%) participants who reported not quitting hazardous drinking, and was negative among 83 (76.1%) participants who reported quitting hazardous drinking. Overall, the level of agreement between the PEth result and self-reported drinking status was 23.7% for participants at baseline, 54.1% at 2-months, and 64.2% at 7-months.

To explore whether the agreement between PEth and self-report will improve by using a less conservative cut-off point for PEth or using “any drinking” (defined as consumed at least one drink during the past four weeks) for self-report, we conducted additional analyses using ≥ 8ng/ml as the cut-off and self-reported any drinking (See Table 2 for details). In general, the overall consistency between PEth and self-report remained at the low end (about 60% maximum). Kappa statistics showed significant but low agreement (< .20) between PEth determined and self-reported drinking status regardless of waves, cut-off points, and self-reported drinking type (i.e., any or hazardous). The overall consistency between PEth and self-reported “any drinking” was somewhat lower than that between PEth and self-reported hazardous drinking, regardless of cut-off points. The sensitivity of PEth was lower when using 50ng/ml (24–59%) as cut-off than 8ng/ml (47–64%), but the specificity was higher using 50ng/ml (76–84%) than 8ng/ml (60–65%).

Additional analyses were conducted to identify potential influential factors contributing to the inconsistency between PEth and self-reported drinking status. Chi-square tests showed no significant differences in demographics (i.e., age, race/ethnicity, marital status, education, employment) and health conditions (i.e., liver disease/hepatitis and diabetes) when comparing those whose self-report was consistent with PEth to those who had inconsistency (detailed data not shown). BMI was the only variable that differed between these two subgroups. Those who had inconsistency between PEth and self-report had a significantly higher BMI (M = 31.1, SD = 8.6) than those who did not (M = 27.7, SD = 6.9) at baseline. At 2-months, the BMI of those with consistent PEth and self-report was significantly lower

(M = 29.0, SD = 6.9) than those who had negative PEth but self-reported as hazardous drinker (M = 32.8, SD = 10.1), and significantly higher than those who had positive PEth but self-reported as quitting hazardous drinking) (M = 26.4, SD = 5.4). However, at 7-months, these differences were not significant (M = 30.0, 31.0, 28.0 respectively). Overall, BMI was significantly higher among those who had negative PEth than those who had positive PEth, for all three waves (t = 2.40, 2.24, 2.56, respectively, p's < .05). Table 3 provides the means and standard deviations of BMI for each subgroup at each wave.

3.3 Spearman's rank correlation analysis

Table 4 summarizes the correlation coefficients from Spearman's rank correlation analysis. Overall, PEth was positively associated with self-reported number of drinks for the whole sample at the three time points. No obvious trend was observed in the correlation coefficients between PEth and self-reported drinking as the durations changed from past one to four weeks; but there was an increase in the correlation coefficients along with the time of assessment with the association being the smallest at baseline and the largest at the 7 months follow-up. When analyzed by subsamples divided using PEth results (positive vs. negative, using 50 ng/ml as cut-off point) at the baseline visit, the correlations between PEth and self-reported drinking at three time points were all stronger for participants with a positive PEth value at the baseline.

3.4 Changes in self-reported drinking and PEth using mixed effects model

Mixed effects model showed significant main effect of time and interaction between group and time for both self-reported number of drinks in the past week and PEth (log-transformed) as the outcome variable, respectively. While the number of drinks was similar at the baseline, the naltrexone treatment group showed significantly greater reductions compared to the placebo group at the 2- and 7-month visits, suggesting a significant intervention effect. Similarly, when PEth was used as the outcome, the naltrexone treatment group also showed more reduction compared to the placebo group, but only at 7-months. More detailed results are presented in Table 5.

4. Discussion and Conclusions

Our study contributes to the literature by providing information comparing PEth and self-reported drinking behaviors with longitudinal data from a randomized controlled trial for reducing hazardous drinking among women living with HIV. Results from this study showed that PEth as a biomarker was positively associated with self-report. The intervention effect on PEth was consistent with the self-reported drinking as the outcome variable, although the significant intervention effect was only observed for PEth at 7-months. These findings were consistent with prior clinical trial research showing a significant correlation of PEth with self-reported alcohol consumption (Walther et al., 2015, de Bejczy et al., 2015, Papas et al., 2016).

Although PEth measures were positively associated with drinking, the strength of correlations were noticeably lower (in the range of .20 –.30 for whole sample) in the current study than those reported from most previous studies (ranging from .50 to .80) (Helander et

al., 2012, Asiimwe et al., 2015, de Bejczy et al., 2015), but comparable to the correlation reported in a recent study of Russian women living with HIV (Littlefield et al., 2017). There was a trend of increased consistency between PEth and self-report over the course of this trial. The overall agreement between PEth and self-reported drinking status improved from 24% at the baseline to 64% at the 7-month follow-up, and similar results were observed using a less conservative cut-off point (i.e., 8ng/ml) or using any drinking for self-report; and the correlation coefficients were larger at the follow-ups (~.30) than the baseline (~ .20). This increase in agreement between PEth and self-report may be explained by the possibility that some participants exaggerated their alcohol consumption level at the baseline in order to qualify for the trial. However, when we examined those with positive (≥50 ng/ml) PEth results at baseline, the correlations increased to around .20 at baseline and .40–.50 at months 2 and 7, still on the lower end compared to other studies conducted in different settings (Littlefield et al., 2017, Asiimwe et al., 2015, de Bejczy et al., 2015). Although there has been evidence showing PEth as a useful biomarker for alcohol consumption (Marshall et al., 2017, Hahn et al., 2012a), there is also some literature showing a lack of agreement between PEth and self-report data among HIV-infected women (Papas et al., 2016, Littlefield et al., 2017). Additional research is needed to further examine discrepancies between PEth and self-report with carefully designed studies, which include gold-standard measurements of alcohol use and carefully controlled specimen collection methods.

In this study, we also explored whether any demographic characteristics or health conditions contributed to the inconsistency between PEth and self-reported drinking status. Age, race/ethnicity, education, and employment all had no significant influence on whether PEth-determined drinking status was consistent with participants' self-report. Similarly, preexisting health conditions including liver disease/hepatitis and diabetes had no impact on whether PEth is concordant with self-report. These findings are in line with previous research (Stewart et al., 2009, Littlefield et al., 2017), and suggest further exploration is needed to identify other potential contributing factors to the discordance between PEth and self-report. The only significant factor was BMI, which was higher among those whose self-reported drinking status was inconsistent with PEth at baseline. At 2-months, the subgroup with negative PEth but self-reported hazardous drinking had the largest BMI while the subgroup with positive PEth but self-reported as non-hazardous drinking had the smallest BMI. Overall, BMI was higher among those with negative PEth than those with positive PEth at all waves. It should also be noted that about 45% of participants in this study were obese (BMI ≥ 30) and 7% of them fell into the "extreme obesity" category (BMI ≥ 40) (CDC, 2016). One possible explanation of this finding is that higher BMI is associated with lower alcohol metabolism which can result in a lower PEth (Hahn et al., 2016a). Although some prior studies showed no significant impact of BMI on PEth test characteristics (Viel et al., 2012, Helian et al., 2016), our results suggest BMI should still be considered as an important factor leading to possible discrepancy between PEth test result and self-reported drinking, at least among HIV+ women.

Limitations and Conclusions

Our study has several limitations. The relatively small sample size has limited the potential for generalizability; and this investigation of the comparison between PEth and self-report

was not the primary aim of the clinical trial. In addition, we only used self-reported survey data and PEth for alcohol use measurement, so it remains inconclusive whether the self-report or PEth value is more prone to errors. With recent technological advances in biosensor, the use of wearable transdermal monitors (e.g., SCRAM) may provide additional objective data regarding alcohol use patterns in a more real-time and ecologically valid manner (Dougherty et al., 2014, Sakai et al., 2006, Selvam et al., 2016). Another possibility is the use of multiple markers to get a better picture of hazardous alcohol use (Kummer et al., 2016). Nevertheless, our study showed a low correlation between PEth and self-reported alcohol consumption in a clinical trial setting, suggesting additional objective measures with better capacity to identify drinking patterns may be needed.

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Table 1

Sample characteristics (N = 194), by randomization group/baseline PEth, n (%)

	Randomization group		Baseline PEth		
	Naltrexone (n = 96)	**Placebo (n = 98)**	**PEth+ (n = 46)**	**Peth− (n = 148)**	**Total (N = 194)**
Age					
Mean(SD)	47.7(8.5)	48.9(8.9)	47.8(7.6)	48.5(9.1)	48.3(8.7)
Race/Ethnicity					
White	3(3.1)	5(5.1)	3(6.5)	5(3.4)	8(4.1)
Black	81(84.4)	80(81.6)	40(87.0)	121(81.8)	161(83.0)
Hispanic	11(11.5)	11(11.2)	3(6.5)	19(12.8)	22(11.3)
Other	1(1.0)	2(2.0)	0(0.0)	3(2.0)	3(1.6)
Marital Status					
Single	80(83.3)	83(84.7)	38(82.6)	135(84.5)	163(84.0)
In relationship	16(16.7)	15(15.3)	8(17.4)	23(15.5)	31(16.0)
Education					
Less than high school	40(41.7)	44(44.9)	18(39.1)	66(44.6)	84(43.3)
High school graduate	38(39.6)	28(28.6)	19(41.3)	47(31.8)	66(34.0)
Some college/college graduate	18(18.7)	26(26.5)	9(19.6)	35(23.6)	44(22.7)
Employment					
Employed	11(11.5)	9(9.18)	5(10.9)	15(10.1)	20(10.3)
Not employed	85(88.5)	89(90.8)	41(89.1)	133(89.9)	174(89.7)
Liver disease					
Yes	18(18.7)	18(18.4)	6(13.0)	30(20.3)	36(18.5)
Diabetes					
Yes	8(8.3)	12(12.2)	6(13.0)	14(9.4)	20(10.3)
BMI					
Mean(SD)	30.1(8.5)	30.4(8.2)	27.7(6.9)	31(8.6)	30.3(8.3)
Self-reported drinks/week					
Median(IQR)	43(46)	42(67)	59(56)	39(58)	43(58)

Note. PEth+ or PEth− was based on the baseline PEth value using 50ng/ml as the cut-off. IQR = interquartile range. Chi-square test (or *t*-test for continuous variables) showed no significant differences in demographics and health conditions between PEth+ and PEth− groups, except a significantly higher BMI for PEth− group ($t = 2.40$, $df = 192$, $p < .05$).

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Table 2

Agreement between PEth and self-reported drinking status, by wave

	Self-reported hazardous drinking		Kappa	Self-reported any drinking		Kappa
	Yes	No		Yes	No	
Drinking status by PEth						
50ng/ml as cut-off						
PEth at baseline						
≥50ng/ml (Yes)	46(23.7)	-		46(23.7)	-	
<50ng/ml (No)	148(76.3)	-		148(76.3)	-	
PEth at 2 month						
≥50ng/ml (Yes)	34(32.1)	12(15.6)		40(27.6)	4(12.1)	
<50ng/ml (No)	72(67.9)	65(84.4)	.149*	105(72.4)	29(87.9)	.071
PEth at 7 month						
≥50ng/ml (Yes)	23(58.9)	26(23.8)		33(38.8)	16(20.0)	
<50ng/ml (No)	33(41.1)	83(76.2)	.178*	52(61.2)	64(80.0)	.186**
8ng/ml as cut-off						
PEth at baseline						
≥8ng/ml (Yes)	92(47.4)	-		92(47.4)	-	
<8ng/ml (No)	102(52.6)	-		102(52.6)	-	
PEth at 2 month						
≥8ng/ml (Yes)	58(54.7)	27(35.1)		72(49.7)	9(27.3)	
<8ng/ml (No)	48(45.3)	50(64.9)	.189**	73(50.3)	24(72.7)	.128*
PEth at 7 month						
≥8ng/ml (Yes)	35(62.6)	43(39.4)		50(58.8)	28(35.0)	
<8ng/ml (No)	21(37.4)	66(60.6)	.210*	35(41.2)	52(65.0)	.238*

Note.

* $p < .05$.

** $p < .01$.

Table 3

BMI (M, SD) and consistency between PEth and self-reported drinking status, by wave

	Self-reported hazardous drinking		Self-reported any drinking	
	Yes	**No**	**Yes**	**No**
Drinking status by PEth				
50ng/ml as cut-off				
PEth at baseline				
≥50ng/ml (Yes)	27.7(6.9)	-	27.7(6.9)	-
<50ng/ml (No)	31.1(8.6)	-	31.1(8.6)	-
PEth at 2 month				
≥50ng/ml (Yes)	28.5(7.7)	26.4(5.4)	28.4(7.4)	25.7(4.0)
<50ng/ml (No)	32.8(10.1)	29.3(6.5)	31.5(9.2)	29.6(7.0)
PEth at 7 month				
≥50ng/ml (Yes)	26.7(6.7)	28.0(5.9)	26.3(6.0)	29.8(6.4)
<50ng/ml (No)	31.0(8.2)	30.9(8.8)	29.2(7.7)	32.3(9.1)
8ng/ml as cut-off				
PEth at baseline				
≥8ng/ml (Yes)	28.4(7.0)	-	28.4(7.0)	-
<8ng/ml (No)	31.9(9.0)	-	31.9(9.0)	-
PEth at 2 month				
≥8ng/ml (Yes)	29.4(8.1)	27.6(5.7)	29.0(7.8)	27.7(4.3)
<8ng/ml (No)	34.0(10.6)	29.6(6.7)	32.4(9.5)	29.7(7.5)
PEth at 7 month				
≥8ng/ml (Yes)	27.5(6.5)	29.0(6.4)	27.1(6.1)	30.4(6.4)
<8ng/ml (No)	32.1(9.3)	31.0(9.3)	29.4(8.4)	32.5(9.6)

Table 4

Spearman's rank correlations between PEth and self-reported drinking behaviors

	Self-reported drinks for different durations			
	1 week	**2 weeks**	**3 weeks**	**4 weeks**
Baseline PEth (n = 194)				
All (n = 195)	.21**	.16*	.16*	.18*
Among those with PEth ≥50 at baseline (n = 46)	.26+	.25	.19	.22
Among those with PEth <50 at baseline (n = 148)	.04	.01	.02	.03
2 month PEth (n = 183)				
All	.30**	.25**	.23**	.21**
Those with PEth ≥50 at baseline	.49**	.48**	.49**	.48**
Those with PEth <50 at baseline	.16+	.14+	.12	.10
7 month PEth (n = 165)				
All	.28**	.30**	.29**	.28**
Those with PEth ≥50 at baseline	.42**	.42**	.41**	.42**
Those with PEth <50 at baseline	.22*	.25**	.24**	.23*

Note. Total number of drinks reported in TLFB was used for the analysis. The spearman's rank correlation was used due to the highly skewed distribution of data. Correlations were calculated for the whole sample (N = 194) and subsamples with positive (n = 46) vs. negative (n = 148) baseline PEth values (i.e., ≥ 50 ng/ml or <50 ng/ml).

* $p < .05$,

** $p < .01$.

Table 5

Mixed effects modeling analysis of the effect of naltrexone on alcohol use with self-reported drinking (i.e., number of drinks in past week) and PEth as outcome respectively

	Self-reported drinking		PEth (log-transformed)	
	Coefficient *b*	**95% CIs**	**Coefficient *b***	**95% CIs**
Intercept	3.52 **	[2.95, 4.09]	3.36 **	[0.85, 5.88]
Wave				
Month 2	−0.72 **	[−0.76, −0.67]	0.07 **	[0.03,0.12]
Month 7	−1.56 **	[−1.63, −1.49]	0.55 **	[0.51, 0.60]
Intervention				
Naltrexone	0.03	[−0.26, 0.32]	0.25	[−0.98, 1.48]
Wave * naltrexone				
Month 2	−0.56 **	[−0.64, −0.48]	0.06	[−0.00, 0.13]
Month 7	−0.60 **	[−0.72, −0.48]	−0.45 **	[−0.51, −0.38]

Note. PROC Glimmix (Poisson distribution with logit as link function, using quasi-likelihood estimation function to deal with over-dispersion) was used to analyze self-reported alcohol use (number of drinks) and PEth value. For analysis on self-reported drinking, those reporting more than 50 drinks per day on average (i.e., 350 drinks per week) were excluded (n = 4) as outliers (Helian et al., 2016). We also conducted the analysis including the 4 outliers and found minimal changes in the result. BMI was entered as a covariate because it was significantly associated with PEth (spearman's *r* ranged from -.22 to -.19 across waves).

* $p < .05$,

** $p < .01$.