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Filling the gap between lab and clinical impact: An open randomized diagnostic trial comparing urinary ethylglucuronide and ethanol in alcohol dependent outpatients

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ABSTRACT

Background: Efforts aimed at reducing alcohol-related harm include early detection of risky drinkers as well as detection of early relapse in patients with alcohol dependence. Ethyl glucuronide (EtG) has been proven to be a reliable biomarker for the detection of recent drinking; however, no randomized, diagnostic trial to date has tested its impact on drinking outcomes. The aim of this study was to assess, in a randomized design, the implications of EtG screening on alcohol outcomes, compared to screening with a low sensitivity biomarker such as ethanol.

Methods: Alcohol dependent outpatients were randomized to either 24 weeks of continuous screening with EtG or ethanol. Patients were aware of screening methods and results. After 24 weeks, all participants were screened with EtG. Self-reports were also gathered. A logistic regression compared the rate of EtG positive results at study end between groups. Generalized estimating equations evaluated the descending monthly rate of EtG positive patients in the EtG group.

Results: A total of 162 patients were randomized. During the study period, the ethanol group showed less patients with positive screens (19/64 (29.7%) vs 58/98 (59%)). After 24 weeks, the EtG group showed a greater number of patients having a negative screening test compared to ethanol subjects when they were all screened with EtG (5/62 (8.1%) vs 13/39 (33.3%)). A significant decrease in the rate of EtG positive patients was found for the first three months of the study.

Conclusions: Routine screening with EtG seems to reduce drinking and improve abstinence rates in alcohol dependent outpatients.

1. Introduction

Alcohol is an established contributor to the global burden of disease, only second to tobacco and hypertension worldwide (Mohapatra et al., 2010; Rehm et al., 2009). Its deleterious effects range from minor risks to deadly harms. Although different terminologies and systems exist regarding the classification of patterns of alcohol consumption, Alcohol Dependence (AD), now labeled Moderate and Severe Alcohol Use Disorder (AUD) under DSM-V (American Psychiatric Association, 2013), can be considered the severest form of alcohol use. It is better conceptualized as a chronic, relapsing-remitting disease, with a complex pathogenesis, where multiple and complex environment-genetic interactions occur (Agrawal and Lynskey, 2008).

In line with this complexity, no isolated management strategy has emerged as fully satisfactory in the treatment of AD. Therefore, a combination of elements, mainly from the psychosocial and pharmacological spectrum, is thought to work best for AD management (Soyka et al., 2008).

Especially in abstinence oriented settings, the use of biological markers capable of monitoring alcohol consumption with a high

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sensitivity and specificity is a frequently employed strategy (American Society of Addiction Medicine, 2014). By regularly assessing patients' urine, alcohol screening tests become, at least theoretically, a useful tool to strengthen patients' abstinence and prevent relapse, and therefore health and social problems related to alcohol use are reduced. There are two important concerns regarding this widely used strategy.

The first is a shortage of evidence supporting the usefulness of urine screening in the management of addiction patients. A recent systematic review on the usefulness of urine drug screening (Dupouy et al., 2014) concluded that more pragmatic studies were needed in order to affirm that, when conducting regular urine drug and alcohol screening, we are indeed adding value and efficacy to the care delivered. It is interesting to note that, in spite of wide inclusion criteria, only 8 studies were included, the majority of which were of poor methodological quality.

The second reason is related to the biological markers used in urine screening, which remain suboptimal with regard to sensitivity and specificity, especially when it comes to detecting recent drinking, a goal of paramount importance in abstinence-oriented settings. Ethanol remains detectable only for about 8–12 h post ingestion, whereas traditional markers such as gamma glutamyl transferase (GGT), mean corpuscular volume (MCV) or carbohydrate deficient trasnferrin (CDT) need persistent consumption of higher amounts of alcohol (> 2 weeks, > 1000 g of ethanol in 2 weeks) to become elevated (Conigrave et al., 1995; Hock et al., 2005; Mihas and Tavassoli, 1992).

Fortunately, in recent years new biomarkers have emerged, the features of which allow for a significant improvement in the field of alcohol screening (Schröck et al., 2014; Wurst et al., 2015). Such is the case of ethylglucuronide, a non-volatile, water-soluble, stable, direct metabolite of ethanol. Although only about 0.5% of all the ethanol ingested undergoes this degradation pathway, it remains detectable in urine for up to 70 h, depending on the amount of ethanol ingested (Halter et al., 2008). Therefore, it expands the time window for the detection of recent alcohol consumption in urine samples. This might offer relevant improvements in clinical practice, in so much as covert drinking might be more frequently detected and so earlier addressed (Barrio et al., 2017a). Also, it might facilitate an open discussion with patients about difficulties in achieving and maintaining abstinence.

The majority of EtG studies conducted so far show a high discrepancy between the detection capacity of EtG and that of other biomarkers (Barrio et al., 2016b; Lahmek et al., 2012; Reisfield et al., 2011; Skipper et al., 2004; Wurst et al., 2004). For example, in a recent study comparing EtG against urine ethanol, 15 EtG-positive samples were detected for each ethanol-positive sample (Barrio et al., 2016b). Thus, data suggest EtG might perform much better than ethanol in relapse prevention, one of the main objectives of regular urine screening (Barrio et al., 2017b).

To date, there is no study assessing the performance of EtG in relapse prevention in a randomized design. In fact, randomized studies of diagnostic techniques have been largely neglected in many health areas (Lord et al., 2006; Lu and Gatsonis, 2013; Rodger et al., 2012). Just as drug therapies and behavioral interventions ultimately rely on randomized trials to establish clinical significance, so should diagnostic techniques. Therefore, comparing sensitivity and specificity of diagnostic techniques in a transversal design, as it is usually done when developing new diagnostic strategies, precludes the ability to draw firm conclusions about the ultimate relevant consequence of diagnostic tools: its clinical impact.

This lack of randomization becomes even more troublesome when it comes to a diagnostic test such as alcohol screening. First, it is reasonable to believe that the diagnostic work also conveys a therapeutic effect via feedback to the patient. So, ideally, this therapeutic component of every screening needs a randomized assessment. Second, unlike other diseases where a positive diagnostic test might be followed by a highly standardized intervention, in the addiction field, there is no such standardization, and the gap between a positive screening and the clinical consequences needs to be elucidated.

Thus, in order to fully discern the real contribution of EtG to the management of alcohol use disorder, its well established superior diagnostic performance in urine screening is not enough. The aim of the present study is to investigate, in a randomized design, the impact EtG might yield in the management of alcohol use disorders, as compared to traditional ethanol urine screening, with special attention to relapse prevention.

2. Material and methods

2.1. Study design

This study was an open diagnostic randomized controlled trial, with a naturalistic follow-up of 24 weeks, comparing the clinical impact of regular urine screening with EtG to that of ethanol.

2.2. Subjects and setting

The study was conducted in the outpatient setting of an addictions unit belonging to a tertiary, urban hospital. To be included, subjects had to be diagnosed with alcohol dependence according to DSM-IV-TR (American Psychiatric Association, 2000), they had to undergo regular urine screening as part of their treatment, and they had to be willing to give written informed consent. The local Ethics Committee granted study approval.

2.3. Procedure

Subjects were recruited consecutively in the outpatient setting, irrespective of patient antiquity in the screening program. Thus, some participants were already existing patients, whereas others were new patients starting their treatment. After giving consent, they were randomized to either ethanol or ethyl glucuronide routine urine screening. Ethanol was analyzed with molecular absorption spectroscopy, and ethyl glucuronide was analyzed with a commercially available enzyme immunoassay (EIA) method (DRI-EtG EIA, Thermo Fisher Scientific Diagnostics, Hemel Hempstead, UK). The attending nurse, who usually receives patients and stores urine samples, was responsible for the randomization procedure, which was based on the last number of a random, computer-generated number, which in this case was the number of patients' history file. After 6 months, patients were asked to self-report their drinking status (abstinent: yes or no). They also, at study end, underwent at least one urine screening with EtG. Given the naturalistic approach, no further procedure related to the study was conducted. Therefore, patients continued to receive their usual treatment, which could include both pharmacological and psychosocial strategies, which consisted mainly of psychological support based on motivational interviewing. As part of treatment as usual, patients received feedback about all positive screening tests, either by the attending nurse or their therapist.

2.4. Outcome variables and statistical analysis

The main outcome investigated in this study was how EtG improved patients' abstinence rate. For that purpose, two main outcomes were established.

The first outcome variable was the rate of abstinent patients at study end, according to urine screening in each group. Given that EtG has shown a robustly higher sensitivity in urine screening, after the 24-week period, all subjects underwent at least one EtG urine screening in order to compare the rate of EtG positivity between study groups. A logistic regression model was employed for the difference in positive samples between groups. Age, sex, presence of addictive comorbidities, whether positive for other drugs, total number of screenings, positivity of screening at study entrance and length of screening were entered stepwise as the main independent variables.

The second outcome was measured as the descending rate of EtG positive patients in the EtG group, measured month to month. For that purpose, for each patient, the presence of a positive sample in any given month was assessed. Generalized estimating equations were used, with time, age, sex, total number of urine screenings and positive screenings for other drugs as main effects.

As a secondary outcome, we assessed the validity of self-reports compared to urine screening at study end. For that purpose, receiving operator curves were plotted with ethyl glucuronide as a gold standard. Also, to investigate self-reports validity and utility, the logistic regression analysis was repeated with abstinence at study end measured with self-reports.

2.5. Sample size calculation

For sample size calculation, assuming a power of 80% and an alpha level of 5%, 70 patients per group could find significant differences of 30% in the rate of positive samples between groups. Assuming a 10% of drop-out rate, a total sample size of 160 was deemed adequately powerful for the study purposes.

3. Results

A total of 162 patients were included and randomized into study groups, with 101 patients completing at least one urine screening at the end of the 24 week-period. That means 63% of EtG patients and 61% of ethanol patients completed the study procedures. Fig. 1 shows the complete flowchart of the study.

Table 1 describes the main psychosocial and clinical variables of both groups. As expected, during the study period, more patients in the EtG group screened positive as compared to the ethanol group (58.2% vs 12.5%), a fact that also led to a higher rate of abstinence (operationalized as no positive urine screenings and no clinical diagnosis of relapse) in the ethanol group (40.8% vs 70.3%); however in the post-study assessment, where all patients were screened with EtG, the EtG

Table 1
Sociodemographic characteristics of the sample.

Variable	EtG (n = 98)	Ethanol (n = 64)	Total (n = 162)
Age: mean (SD)	52.5 (10.2)	52.8 (12.7)	52.6 (11.2)
Sex: male (%)	64.3%	75%	68.5%
Lenght of screening	20.3 (25.8)	20.6 (19.6)	20.4 (23.5)
Number of screenings: mean (SD)	27.3 (21.6)	24.3 (19.5)	26.1 (20.8)
Patients hospitalized: n (%)	6 (6.1%)	4 (6.25%)	10 (6.2%)
Co-screening of other drugs	44 (44.9%)	25 (39.1%)	42.6%
Positive to other drugs	23 (23.5%)	12 (18.8%)	21.6%
Taking alcohol medication: n (%)	38 (39%)	18 (28%)	57 (35.2%)
antabuse	31 (32%)	13 (20.3%)	44 (27.3%)
nalmefene	4 (4.1%)	4 (6.3%)	8 (5%)
other medications	3 (3.1%)	1 (1.6%)	4 (2.5%)
Group therapy: n (%)	8 (8.2%)	6 (9.4%)	14 (8.7%)
Abstinent during study period: n (%)	40 (40.8%)	45 (70.3%)	85 (52.5%)
Patients screening positive during study period: n (%)	57 (58.2%)	8 (12.5%)	65 (40.1%)
Lost to follow-up: n (%)	21 (21.9%)	14 (21.9%)	35 (22%)
Patients providing screening post-study: n (%)	62 (63.3%)	39 (61%)	101 (62.3%)
Patients screening positive in post-study assessment with EtG: n (%)	5 (8.1%)	13 (33.3%)	18 (17.8%)

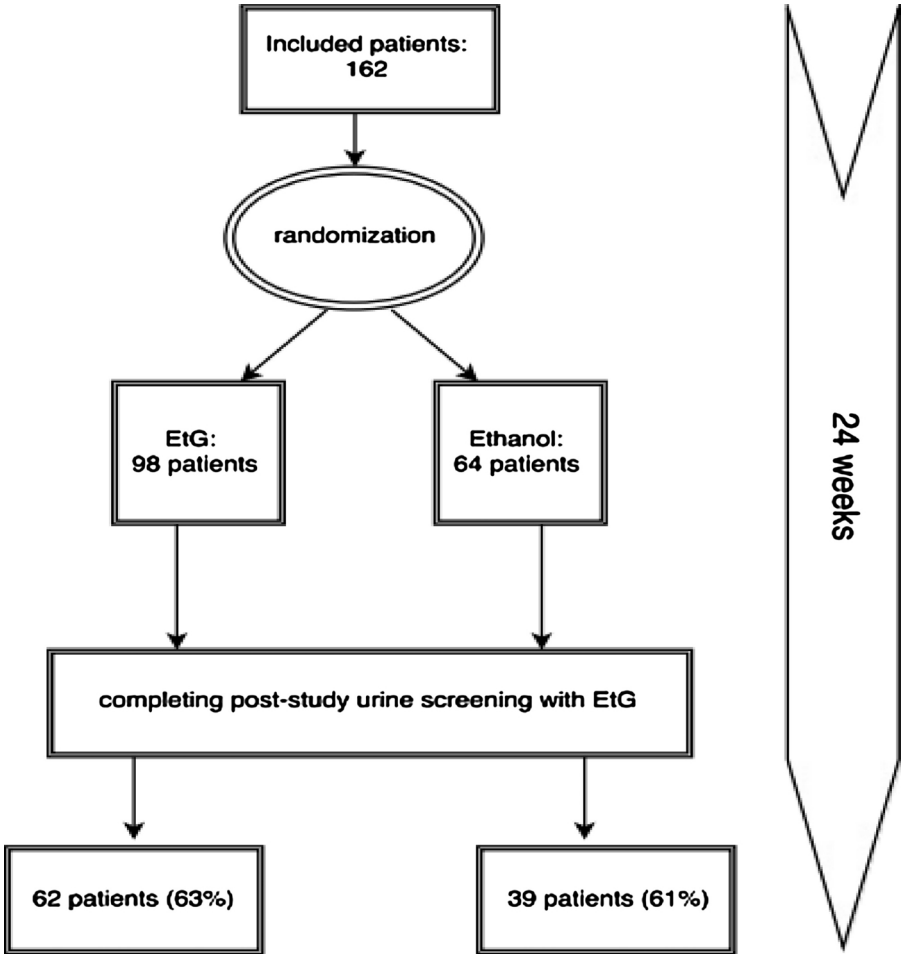

Fig. 1. Study flow-chart.

Table 2
Logistic regression with final abstinence assessed with ethylglucuronide. (nagelke rsquare = 0.284).

	B	S.E.	Sig.	Odds ratio	95% C.I.for Odds ratio	
					Lower	Upper
Sex	−0.369	0.634	0.560	0.691	0.200	2.394
Age	−0.004	0.034	0.909	0.996	0.932	1.065
Positivity of first study screening	−1.398	0.847	0.099	0.247	0.047	1.299
Group	2.336	0.733	0.001	10.344	2.461	43.479
Total of urine screenings	−0.017	0.016	0.283	0.983	0.954	1.014
Positive to other drugs	−1.530	1.223	0.211	0.217	0.020	2.379
Co-screening	1.755	1.197	0.143	5.784	0.553	60.462
Lengh of screening	−0.007	0.011	0.529	0.993	0.972	1.015

B = regression coefficient; S.E. = standard error; Sig. = statistical significance; 95% C.I. = 95% confidence interval.

group showed a higher rate of abstinent patients, with only 8.1% of patients screening positive, compared to 33.3% of ethanol group patients screening positive. In the logistic regression analysis, study group was the only significant predictor with an odds ratio of 10.34 (95% IC 2.461–43.5). Table 2 shows the full results of the logistic regression.

A total of 80 patients provided self-reports at study end (33 in the ethanol group and 47 in the EtG group). Table 3 shows the validity of self-reports when using EtG as a gold standard for each study group. As can be seen in the table, while 4.9% of patients in the EtG group self-reported abstinence with an EtG positive result, this percentage was 23.1% in the ethanol group. When the same logistic regression was conducted, but final abstinence was assessed with self-reports, study group ceased to be a significant predictor, with only the total number of urine screenings having a marginal statistical significance (full results shown in Table 4). In the ROC analysis, self-reports yielded an area under the curve of 0.66. If the ROC analysis was performed separately by study groups, the EtG group showed a ROC curve of 0.703 and the ethanol group of 0.635.

Fig. 2 shows the evolution of the percentage of patients screening positive month to month in the EtG group. The GEE analysis showed a significant decrease over time for the first three months, with none of the other model main effects reaching statistical significance.

4. Discussion

In this study, the first to evaluate the performance of a highly sensitive alcohol biomarker in a randomized design, we found that the monitoring of abstinence in alcohol dependent outpatients with EtG improves drinking outcomes, measured as a reduced rate of positive urine screenings at study end.

At first glance, the results of the post-study assessment are in sharp contrast to the results obtained during the 24-week period, where ethanol patients displayed a higher rate of abstinence, showed by both negative urine screenings as well as no clinical evidence of drinking.

Table 3
Results of self-reports with EtG as a gold standard.

	EtG results at study end		
		Not abstinent	Abstinent
Ethanol Patients Self-report	Abstinent	6 (23.1%)	20 (76.9%)
	Not abstinent	4 (57.1%)	3 (42.9%)
EtG Patients Self-report	Abstinent	2 (4.9%)	39 (95.1%)
	Not abstinent	2 (33.3%)	4 (66.7%)

Table 4
Logistic regression with final abstinence assessed with self-reports. (nagelke rsquare = 0.196).

	B	S.E.	Sig.	Odds ratio	95% C.I.for Odds ratio	
					Lower	Upper
Group	−0.404	0.664	0.543	0.668	0.182	2.455
Sex	0.664	0.688	0.335	1.942	0.504	7.483
Positivity of first study screening	1.556	0.957	0.104	4.741	0.727	30.932
Age	−0.048	0.038	0.210	0.953	0.884	1.027
Lengh of screening	−0.011	0.016	0.496	0.989	0.959	1.020
Co-screening	0.010	0.847	0.991	1.010	0.192	5.311
Positive to other drugs	−0.321	0.997	0.748	0.725	0.103	5.123
Total of urine screenings	−0.045	0.023	0.048	0.956	0.914	1.000

B = regression coefficient; S.E. = standard error; Sig. = statistical significance; 95% C.I. = 95% confidence interval.

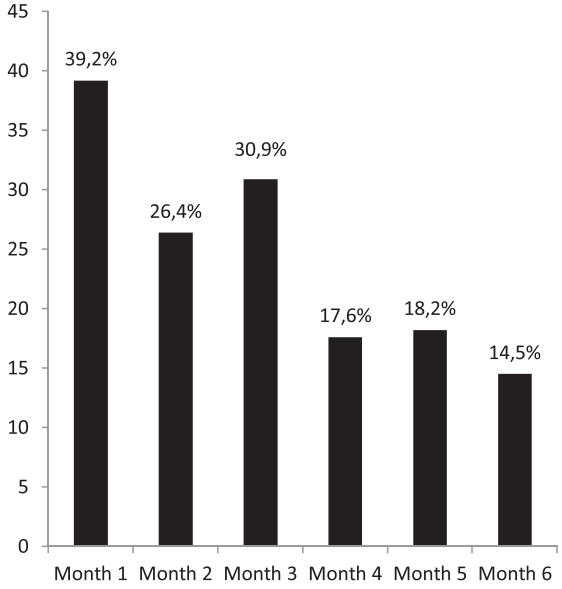

Fig. 2. Percentage of subjects screening positive in the Ethylglucuronide group according to each month of study period.

That being said, when contrasting these findings with previous literature, this phenomenon is not surprising. In fact, all the existing studies where EtG has been compared to ethanol show that performing urine screening with ethanol has a very low sensitivity (Barrio et al., 2016a,b; Jatlow et al., 2014; Skipper et al. 2004; Stewart et al., 2013; Wurst et al., 2006). The most plausible explanation would be that a high proportion of ethanol patients were erroneously deemed as abstinent during the study period, whereas the rate of EtG abstinent patients, thanks to the better diagnostic performance of ethyl glucuronide, was much closer to reality. Although this study employed EtG as the more sensitive biomarker, it would not be surprising to see similar results if other similar, available biomarkers would have been used, such as ethyl sulfate or phosphatidylethanol, which have been shown to provide a similar sensitivity to that of EtG (Wurst et al., 2006; Schröck et al., 2017). Importantly, the data displayed by this study suggest that onc patients become aware of ethyl glucuronide extended sensitivity, they somehow regulate their drinking so as to reduce the number of positive samples they provide when undergoing routine urine screening. Interestingly, and supporting this speculation, the rate of EtG positive patients in the ethanol group at study end is very similar to the rate of EtG

positive patients in the first months of the study period in the EtG group. In trying to find an explanation for these findings, the feedback received by EtG patients emerges as probably the most important mechanism. By continuously being provided with screening results, EtG subjects were made aware of EtG increased sensitivity for the detection of recent drinking, therefore making it possible for them to adapt to this new situation. Acknowledging the important social desirability component present in regular urine screening in the field of alcohol dependence (Barrio et al., 2017b; Zemore, 2012), it is not surprising that EtG patients would have reduced their drinking so as to avoid positive tests. All considered, it is also surprising that the follow-up rate between groups was very similar, since previous studies suggest that patients who screen positive are more likely to abandon treatment (Barrio et al., 2017a). It raises the question about which was the main factor keeping patients into treatment. Was it improved motivation, or was it increased external pressures, or was it both? This question clearly deserves further research.

When analyzing the clinical impact these results provide, it is important to acknowledge that reducing the number of patients screening positive should ideally be complemented with a harder, more clinically relevant variable, such as the number of hospitalizations, in order to fully validate the meaning and the contribution of EtG in the management of alcohol dependence. In this study, the rate of hospitalizations during the study period was very similar between groups. It could be argued that, probably, a longer time period is necessary to observe differences in this outcome. It is interesting to note in this respect that, in a previous study conducted with the same population (Barrio et al., 2017a), the presence of an initial EtG positive test was predictive of a greater rate of relapse and hospitalization, suggesting that reducing the number of subjects screening positive for EtG could indeed have an impact on the hospitalization and relapse rate of alcohol patients, at least in the long run.

When analyzing self-reports, it is interesting to note the difference found between study groups, especially when it comes to self-reports stating abstinence. Though a larger number of respondents would be needed to draw firm conclusions, it seems that EtG patients tend to give lesser false reports of abstinence, suggesting that after long-term screening with EtG, patients become aware of their increased sensitivity and are therefore less prone to inaccurate self-reports of abstinence. It is also worth mentioning that, despite not being statistically significant, the regression analysis using self-report as the final measurement of abstinence suggested ethanol patients had higher chances of achieving abstinence. It must also be noted that EtG does not capture all positive self-reports. Therefore, despite not showing an excellent validity, self-reports should be regarded as a complement of biomarkers in abstinence-oriented settings, as has been previously noted (Substance Abuse and Mental Health Services Association, 2012; Del Boca and Darkes, 2003). Also regarding self-reports, it must be stated that not all patients providing urine samples provided self-report, probably due to the naturalistic design of the study.

Some limitations must be taken into account in this study. First, the treatment allocation procedure, despite being randomized, did not produce size-balanced groups. Notwithstanding, it could be expected that the total study sample size and the statistical procedures employed in this study have overcome this limitation. As is the case with many alcohol studies, liver disease could also be a potential confounding variable. However, previous research suggests that EtG validity is not compromised by alcohol-induced liver injury (Stewart et al., 2013). Another limitation worth discussing is the fact that this was a naturalistic study, wherein we tried to minimize experimental procedures. While this could also be seen as a strength of the study, it must be noted that highly controlled studies usually yield higher internal validity. This might also explain why the mean age of our participants was higher than that observed in other alcohol treatment studies. Similarly, the proportion of patients undergoing group therapy was rather low, a fact that could undermine comparisons with other settings where group therapy might be more frequently used. Also relevant is the fact that study drop-outs were larger than expected, and that made post-study comparisons more subject to random error. That being said, most of the study results reached statistical significance. Finally, as it has been already noted, the main outcomes of the study were derived from urine screening test results. While previous evidence in the addiction field (Barrio et al., 2016a; Batalla et al., 2013; Junghanns et al., 2009) links this data to more clinically relevant variables, in our study we could not provide direct evidence linking the two.

As a conclusion, and in light of the data provided by this study, it seems reasonable to state that routine urine screening with highly sensitive biomarkers such as ethylglucuronide does have an impact on alcohol dependent outpatients, leading to increased abstinence rates. Therefore, the results and the naturalistic nature of this study, added to the more efficient, seriated and economically affordable measurement of EtG via immunoenzimatic techniques suggests that a wider, clinical implementation of EtG in clinical settings should be highly encouraged.

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Contributors

Authors PB, LT, LO, AL, EV, NR and AG developed and designed the study. PB undertook the data analysis and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict declared.

References

Agrawal, A., Lynskey, M.T., 2008. Are there genetic influences on addiction: evidence from family, adoption and twin studies. Addiction 103, 1069–1081.
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC text rev.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, Washington, DC.
American Society of Addiction Medicine, 2014, 2014. Drug Testing A White Paper of the American Society of Addiction Medicine (ASAM). pp. 1–116.
Barrio, P., Ortega, L., Bona, X., Gual, A., 2016a. Development, validation, and implementation of an innovative mobile app for alcohol dependence management: protocol for the SIDEAL trial. JMIR Res. Protoc. 5, e27.
Barrio, P., Teixidor, L., Rico, N., Bruguera, P., Ortega, L., Bedini, J.L., Gual, A., 2016b. Urine ethyl glucuronide unraveling the reality of abstinence monitoring in a routine outpatient setting: a cross-sectional comparison with ethanol, self report and clinical judgment. Eur. Addict. Res. 22, 243–248.
Barrio, P., Mondon, S., Teixidor, L., Ortega, L., Vieta, E., Gual, A., 2017a. One year clinical correlates of etg positive urine screening in alcohol-dependent patients: a survival analysis. Alcohol Alcohol. 52, 460–465.
Barrio, P., Teixidor, L., Ortega, L., Balcells, M., Vieta, E., Gual, A., 2017b. Patients' knowledge and attitudes towards regular alcohol urine screening. J. Addict. Med. 11, 300–307.
Batalla, A., Garcia-Rizo, C., Castellví, P., Fernandez-Egea, E., Yücel, M., Parellada, E., Kirkpatrick, B., Martin-Santos, R., Bernardo, M., 2013. Screening for substance use disorders in first-episode psychosis: implications for readmission. Schizophr. Res. 146, 125–131.
Conigrave, K.M., Saunders, J.B., Whitfield, J.B., 1995. Diagnostic tests for alcohol consumption. Alcohol Alcohol. 30, 13–26.
Del Boca, F.K., Darkes, J., 2003. The validity of self-reports of alcohol consumption: state of the science and challenges for research. Addiction 98, 1–12.
Dupouy, J., Mémier, V., Catala, H., Lavit, M., Oustric, S., Lapeyre-Mestre, M., 2014. Does urine drug abuse screening help for managing patients? A systematic review. Drug Alcohol Depend. 136, 11–20.
Halter, C.C., Dresen, S., Auwaerter, V., Wurst, F.M., Weinmann, W., 2008. Kinetics in serum and urinary excretion of ethyl sulfate and ethyl glucuronide after medium dose ethanol intake. Int. J. Legal Med. 122, 123–128.
Hock, B., Schwarz, M., Domke, I., Grunert, V., Wuertemberger, M., Schiemann, U., Horster, S., Limmer, C., Stecker, G., Soyk, M., 2005. Validity of carbohydrate-deficient transferrin (%CDT), γ-glutamyltransferase (γ-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 100, 1477–1486.
Jatlow, P.I., Agro, A., Wu, R., Nadim, H., Toll, B.A., Ralevski, E., Nogueira, C., Shi, J., Dziura, J.D., Petrakis, I.L., O'Malley, S.S., 2014. Ethyl glucuronide and ethyl sulfate assays in clinical trials, interpretation, and limitations: results of a dose ranging alcohol challenge study and 2 clinical trials. Alcohol. Clin. Exp. Res. 38, 2056–2065.
Junghanns, K., Graf, I., Pflüger, J., Wetterling, G., Ziems, C., Ehrenthal, D., Zöllner, M., Dibbelt, L., Backhaus, J., Weinmann, W., Wurst, F.M., 2009. Urinary ethyl glucuronide (EtG) and ethyl sulphate (EtS) assessment: valuable tools to improve verification of abstention in alcohol-dependent patients during in-patient treatment and at follow-ups. Addiction 104, 921–926.
Lahmek, P., Michel, L., Diviné, C., Meunier, N., Pham, B., Cassereau, C., Aussel, C., Aubin, H.-J., 2012. Ethyl glucuronide for detecting alcohol lapses in patients with an alcohol use disorder. J. Addict. Med. 6, 35–38.
Lord, S.J., Irwig, L., Simes, R.J., 2006. When is measuring sensitivity and specificity sufficient to evaluate a diagnostic test, and when do we need randomized trials? Ann. Intern. Med. 144, 850–855.
Lu, B., Gatsonis, C., 2013. Efficiency of study designs in diagnostic randomized clinical trials. Stat. Med. 32, 1451–1466.
Mihas, A.A., Tavassoli, M., 1992. Laboratory markers of ethanol intake and abuse: a critical appraisal. Am. J. Med. Sci. 303, 415–428.
Mohapatra, S., Patra, J., Popova, S., Duhig, A., Rehm, J., 2010. Social cost of heavy drinking and alcohol dependence in high-income countries. Int. J. Public Health 55, 149–157.
Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., Patra, J., 2009. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 373, 2223–2233.
Reisfield, G.M., Goldberger, B.A., Pesce, A.J., Crews, B.O., Wilson, G.R., Teitelbaum, S.A., Bertholf, R.L., 2011. Ethyl glucuronide, ethyl sulfate, and ethanol in urine after intensive exposure to high ethanol content mouthwash. J. Anal. Toxicol. 35, 264–268.
Rodger, M., Ramsay, T., Fergusson, D., 2012. Diagnostic randomized controlled trials: the final frontier. Trials 13, 137.
Schröck, A., Thierauf, A., Wurst, F.M., Thon, N., Weinmann, W., 2014. Progress in monitoring alcohol consumption and alcohol abuse by phosphatidylethanol. Bioanalysis 6, 2285–2294.
Schröck, A., Wurst, F.M., Thon, N., Weinmann, W., 2017. Assessing phosphatidylethanol (PEth) levels reflecting different drinking habits in comparison to the alcohol use disorders identification test – C (AUDIT-C). Drug Alcohol Depend. 178, 80–86.
Skipper, G.E., Weinmann, W., Thierauf, A., Schaefer, P., Wiesbeck, G., Allen, J.P., Miller, M., Wurst, F.M., 2004. Ethyl glucuronide: a biomarker to identify alcohol use by health professionals recovering from substance use disorders. Alcohol Alcohol. 39, 445–449.
Soyka, M., Kranzler, H.R., Berglund, M., Gorelick, D., Hesselbrock, V., Johnson, B.A., Möller, H.J., 2008. The WFSBP task force on treatment, 2008. World federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of substance use and related disorders, part 1. Alcohol. World J. Biol. Psychiatry 9, 6–23.
Stewart, S.H., Koch, D.G., Burgess, D.M., Willner, I.R., Reuben, A., 2013. Sensitivity and specificity of urinary ethyl glucuronide and ethyl sulfate in liver disease patients. Alcohol. Clin. Exp. Res. 37, 150–155.
Substance Abuse and Mental Health Services Association, 2012. Substance Abuse and Mental Health Services Association 2012 The role of biomarkers in the treatment of alcohol use disorders. Revision Advisory. pp. 11.
Wurst, F.M., Wiesbeck, G.A., Metzger, J.W., Weinmann, W., 2004. On sensitivity, specificity, and the influence of various parameters on ethyl glucuronide levels in urine–results from the WHO/ISBRA study. Alcohol. Clin. Exp. Res. 28, 1220–1228.
Wurst, F.M., Dresen, S., Allen, J.P., Wiesbeck, G., Graf, M., Weinmann, W., 2006. Ethyl sulphate: a direct ethanol metabolite reflecting recent alcohol consumption. Addiction 101, 204–211.
Wurst, F.M., Thon, N., Yegles, M., Schrück, A., Preuss, U.W., Weinmann, W., 2015. Ethanol metabolites: their role in the assessment of alcohol intake. Alcohol. Clin. Exp. Res. 39, 2060–2072.
Zemore, S.E., 2012. The effect of social desirability on reported motivation, substance use severity, and treatment attendance. J. Subst. Abuse Treat. 42, 400–412.