Ethylglucuronide replacing ethanol in the routine screening of alcohol dependent outpatients: clinical implications

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Thesis submitted in order to obtain the academic degree of Doctor at the University of Barcelona

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Line of Research: Biological bases of psychiatric disorders and nuclear psychiatry

Framework

This work is presented to the University of Barcelona in fulfillment of the requirements and procedures for the degree of Doctor in the format of article publication. Hereby, the published articles included in this thesis are part of a line of research and a series of national and international congress presentations, posters and scientific papers regarding the clinical implications of routinely screening alcohol dependent outpatients with urine ethyl glucuronide. As per to the requirements, at least two of them are original published articles authored by the doctorate candidate within the first two quartiles of the field.

Most of the research work presented in this thesis has been conducted and published by the, or with the participation of the, Addictive Behaviors Unit of the Hospital Clínic de Barcelona, part of the Institut d' Investigacions Biomédiques August Pi y Sunyer (IDIBAPS), the University of Barcelona (UB), the Centro para la Investigación Biomédica en Red de la Salud Mental (CIBERSAM) and the Red de Trastornos Adictivos (RTA).

The indexed publications are listed below sorted by thematic sequence order:

1. Title: 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. Authors: **Barrio P**, Teixidor L, Rico N, Bruguera P, Ortega L, Bedini JL, Gual A. Eur Addict Res. 2016;22(5):243-8. doi: 10.1159/000445741.

2. Title: One Year Clinical Correlates of EtG Positive Urine Screening in Alcohol-Dependent Patients: A Survival Analysis. Authors: **Barrio P** ,Mondon S, Teixidor L, Ortega L, Vieta E, Gual A. Alcohol and Alcoholism, 2017, 1–6 doi: 10.1093/alcalc/agx012.

3. Title: Patients' Knowledge and Attitudes towards Regular Alcohol Urine Screening: a Survey Study. Authors: **Barrio P**, Teixidor L, Ortega L, Balcells M, Vieta E, Gual A. Journal of Addiction Medicine, 2017. doi: 10.1097/ADM.

To Maria and Martí, for bringing joy to my life.

"When the Lord created the world and people to live in it -- an enterprise which, according to modern science, took a very long time -- I could well imagine that He reasoned with Himself as follows: "If I make everything predictable, these human beings, whom I have endowed with pretty good brains, will undoubtedly learn to predict everything, and they will thereupon have no motive to do anything at all, because they will recognize that the future is totally determined and cannot be influenced by any human action. On the other hand, if I make everything unpredictable: they will gradually discover that there is no rational basis for any decision whatsoever and, as in the first case, they will thereupon have no motive to do anything at all. Neither scheme would make sense. I must therefore create a mixture of the two. Let some things be predictable and let others be unpredictable. They will then, amongst many other things, have the very important task of finding out which is which."

From E. F. Schumacher's "Small is Beautiful"

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Abstract

Abstract (english)

Background

The development of an alcohol biomarker is a long process where different stages take place over time. From discovery to full clinical use and implementation, each accomplished stage increases the confidence in and the relevance of such biomarkers. In recent years, new biomarkers have been discovered, with outstanding improvements in the sensibility and specificity for the detection of recent drinking. However, the clinical, therapeutic and economical consequences of such biochemical improvements remain to be determined. With the present thesis we expect to investigate the clinical implications of such new biomarkers, with a special focus on urine ethyl glucuronide (EtG), in order to fully establish its contribution to the field of alcohol use disorders. It comprises three articles: the first (Study 1) compares the screening performance of ethyl glucuronide versus ethanol, clinical judgment and self report, under routine, real circumstances in alcohol dependent outpatients. The second one (Study 2) investigates the differential, one-year clinical evolution of patients screening positive and negative in Study 1, taking into account both clinical and economic consequences. Finally, Study 3 evaluates patients' knowledge and attitudes towards regular alcohol urine screening.

Methods

Study 1 consisted of a cross-sectional comparison aiming at clinically validating EtG under real, routinely clinical conditions. For that purpose, 613 consecutive urinary samples, provided by 188 outpatients with alcohol dependence were analyzed for ethanol and EtG. Study 2 retrospectively assessed the clinical evolution of patients participating in Study 1. A survival analysis was conducted in order to compare the rate of relapse between EtG positive and negative patients. Regression models were performed to compare the mean number of days hospitalized between groups, the risk of being lost to follow-up and treatment expenses. In Study 3 a cross-sectional survey among alcohol dependent outpatients was conducted. In consonance with the principles of patient centered care, it aimed at investigating patients' attitudes and beliefs towards regular alcohol urine screening. For attitudes' assessment, we adapted the Drug Attitude Inventory (DAI-10) to the field of alcohol urine screening. Internal consistency, test-retest reliability and concurrent validity were evaluated for the adapted questionnaire.

Results

Study 1 showed an overriding superiority of EtG over ethanol, clinical judgment and self report, detecting a significant greater number of positive samples in routine, real circumstances. Study 2 revealed a clearly different clinical evolution between EtG positive and negative patients during the following 12 months, with EtG positive patients being at greater risk of relapse, hospitalization and incurring in more treatment expenses. Study 3 suggested that regular alcohol screening is highly valued by alcohol outpatients. It also showed that besides relapse prevention, other functions related to therapeutic alliance building, social desirability and impression management play a key role as well.

Conclusions

Regular alcohol urine screening with ethyl glucuronide seems to have an impact on the clinical management of alcohol dependent outpatients, offering a better detection of recent drinking and the possibility of an improved relapse prevention strategy.

Abstract (spanish)

Introducción

El desarrollo de biomarcadores para el consumo de alcohol es un proceso largo y laborioso, donde múltiples etapas se suceden en el tiempo. Desde su descubrimiento en el laboratorio hasta su total implementación clínica, cada etapa superada incrementa la confianza y la relevancia de dicho marcador. En los últimos años se han descubierto marcadores que cuentan con una notable sensibilidad y especificidad en cuanto a la detección de consumo reciente se refiere. Sin embargo, las implicaciones clínicas, terapéuticas y económicas de dichos marcadores todavía no han sido esclarecidas con total claridad. Con la presente tesis se pretende investigar las implicaciones clínicas de dichos nuevos marcadores, específicamente del etilglucurónido (EtG), con el objetivo de determinar su verdadera aportación al campo de los trastornos por uso de alcohol. Esta tesis está compuesta de tres artículos. El primero (Estudio 1) compara el rendimiento en el cribado de consumo de alcohol del etilglucurónido frente al etanol, el juicio clínico y el autoinforme, bajo condiciones rutinarias y reales en pacientes dependientes del alcohol ambulatorios. El segundo artículo (Estudio 2) investiga la evolución clínica diferencial entre los pacientes que obtuvieron un resultado positivo y uno negativo en el Estudio 1, durante los siguientes 12 meses. Finalmente, el tercer artículo (Estudio 3) evalúa los conocimientos y la actitud que los pacientes presentan ante el cribado rutinario de alcohol.

Métodos

El Estudio 1 consistió en una comparación transversal cuya finalidad fue la de evaluar el uso de EtG bajo condiciones clínicas rutinarias de elevada validez externa. Para ello 613 muestras de orina consecutivas, proporcionadas por 188 pacientes ambulatorios con dependencia al alcohol, fueron analizadas para etanol y etilglucurónido. El Estudio 2 evaluó retrospectivamente la evolución clínica de los participantes del Estudio 1. Se llevó a cabo un análisis de supervivencia con el fin de comparar la tasa de recaída entre pacientes con un resultado positivo y negativo a etilglucurónido. Se realizaron análisis de regresión para comparar entre grupos el número medio de días hospitalizados, el riesgo de abandonar tratamiento y los costes medios del tratamiento. En el Estudio 3, en consonancia con los principios de la medicina centrada en el paciente, se realizó una encuesta a pacientes con dependencia del alcohol ambulatorios con la finalidad de evaluar sus actitudes, creencias y conocimientos en relación al cribado rutinario de alcohol en orina. Para la evaluación de sus actitudes se adaptó la escala Drug Attitude Inventory (DAI-10), analizándose su consistencia interna, su fiabilidad test-retest y su validez concurrente.

Resultados

El Estudio 1 mostró una clara superioridad del EtG sobre el etanol, el juicio clínico y el autoinforme, detectando un mayor número de positivos en condiciones reales de elevada validez externa. El Estudio 2 demostró una clara y diferente evolución clínica entre los pacientes que fueron EtG positivo y EtG negativo durante los siguientes 12 meses, presentando los pacientes EtG positivo un mayor riesgo de recaída, de hospitalización así como mayores costes de tratamiento. El Estudio 3 sugirió que el cribado rutinario de alcohol en orina es percibido por los pacientes dependientes al alcohol como un elemento valioso de su tratamiento. Se observó también que, además de cumplir una función de prevención de recaídas, otras funciones relacionadas con el vínculo terapéutico, la conveniencia social y la gestión de impresiones juegan también un papel clave.

Conclusiones

El cribado rutinario de alcohol mediante EtG parece tener un impacto en el manejo de los pacientes dependientes al alcohol ambulatorios, ofreciendo una mejor detección del consumo reciente de alcohol así como la posibilidad de una mejor prevención de recaídas.

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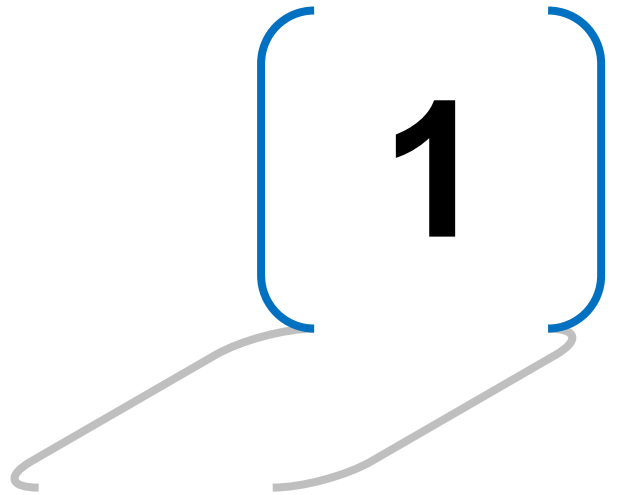
Introduction

Introduction

The burden and size of the problem

The global burden of disease from alcohol use is second only to tobacco and hypertension (1). Alcohol is responsible for 5,9% of mortality worldwide (2), meaning that 2,5 million people die each year because of alcohol (3). In the U.S. it represents the third leading cause of preventable death (4), while Europe, with 15 million people affected by alcohol use disorders (5), has the highest alcohol-attributable deaths and disability-adjusted life years (DALYs) in the world (13.3% of deaths and 12.8% of DALYs are attributable to alcohol) (2). On top of that, the well-known treatment gap of alcohol use disorders (6–8), where approximately only 1 in 10 patients receive treatment, increases the magnitude of this burden. But not only affected individuals, treated or not, must assume alcohol consequences. Societies as a whole do also suffer its consequences. In fact, a recent systematic review concluded that most of the costs alcohol produces are born by non-affected individuals, i.e., society as a whole (9). Therefore, the size and the consequences of the problem clearly suggest that alcohol should be a top priority from a public health perspective.

Alcohol use disorders

Most of the consequences and burden of disease produced by alcohol stem from people affected by the severest form of alcohol use disorder (AUD) (10), formerly called alcohol dependence under DSM-IV (11). A solid body of evidence demonstrates that severe AUD (or alcohol dependence) is a chronic condition, usually with a relapse-remitting course (12–14). Studies also suggest it is a multifactorial disease, where complex genetic-environmental interactions occur. Both twin studies (15) and genome wide association studies (GWAS) (16) show that genetic influences exert a moderate to high etiological influence in its development (17).

The consequences suffered by affected individuals are several and diverse. From organic to psychiatric symptoms, manifestations of alcohol use may appear on any organ system of the body (18,19). Common behavioral, psychiatric, social, or medical manifestations of alcohol dependence include trauma or injury, anxiety, depression, suicidality, hypertension, gastrointestinal symptoms, cardiac symptoms, central or peripheral neurologic symptoms, electrolyte disturbances, sleep

disturbances, increased liver enzymes, macrocytosis and social or legal problems. Importantly, alcohol remains the most common cause of liver cirrhosis in Western World (20).

In consonance with the prevalence, magnitude and consequences of alcohol use, a majority of guidelines advocate for the universal implementation of screening for alcohol use disorders in primary care (21,22). Systematic screening should allow primary care physicians to identify and offer treatment to mild and moderate forms of AUD, while at the same time identify more severe forms and refer them to specialized treatment. Screening of AUD in primary care is usually conducted with short and easy to use questionnaires, such as the AUDIT-C. Ancillary tests, such as blood examination, can play also a part in identifying affected individuals.

Regarding the treatment of alcohol use disorders, It is widely agreed that the basis of treatment remains psychosocial in essence (23). However, it is probable that the combination of psychosocial and pharmacological treatments might offer the most efficacious treatment for affected individuals (24).

While a full review of the treatment of AUD is beyond the scope of this thesis, it can be said that a variety of options with solid evidence exist for both psychosocial and pharmacological treatments. In the area of psychosocial interventions, motivational interviewing, cognitive behavioral therapy, peer support groups, family therapy, contingency management and social behavioral network therapy have proven its efficacy (25–32). From the pharmacological point of view, different treatments have proven efficacy, such as naltrexone, acamprosate, disulfiram, baclofen and topiramate (33–37).

Treatment goals in alcohol use disorders

A relevant question in the treatment of alcohol use disorders, such as in any other disease, are treatment goals. Broadly speaking, restoration of physical, mental and social well-being could be considered the main treatment aims. This broad definition encompasses the idea that outcome expectancies in alcohol dependence treatment should not be limited to the amount of alcohol ingested (38). However, it is almost self-evident that, in fact, the amount of drinking is of paramount importance

when evaluating patients' clinical evolution and response to treatment, and that the amount of alcohol has a direct causal relationship with many of the problems that patients have on multiple life areas (39). Putting it simple, when it comes to specific drinking outcomes, usually two options arise: reduced/controlled drinking or abstinence.

Despite harm reduction strategies being frequently considered and used in addiction settings, and despite some controversies in the field (40–42), abstinence has been the prevailing therapeutic goal in most of the existing settings, being considered the safest and most efficient pathway to early recovery (43,44). This fact is not surprising, since addiction has usually been conceptualized as impaired control over a substance. Moreover, longitudinal studies have called into question the adequacy of controlled-drinking paradigms as long-term strategies for moderate and severe alcohol dependent patients (45,46).

Therefore, it becomes clear that being able to properly monitor abstinence is of key importance in the field of alcohol use disorders.

Monitoring abstinence in alcohol use disorders

Professionals dispose mainly of two types of tools to undertake this salient job. First, patients' self-reports. For many years, they were, besides clinician's' judgment, the only available instrument. Despite all the advances in biological markers, they remain as one key component of routine clinical care in many settings (47). Nonetheless, they suffer from some important pitfalls, especially regarding their sensitivity in detecting alcohol consumption. Some of the reasons underlying this shortcoming might be cognitive deficits, fear of putting treatment in danger, fear of legal consequences or social desirability (48). Some of these might be overcome with alcohol biomarkers. They should not be considered as substitutes of self-reports, but rather a complementary element that might yield important contributions in different situations, such as outcome measures in research studies, screens for alcohol problems in individuals unable to provide accurate self- reports, or as an instrument to increase the accurateness of abstinence monitoring (49).

Alcohol biomarkers can be obtained from a variety of sources. Blood, breath and urine are the most common. While some of them should be considered as markers of heavy use over time, others are better suited for abstinence monitoring. For example, traditional markers such as gamma-glutamyl

transferase (GGT) or mean corpuscular volume (MCV) need prolonged ingestion of relatively high amounts of alcohol to become elevated (50,51). Even carbohydrate deficient trasnferrin (CDT), which certainly improves the specificity of traditional biomarkers, requires at least a few drinks a day for two weeks to become elevated (52). Hence, they do not seem feasible candidates for a proper abstinence monitoring system, since they would be unable to detect single lapses or short term relapses. Moreover, they are measured in blood samples, a fact that limits its usefulness as a routine screening method.

In this sense, urine offers some relevant advantages over blood specimens as screening tests in routine clinical practice, especially when patients have to undergo frequent testing. It is indeed frequent practice in many abstinence oriented settings, where patients undergo regular urine screening to monitor abstinence (53).

Until recently, urinary ethanol had been the main marker used. Similar to breath alcohol testing, its main pitfall is that it only remains positive for a few hours after alcohol ingestion, therefore precluding a proper monitoring of abstinence (54). Fortunately, in the field of alcohol biomarkers, some recent advances display promising features, that could allow the overcoming of some of the previously mentioned shortcomings.

Ethyl glucuronide

The most relevant biomarker and the subject of the present thesis is urine ethyl glucuronide (EtG), a non-volatile, water-soluble, stable, direct metabolite of ethanol. Its formation takes place via glucuronidation after ethanol ingestion. Although only about 0.5% of all the ethanol ingested undergoes this degradation pathway, it remains detectable in urine for up to 72h, depending on the amount of ethanol ingested (55). 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 as much as covert drinking might be more frequently detected and so earlier addressed, both in a feasible and cost-effective manner. While the gold standard for EtG measurement is liquid chromatography–tandem mass spectrometry (LC–MS/MS), the appearance of a commercially available enzyme immunoassay (EIA) method based on a monoclonal antibody (DRI Ethyl

Glucuronide Enzyme Immunoassay, DRI-EtG EIA, Thermo Fisher Scientific Diagnostics, Hemel Hempstead, UK) has made the seriated measurement of EtG a feasible and price-affordable reality in routine clinical settings.

It is important to note that other recent alternatives exist besides EtG. However, none of them seems nowadays optimal enough for a routine clinical use. For example, transdermal alcohol monitors allow for continuous assessment of alcohol concentrations, but cost, stigma and feasibility deterrents preclude its wide implementation (56). Phosphatidylethanol is another recent biomarker that has shown a relatively good potential to detect recent drinking with a detection window of up to 2 weeks. Due to improvements in its measurement, based on LC-MS/MS techniques, its sensitivity has increased for the detection of low quantities of drinking. However, it is only measurable in blood (57,58). Finally, ethyl sulfate is another biomarker that performs well for recent drinking detection, but no commercially available immunoassay exists to date, making its routine implementation more costly and difficult (57,59).

Justification of this thesis

Several studies exist up to date focused on urine ethyl glucuronide. While many studies have focused on the kinetics of EtG under controlled drinking designs (60–63), the ultimate relevance of EtG, as with any other diagnostic tool, is how it performs with real patients in real circumstances. In this sense, many studies have tested urinary EtG for the detection of recent drinking, consistently reporting a better detection capacity compared to other biomarkers, usually self-reports or breath alcohol. However, the majority of these studies have been conducted in artificial conditions or experimental settings, or have been embedded in trials aimed at other investigations (61,64–67). While experimental designs are essential for internal validity assessment, it has been extensively noted in many areas that external validity remains disproportionally neglected (68–70). This fact might yield relevant consequences, such as the fact that patients from experimental settings might differ significantly from patients in routine settings (71,72), ultimately jeopardizing the feasibility, applicability and even the relevance of experimental findings (73). Other concerns regarding previous EtG studies are small sample sizes or the use of inpatient populations (74–77). Therefore, we believe that it is

important to assess the performance of EtG in "the real world". This is in fact the aim of **Study 1**, where EtG performance was compared to that of ethanol, self report and clinical judgment under routine, clinical circumstances in a cross-sectional design.

Other relevant concerns remain in the field of routine urine testing for abstinence monitoring in alcohol dependent outpatients. Despite the intuition that a higher detection capacity would translate into more efficacious and efficient clinical care, there is a paucity of data addressing this question. A recent systematic review (78) found little evidence in favor of the clinical utility of conducting urine drug screening, outlining that only a few, ill-powered studies have directly addressed this question. Taken together, it seems like, despite being such a frequent technique (53) there is a paucity of evidence supporting its utility. In fact, no previous research has evaluated the clinical implications of an EtG positive screen, in terms of relapse risk, treatment expenses and risk of subsequent hospitalization. This question will be addressed in **Study 2**, where patients participating in Study 1 were followed during the next 12 months, in order to conduct a survival analysis aimed principally at investigating the differential relapse and hospitalization risk between EtG positive and negative patients.

Taking all previous existing research into account, it seems that, so far, conventional urine screening for alcohol outpatients, conducted with suboptimal biomarkers, has been far from satisfactory in monitoring abstinence. When assessing this fact, some related questions seem to emerge: what are the reasons underlying this poor effectiveness? Does urine screening serve other functions besides monitoring abstinence, such as offering ongoing support? What do patients know about urine screening, and what are their attitudes towards it? **Study 3** tries to unravel some of the answers to these questions by focusing on patients' knowledge and attitudes towards regular alcohol urine screening. It is important to remember that, in line with the increasing importance of patient-centered care as a central tenet of high-quality health care delivery (79) also in the field of alcohol dependence (80,81), patients always have a unique perspective on any service or intervention they receive. Hence, their input becomes an essential component of service evaluation and improvement. While there a multiple surveys among professionals regarding urine drug screening (82–86), to the best of our knowledge this is the first time that patients become the target population of the survey.

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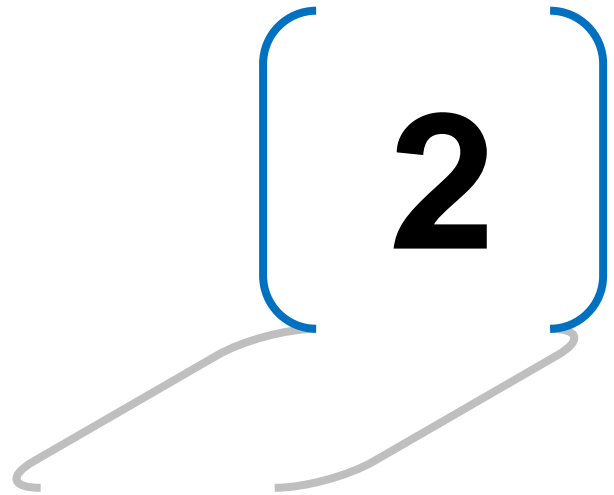
Aims and hypothesis

Aims

Primary aims

1. To increase the available evidence supporting the utility of routine urine screening for the management of alcohol use disorder patients.

2. To investigate, under routine clinical conditions, the differential sensitivity of urinary ethanol and urine ethyl glucuronide for the detection of recent drinking, in alcohol dependent outpatients attending an abstinence oriented program.

3. To investigate whether a positive urine ethyl glucuronide predicts a greater number of hospitalizations and health resource consumption during the following 12 months.

4. To investigate whether a single urine ethyl glucuronide positive screening could predict relapse in the following 12 months, and compare the risk of relapse between positive and negative ethyl glucuronide patients in the following 12 months.

5. To assess the reasons why alcohol dependent outpatients attend a routine urine screening program.

6. To investigate patients' attitudes towards routine alcohol urine screening, as well as their perceived utility.

Secondary aims

1. To investigate the accuracy of self-report using ethyl glucuronide as a gold standard

2. To investigate the validity of clinical judgment for the detection of recent drinking using ethyl glucuronide as a gold standard.

3. To investigate whether an ethyl glucuronide positive screening increases the risk of treatment abandonment.

4. To investigate patients' knowledge about different possibilities for alcohol urinary screening, as well as their pertinent detection windows, with a special focus on EtG.

Hypotheses

1. Given its higher sensibility, and specially its longer detection window, we hypothesize that ethyl glucuronide performance in urine screening will result in a greater number of positives compared to ethanol in the detection of recent drinking. We also hypothesize that ethyl glucuronide will detect more patients with recent drinking than clinical judgment.

2. Given that relapses are frequently initiated in the form of lapses, a more sensible biomarker, such as ethyl glucuronide, could help identify patients in the early phases of relapse, therefore we hypothesize that patients with a positive baseline ethyl glucuronide will have a greater number of relapses and health resource consumption during the following 12 months, as compared to patients with a negative result.

3. Due to its novelty and its technical aspects, we expect patients to have a low level of knowledge regarding EtG as well as other concepts related to urine screening, including the detection window of EtG.

4. Assuming alcohol dependent patients have diverse reasons and expectations towards regular urine screening, we hypothesize that patients will show mixed results regarding their attitudes towards urine screening. It is expected that some of them will see it as a helpful aid in maintaining abstinence, whereas others will show feelings of obligation and dislike towards it.

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Study 1

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

Study 1

Summary

Reference

Aims

Based on hypothesis #1, the aim of this study was to investigate, under routine clinical conditions, the differential screening performance of urinary ethanol and ethyl glucuronide for the detection of recent drinking, in alcohol dependent outpatients attending an abstinence oriented program. We further evaluated the differential screening performance of ethyl glucuronide and clinician judgment for the detection of recent drinking, and also tried to investigate variables associated with a positive EtG result.

Methods

We performed a cross sectional study comparing the detection capacity of ethanol and EtG in urine samples provided from subjects attending the outpatient service of the Addictive Behaviors Unit in a tertiary care Hospital in Barcelona.

Urine samples were collected from patients attending the outpatient service of the Addictive Behaviors Unit, where routine urine screen is an established procedure for the monitoring of abstinence and relapse prevention. Both patients and their treating professionals were unaware of study procedures and results.

EtG was measured with a commercially available enzyme immunoassay (EIA) method based on a new monoclonal antibody (DRI Ethyl Glucuronide Enzyme Immunoassay , DRI-EtG EIA, Thermo Fisher Scientific Diagnostics, Hemel Hempstead, UK). The comparison of the DRI-EtG EIA

with a reference LC-MS method for 126 urine samples (100 – 50.000 ng/mL) was made with Passing-Bablok regression (EIA= -0,104 + 0,960 LC-MS). Both methods showed an overall good and statistically significant agreement r2=0,961 (P<0,0001).

The DRI-EtG EIA is a semi-quantitative method with a clinical cut off of 500 ng/mL. It also offers a low and clinically relevant analytical range (15.3 – 2000 ng/mL). Samples with EtG above 2000 ng/mL were diluted 1/10 increasing its analytical range until 20000 ng/mL. This method has been adapted to the ADVIA 1800 Chemistry System, (Siemens Healthcare Diagnostics, Tarrytown, USA) to improve the throughput and the easiness of the analysis. Before analyzing the samples, two control levels (375 ng/mL and 625 ng/mL) were processed in order to ensure a correct analysis.

Routine sociodemographic as well as disease characteristics were collected from patients' medical chart. The attending nurse, an experienced clinician in the field of addiction, meets every patient that undergoes urine screening. The encounter usually takes the form of a brief (usually less than 5 minutes), non structured meeting, where patients' self-report is collected, and in case it is necessary, other clinical information is exchanged, sometimes in the form of brief advice, sometimes in a more informal manner. It was during these meetings that the nurse also provided her clinical judgment regarding the drinking status of the patient, in a qualitative way (patient is totally abstinent: yes, no).

We also collected whether patients were on disulfiram or another aversive medication, whether other substances were searched in the urine sample, and if any of the co-screenings resulted in a positive result. Weekly frequency of urine testing (less than once weekly, once weekly or more than once weekly) was also collected.

Sociodemographic characteristics of the sample were described for all subjects providing urine samples. Quantitative comparative analyses were performed between the rate of positive results of ethanol and EtG. In ethanol negative subjects, comparisons were conducted between subjects with positive or negative EtG, followed by regression analysis as a mean to investigate if there were any features predicting the positivity of EtG. The detection performance of clinical judgment was further assessed using EtG as a gold standard to calculate the area under the receiving operator curve (ROC).

Results

A total of 188 patients provided 613 consecutive urine samples, in a 14-days period.

Regarding the total amount of positives, urinary ethanol resulted in 9 positive samples belonging to 8 patients. EtG yielded 136 positive samples belonging to 74 patients. Most of EtG positive samples (125) were negative for alcohol. It means that 20,4% of the total urine samples (125/613) were discordant regarding EtG and ethanol. All urinary alcohol positives resulted in EtG positives.

The percentage of co-screened samples for other substances was 28,1% (172/613). Cannabis was the main substance investigated (125/613 urine samples), resulting in a 9,6% of positives when calculated for the total sample (59/613). EtG was positive in 14,6% of the samples of patients being on aversive medications and in 26,4% of patients who were not in treatment with aversives. The group being screened less than weekly resulted in a 30,8% of positive EtG urine samples, those screened once weekly in 16,1% of positives and those screened more than once weekly in 23,5% of positive samples.

In the logistic regression model the following variables were entered: sex, age, duration and frequency of urine screening, coscreening to other substances, positive to other substances, clinical judgment and being on aversive medication. Of these, only being on aversive medication and clinical judgment resulted in significant effects.

Regarding the diagnostic performance of the nurse, she judged 89,7% (550/613) of the samples, belonging to 178 patients, as abstinent. She deemed 7,8% (48/613) of the samples, belonging to 26 patients, as not abstinent, and was unsure in 15 samples from 15 patients. When comparing it against EtG, it resulted in an area under the ROC curve of 0.592.

Conclusions

EtG performed largely better than ethanol for urine screening in alcohol outpatients, detecting an extra 20,4% (125 out of 613) of positives. It means that for each ethanol positive

sample, there were approximately 15 EtG positive samples. Although better than ethanol, clinician judgment performed also deficiently. Taken together, both the possibility of a more cost-effective quantification method and the confirmation of a clearly better performance in routine clinical conditions for the screening of alcohol dependent outpatients, suggest that EtG implementation should be a priority in abstinence oriented settings, where it might bring relevant improvements.

Research Report

European Addiction Research

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

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Abstract

Aims: To test the screening performance of urinary ethyl glucuronide (EtG) under routine clinical conditions in a sample of alcohol-dependent outpatients, comparing it against urinary ethanol, self reports and clinical judgment. *Methods:* A cross-sectional study under routine conditions was conducted in February 2015, where 613 consecutive urinary samples, provided by 188 outpatients with alcohol use disorders, were analyzed for ethanol and EtG (cut-off level = 500 ng/ml). Clinical variables such as the presence of aversive medication, comorbidities and clinician judgment were also collected. The discrepancy between the number of alcohol and EtG positives was recorded. A logistic regression analysis including clinical variables was conducted to assess for predictors of EtG positivity. *Results:* Urinary alcohol yielded 9 positives (1.5% of all urine samples) belonging to 8 patients. EtG yielded 136 positives (22% of all urine samples) belonging to 74 patients. Of these, 93.4% (127 of 136) were negative for alcohol. All urinary alcohol positives resulted in EtG positives. The clinician judged 48 samples from 26 patients as belonging to not abstinent patients and 550 samples from 178 patients as belonging to abstinent patients. She was unsure in 15 samples from 15 patients. When comparing it against EtG as the gold standard, the area under the curve was 0.592. Self reports were extremely unreliable in this study, with only 5 patients reporting drinking in a total of 6 urine samples. In the logistic regression model, only aversive medications (OR 2.1, 95% CI 1.3–3.3) and clinician judgment (OR 2, 95% CI 1.4–2.9) resulted in significant effects. *Conclusions:* EtG performed largely better than ethanol for urine screening in alcohol outpatients, detecting an extra 20.4% (125 out of 613) of positives. It means that for each alcohol-positive sample, there were 15 EtG-positive samples. Although better than ethanol, clinician judgment was also not performed efficiently. If routinely implemented in the screening of alcohol outpatients, EtG might bring relevant changes that merit further research.

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Introduction

The global burden of disease from alcohol is second only to tobacco and hypertension [1]. To prevent and reduce health and social problems related to alcohol use, biological markers capable of monitoring alcohol consumption with a high sensitivity and specificity are re-

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quired. Traditional markers of alcohol consumption, such as gamma glutamyltransferase (GGT), mean corpuscular volume (MCV) or carbohydrate deficient trasnferrin (CDT) reflect persistent consumption of higher amounts of alcohol (>2 weeks, >1,000 g of ethanol in 2 weeks). However, in many instances it is of utmost importance to detect even single-drink or short-term consumption events, for example, in abstinence-oriented programs, where full relapses might get initiated weeks before in the form of 'lapses'. In such cases, traditional markers are usually of low usefulness.

For many years, in abstinence-oriented settings, urine or breath ethanol has been the mainstay of biological testing for alcohol consumption. Nonetheless, some limitations exist regarding its efficacy, mainly with regard to the time spectrum of detection, covering only the 6–8 h following alcohol use. Thus, a notable gap exists between the 8 h after ingestion and the 1–2 weeks needed to see elevations in CDT, GGT or MCV. Ethyl glucuronide (EtG), a non-volatile, water-soluble, stable, direct metabolite of ethanol appears to partly fill the gap. Although only about 0.5% of all the ethanol ingested undergoes this degradation pathway, it remains detectable in urine for up to 72 h, depending on the amount of ethanol ingested [2]. Therefore, it expands the time window for the detection of recent alcohol consumption in urine samples. This might offer relevant improvements in clinical practice; especially with covert drinking, which might be more frequently detected and so earlier addressed both in a feasible and cost-effective manner.

Although some alternatives might exist besides EtG, none of them seems, nowadays, optimal enough for routine clinical use. For example, transdermal alcohol monitors allow for continuous assessment of alcohol concentrations, but cost, stigma and feasibility deterrents preclude its wide implementation [3]. Phosphatidylethanol is another recent biomarker that has shown a relatively good potential to detect recent drinking with a detection window of up to 2 weeks. Due to improvements in its measurement, now based on LC-MS/MS techniques, its sensitivity has increased for detecting low quantities of drinking. However, it is only measurable in blood [4, 5]. Finally, ethyl sulfate is another biomarker that performs well for recent drinking detection, but no commercially available immunoassay exists to date, making its routine implementation more costly and difficult [4, 6].

While many studies have focused on the kinetics of EtG under controlled drinking designs [7–10], the ultimate relevance of EtG, as with any other diagnostic tool, is how it performs with real patients in real circumstances. In this sense, many studies up to date have tested urinary EtG for the detection of recent drinking, consistently reporting a better detection capacity compared to other biomarkers, usually self-reports or breath alcohol. However, a majority of studies have been conducted in artificial conditions or experimental settings, or have been embedded in trials aimed at other investigations [11–15]. While experimental designs are essential for internal validity assessment, it has been extensively noted in many areas that external validity remains disproportionally neglected [16–18]. This fact might yield relevant consequences, such as the fact that patients from experimental settings might differ significantly from patients in routine settings [19, 20], ultimately jeopardizing the feasibility, applicability and even the relevance of experimental findings [21]. Other concerns regarding previous EtG studies are small sample sizes or the use of inpatient populations [22–25]. Therefore, we believe that it is important to assess the performance of EtG in 'the real world'.

In this study, we compared the detection performance of urinary EtG with that of self reports and urinary ethanol in a large sample of outpatients with alcohol use disorders. Also, our design gave us the opportunity to incorporate clinician judgment as a comparator, which is a relevant element in clinical settings that is often neglected in experimental conditions. All in all, we aimed at assessing the performance of urinary EtG for the detection of recent drinking under routine conditions, in an actual outpatient clinical setting, and at evaluating the differences that the implementation of EtG might yield, as compared to the other screening methods investigated in this study.

Methods

Study Design and Study Subjects
We performed a cross-sectional study comparing the detection capacity of ethanol and EtG in urine samples obtained from subjects attending the outpatient service of the Addictive Behaviors Unit in a tertiary care hospital in Barcelona.

Procedure
Ethics approval was obtained from the local Institutional Review Board. Urine samples were collected from patients attending the outpatient service of the Addictive Behaviors Unit, where routine urine screen is an established procedure for monitoring abstinence and relapse prevention. Given that patients are usually required to provide frequent urine samples for a closer monitoring, the number of patients providing the urine samples was expected to be less than the total number of urine specimens.

As part of the clinical routine, the attending nurse stored the consecutive urine samples during the timeframe between 8 a.m. and 12 p.m. Once collected, they were transferred to the central

Table 1. Characteristics of the sample

	Whole sample (n = 613), mean (SD) or %	EtG positive (n = 136), mean (SD) or %	EtG negative (n = 477), mean (SD) or %
Age, years	50 (11.8)	51.5 (10.6)	50 (12.1)
Duration of urine screening, years	3.2 (5.1)	4.2 (7.1)	2.9 (4.4)
Sex, male	69.6%	94 (69.1%)	332 (69.7%)
Co-screen	28.1%	32 (23.5%)	140 (29.4%)
Opioids	0.5%	0 (0%)	3 (0.6%)
Cocaine	9.3%	9 (6.6%)	48 (10.1%)
Cannabis	20.4%	23 (16.9%)	102 (21.4%)
Benzodiacepinas	8.2%	9 (6.6%)	41 (8.6%)
Amphetamines	12.6%	11 (8.1%)	66 (13.8%)
Positive to other substances	59 (9.6%)	16 (11.8%)	43 (9%)
Taking aversive medication	37.6%	33 (25%)	193 (41.2%)
Frequency of urine testing			
Less than once weekly	6.6%	12 (9%)	27 (5.9%)
Once weekly	18.9%	18 (13.4%)	94 (20.4%)
More than once weekly	74.6%	104 (77.6%)	339 (73.7%)
Nurse judgment			
Abstinent	535 (88.6%)	98 (74.2%)	437 (92.6%)
Not abstinent	48 (7.9%)	23 (14.4%)	25 (5.3%)
Unsure	15 (2.5%)	7 (5.3%)	8 (1.7%)
Patient self-discloses drinking	6 (1%)	4 (3%)	2 (4%)

Urinary samples are considered individual units of the sample.

laboratory, where they underwent the analysis for ethanol as well as the analysis for EtG, using the enzymatic immunoassay kits provided by Thermo Fisher Scientific.

EtG Measuring

EtG was measured with a commercially available enzyme immunoassay (EIA) method based on a new monoclonal antibody (DRI-EtG EIA, Thermo Fisher Scientific Diagnostics, Hemel Hempstead, UK). The comparison of the DRI-EtG EIA with a reference LC-MS method for 126 urine samples (100–50,000 ng/ml) was made with Passing-Bablok regression (EIA = −0.104 + 0.960 LC-MS). Both methods showed an overall good and statistically significant agreement $r^2 = 0.961$ (p < 0.0001) [25].

The DRI-EtG EIA is a semi-quantitative method with a clinical cut off of 500 ng/ml. It also offers a low and clinically relevant analytical range (15.3–2,000 ng/ml). Samples with EtG above 2,000 ng/ml were diluted in the ratio 1:10 increasing its analytical range until 20,000 ng/ml. This method has been adapted to the ADVIA 1800 Chemistry System (Siemens Healthcare Diagnostics, Tarrytown, USA) to improve the throughput and to conduct the analysis easily. Before analyzing the samples, 2 control levels (375 and 625 ng/ml) were processed in order to ensure correct analysis.

Data Collection

Routine sociodemographic as well as disease characteristics were collected from patients' medical charts. The attending nurse, an experienced clinician in the field of addiction, meets every patient that undergoes urine screening. The encounter usually takes the form of a brief (usually less than 5 min), non-structured meeting, where patients' self reports are collected, and in case it is necessary, other clinical information is exchanged, sometimes in the

form of brief advice and sometimes in a more informal manner. It was during these meetings that the nurse also provided her clinical judgment regarding the drinking status of the patient, in a qualitative way (patient is totally abstinent: yes, no, unsure).

We also collected information on whether patients were on disulfiram or any another aversive medication, whether other substances were searched for in the urine sample, and if any of the co-screenings yielded positive results. Weekly frequency of urine testing (less than once weekly, once weekly or more than once weekly) was also collected.

Statistical Analysis

Sociodemographic characteristics of the sample were described for all subjects who provided urine samples. Quantitative comparative analyses were performed between the rate of positive results of ethanol and the rate of positive results of EtG. In ethanol-negative subjects, comparisons were conducted between subjects with positive or negative EtG, followed by regression analysis as a means to investigate if there were any features predicting the positivity of EtG. The detection performance of clinical judgment was further assessed using EtG as a gold standard to calculate the area under the receiving operator curve.

Results

A total of 188 patients provided 613 consecutive urine samples, in a 14-days period. Table 1 outlines the main sociodemographic characteristics of the sample.

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Table 2. Independent variables in the logistic regression model

Parameter	OR	95% CI	Significance, p value
Nurse judgment	2	1.4–2.9	<0.001
Disulfiram	2.1	1.3–3.3	0.003
Weekly frequency	1.1	0.7–1.5	0.653
Positive to other drugs	2.2	0.9–4.9	0.062
Sex	0.9	0.6–1.5	0.885
Duration of screening	1.05	1.003–1.091	0.036
Age, years	1.01	0.985–1.03	0.653

In this regression model, urinary EtG is considered the dependent variable, with positivity coded as 1 and negativity as 0.

Regarding the total number of positives, urinary ethanol resulted in 9 positive samples belonging to 8 patients. EtG yielded 136 positive samples belonging to 74 patients. Most EtG positive samples (125) were negative for alcohol. It means that 20.4% of the total urine samples (125/613) were discordant regarding EtG and ethanol. As expected, all urinary alcohol positives resulted in EtG positives.

The percentage of co-screened samples for other substances was 28.1% (172/613). Cannabis was the main substance investigated, with 20.4% of the whole sample (125/613 urine samples), resulting in a 9.6% of positives when calculated for the total sample (59/613). EtG was positive in 14.6% of the samples of patients being on aversive medications and in 26.4% of patients who were not in treatment with aversive medication. The group being screened less than weekly resulted in a 30.8% of positive EtG urine samples, those screened once weekly resulted in 16.1% positives and those screened more than once weekly resulted in 23.5% positive samples.

In the logistic regression model, the following variables were entered: gender, age, duration and frequency of urine screening, co-screening to other substances, positive to other substances, clinical judgment and being on aversive medication. Of these variables, only being on aversive medication and clinical judgment resulted in significant effects (table 2).

Regarding the diagnostic performance of the nurse, she judged 89.7% (550/613) of the samples, belonging to 178 patients, as abstinent. She deemed 7.8% (48/613) of the samples, belonging to 26 patients, as not abstinent, and was unsure in 15 samples from 15 patients. When comparing it against EtG, it resulted in an area under the curve of 0.592.

Discussion

In line with the data reported in previous experimental studies, the results of this study clearly indicate a relevant difference in the detection capacity of urinary ethanol, self reports and urinary EtG. The discrepancy between the 2 metabolites (one yielding only 1.5% of positives, the other 22.2%) is so large that they depict 2 different realities.

If we were to rely only on urinary ethanol, it would look like a great majority of our outpatients do exceedingly well in an abstinence-oriented program, with less than 5% of patients drinking alcohol. On the other hand, if we consider data provided by EtG assessment, the picture is radically different. We no longer have a big population of alcohol patients who cope with their alcohol problems in a way that they are able to maintain abstinence. We indeed have almost a 40% of patients who are not fully abstinent. And, importantly, were it not for EtG, we would not be aware of this huge proportion. In this study, self reports are even less reliable than ethanol. It is indeed well known that self-reports tend to underestimate patients' consumption rates [27–30].

Since the introduction of EtG for urine screening in AUD patients, the studies conducted have almost universally found a higher detection rate of EtG, irrespective of the comparator employed [22, 23, 31, 32]. Most of the studies have compared EtG to self-reports and breath alcohol, both with relevant caveats as screening elements for alcohol patients. Breath alcohol testing offers a short detection window, jeopardizing its validity as a detection instrument for recent alcohol consumption. In this sense, previous studies report even higher numbers than ours when it comes to discrepancies with EtG. For example, Mutschler et al. [32] found in a group of 51 outpatients under supervised disulfiram a 59% discrepancy between EtG and breath alcohol testing. Similarly, Junghanns et al. [14] found a 28% discrepancy between EtG and self reports in 139 outpatients. The studies by Wurst et al. [24] and Skipper et al. [31], in which EtG was compared to urinary alcohol, reported a discrepancy of 9 and 7%, respectively.

Regarding the analysis of the clinical variables and its relation to the EtG results, the strongest predictors of EtG positivity were clinical judgment and the presence of alcohol deterrent medications, such as disulfiram or calcium carbimide, thus reinforcing the perceived utility of these medications. While some of the patients received the medication supervised by the nurse, a majority of them took it at home. This fact might help explain the

high number of patients provided with deterrent medications that yielded an EtG positive (suggesting a low or no medication adherence). The rate of positives suspected by the nurse was halfway between those of EtG and urinary ethanol, suggesting that up to 10.5% of urine samples came from not abstinent patients. In fact, previous studies suggest clinicians are ill equipped when it comes to assess substance intake in their patients [33].

One of the strengths of this study is its observational nature, a fact that allows for a more valid, less biased assessment of reality. While experimental assessments are clearly indispensable, they are found to have various caveats, such as assessment reactivity, Hawthorne's effect, or even social desirability, all well-known biases to scientific research [34, 35].

The huge discrepancy found in this observational study leads to a pressing question: what is the real purpose of urine screening in these patients? Is it about regular control, relapse prevention and contingency management? Or is it about education, habit-changing routines and continuous support? Or is it both? This area deserves further research.

Taken together, the data provided in this study suggest that urinary EtG performs exceedingly well in real outpatient settings, or at least much better than traditional diagnostic methods. What remains to be a matter of concern is the fact that in real clinical settings, where routine urinary or breath screening is conducted aiming at relapse prevention, we might be performing rather poor, even if we incorporate professionals' expertise and judgment into the equation.

Despite its clear results, some limitations must be considered for this study. First, EtG positives are known to occur after the unintentional ingestion of alcohol via mouthwashes or the use of alcohol-containing hand sanitizers. However, this might account only for a residual number of positives. Also, despite the fact that some previous research indicates that a cut-off of 500 ng/ml might produce a relative high risk of unintended positives [36], other recent studies suggest that the specificity of EtG remains acceptably high with this cut-off [37]. Also, EtG/creatinine ratios and EtG-LC-MS/MS confirmation tests were not conducted. Nonetheless, recent studies [11, 12, 38] suggest that this is not necessary. Also, despite being an observational study with an expected high external validity, the results belong to a single center, a fact that might limit the generalization of our results. Finally, it is important to note that this is not a validation study of EtG. Therefore, many of the conclusions reached throughout the paper are based on the assumption that EtG is the closest and most reliable assessment of reality when it comes to determining the drinking status of patients. While this study might not be able to provide direct evidence supporting this claim, there is a notorious body of evidence that makes this inference reasonably valid.

As a conclusion, the data displayed by this and other studies clearly suggest that a wide implementation of EtG in real settings would yield relevant improvements in the monitoring of abstinence in outpatient populations. It follows that relapse prevention would be significantly improved. Further, research will have to specifically address this question, and investigate the clinical and economic consequences of implementing a high-detection capacity tool such as urinary EtG in alcohol disorders' outpatients.

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Study 2

One year clinical correlates of EtG positive urine screening in alcohol dependent patients: a survival analysis

Study 2

Summary

Reference

Authors: Barrio P, Mondon S, Teixido L, Ortega L, Vieta E, Gual A. Title: One Year Clinical

Correlates of EtG Positive Urine Screening in Alcohol-Dependent Patients: A Survival Analysis.

Alcohol and alcoholism 2017 1-6.

Aims

Based on hypotehsis #2, and taking into account the results of Study 1, we aimed at evaluating one year correlates of an EtG positive urine screening, with special attention to relapse and the need of hospitalization. We also tried to estimate costs related to addiction treatment for both EtG positive and EtG negative subjects in the following year.

Methods

After one year, the presence of relapse, the number of hospitalizations and whether patients had abandoned treatment or not were assessed from electronic medical records. A survival analysis was conducted to compare time to relapse between EtG negative and positive subjects. Regression models were performed to compare the mean number of days hospitalized between groups, the risk of being lost to follow-up and treatment expenses.

Relapse was operationalized as meeting any of the following criteria:

1) Need for total or partial (day hospital) hospitalization, or emergency department attendance, due to alcohol consumption.

2) Positivity of a urine screening (performed with ethanol, since at the time of study procedures it was the routine method of screening in our site).

3) Clinical detection, according to patient's medical record, of any alcohol consumption. This could be in the form of patient self-report, significant-others report or clinician report.

Time until relapse was recorded. Other collected variables included the number of visits with an addiction professional that patients attended during the following year, the number of urine screenings performed and whether patients were lost to follow-up or not during this time. For economical evaluations, price per day of total or partial hospitalization and price per visit were obtained from the corresponding local agency.

To compare the differential rate of relapse between EtG positive and EtG negative subjects, a survival analysis was performed. The endpoint was defined as relapse, according to the first occurring criteria of the operationalization described above. Kaplan-Meier survival curves were plotted and compared with the log-rank test. A Cox-regression model was further conducted, including age, sex, addictive comorbidities and length of urine testing in order to adjust the contribution of an EtG positive urine screening at baseline as an indicator of relapse risk during the following year.

To compare hospitalizations between EtG positive and negative groups, a multivariate regression analysis was conducted with the mean number of days of hospitalization as the dependent variable. For this purpose, days of complete hospitalization and days of partial hospitalization (day hospital) were added together. Independent variables included EtG status at baseline, sex, age, addictive comorbidities and length of urine testing.

For economical evaluations, a price per day of total and partial hospitalization was gathered from the pertinent local health agency. A price was also fixed for every outpatient visit that patients completed. A mean price for each group (EtG positive vs. EtG negative) was calculated. Also, a multivariate regression analysis was conducted with mean price as a dependent variable and EtG status at baseline, sex, age, addictive comorbidities and length of urine testing as independent predictors.

Finally, the rate of patients lost during the next year was compared between EtG groups with binary logistic regression incorporating age, sex, addictive comorbidities and length of urine testing as independent variables.

In order to test whether other factors could replicate the prediction capacity of EtG, all models were performed again substituting EtG results by clinician judgment. Given the outlying few positive self-reports we had in the initial study, the use of this variable for another set of analysis was deemed inappropriate.

Results

At baseline, data was extracted from 185 patients, of which 33 were excluded from analysis since they were considered to be actively and overtly drinking. This could be because they had a positive ethanol result at baseline, because their self-report was positive or because the treating clinician had clearly identified the patient was actively drinking in that period of time. Since the main objective of the present paper was the survival analysis, they were excluded because they were considered to have already reached the endpoint before study initiation.

The Kaplan-Meier curves comparing EtG positive and negative groups were clearly different. The Log-Rank test revealed significant differences (chi=58,382 df=1; p<0,001). The mean survival time of EtG positive subjects was 163 days, compared to 329 days in those with a negative result. In the Cox regression model, only EtG positivity yielded significant results, with a hazard ratio of 5,3 (95%CI: 3,1 to 9,1). The positive predictive value of EtG regarding relapse risk was 0,8. The negative predictive value was 0,76.

In the comparison between hospitalizations, the multivariate regression analysis confirmed the significance of a positive EtG result at baseline as a predictor of increased number of days hospitalized, with b=5,3 (95%CI: 2,1 to 8,4). The rest of the covariates were non-significant.

For economical evaluations, the following prices were established according to the local health agency recommendations: day of total hospitalization: 555 €, day of partial hospitalization (day hospital): 117 €, outpatient visit with an addiction professional: 137 €. Calculations yielded a mean cost of 2.167 € for EtG positive patients, and 566 € for EtG negative patients. In the regression analysis, only EtG status was a significant predictor.

Finally, in the binary logistic regression conducted to investigate factors associated with the risk of being lost to follow-up during the year following EtG testing, EtG positivity was significant in the univariate analysis, but only age was a significant predictor in the final, multivariate model, being older associated with a lesser risk of discontinuing treatment (OR= 0,94, 95%CI: 0,89 to 0,98).

When substituting EtG for clinician judgment, none of the models found a significant contribution of this variable. The survival curves according to the different clinician judgment (abstinent vs. non-abstinent) yielded a non significant log-rank test (chi=3,264 df=1; p=0,071).

Conclusions

EtG positive subjects have a clearly differentiated evolution in the following year. It means EtG might help clinicians to identify early signs of relapse, and therefore it could also allow them to early address it, making the whole process more efficient. Also, it looks like the positive predictive value of EtG could allow for a better targeting of those patients that are in need of a more urgent, intense intervention, while, at the same time, the negative predictive value of EtG could reassure clinicians of a favorable evolution for those subjects screening negative, at least in the following months.

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Article

One Year Clinical Correlates of EtG Positive Urine Screening in Alcohol-Dependent Patients: A Survival Analysis

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Received 23 November 2016; Revised 26 January 2017; Accepted 24 February 2017

Abstract

Aims: Little evidence exists supporting the efficacy of regular alcohol urine screening (RAUS) in the management of alcohol dependence, despite recent improvements in urine biomarkers. In this study, we aimed at investigating 1 year, differential clinical correlates between a positive and a negative baseline urine ethyl glucuronide (EtG) screening.

Methods: Alcohol-dependent outpatients participating in a previous cross-sectional study where EtG and ethanol diagnostic performances were compared in a double blind design were included. After 1 year, the presence of relapse, the number of hospitalizations and whether patients had abandoned treatment or not were assessed from electronic medical records. A survival analysis was conducted to compare time to relapse between EtG negative and positive subjects. Regression models were performed to compare the mean number of days hospitalized between groups, the risk of being lost to follow-up and treatment expenses.

Results: Of note, 152 patients (mean age 52, 67% males) were included. The mean time to relapse was of 163 days in EtG positive subjects, compared to 329 days in those with a negative result. In the Cox-regression model, only EtG positivity yielded significant results, with a hazard ratio of 5:3 (95% CI: 3.1–9.1). EtG positive was also the only significant predictor of a greater number of hospitalization days and treatment expenses. Younger age was the only variable predicting a greater risk of treatment abandonment.

Conclusion: RAUS with sensible biomarkers could improve clinicians' ability to assess patients' relapse risk. Further prospective studies will have to determine if this can be translated into a better prevention capacity.

Short summary: Positive urine screenings, when conducted with highly sensible alcohol biomarkers, significantly indicate a greater risk of relapse in alcohol-dependent patients and have the capacity to predict a greater risk of hospitalization and greater treatment expenses.

INTRODUCTION

Alcohol is one of the leading drivers of harm worldwide (Whiteford *et al.*, 2013; Christopher and Murray, 2016). Its consequences affect both individuals and societies as a whole (Barrio *et al.*; in press). Individuals causing the greatest part of this harm are those who are dependent on it (Mohapatra *et al.*, 2010). Therefore, alcohol dependence should be considered as a top priority from a public health perspective (WHO, 2014).

The proper management of alcohol dependence requires the use of several strategies, from psychosocial to pharmacological ones. One frequently used element, especially in abstinence oriented settings, is regular alcohol urine screening (SAMHSA 2012; American Society of Addiciton Medicine, 2014). Traditional markers used for this purpose remain suboptimal with regard to sensitivity and specificity, especially when it comes to detecting recent drinking. Ethanol remains detectable only for ~8–12 h post ingestion, whereas other traditional markers such as gamma glutamyltransferase, mean corpuscular volume or carbohydrate deficient trasnferrin need persistent consumption of higher amounts of alcohol (>2 weeks, >1000 g of ethanol in 2 weeks) to become elevated.

Fortunately, in recent years there has been a noticeable improvement in the sensibility and specificity of biomarkers of alcohol consumption, with the appearance of more sensible and specific markers, such as ethyl glucuronide (EtG), ethyl sulfate or phosphatidylethanol (Wurst *et al.* 2015). They all expand the time window for the detection of recent alcohol consumption in urine samples. This might offer relevant improvements in clinical practice, in as much as covert drinking might be more frequently detected and so earlier addressed, Up to date, EtG has the advantage of an existing commercially available enzyme immunoassay (EIA) method based on a new monoclonal antibody (Diagnostic Reagents Incorporated-EtG EIA, Thermo Fisher Scientific Diagnostics, Hemel Hempstead, UK), that allows for a more cost-effective detection of EtG in urine samples. However, despite the wide use of frequent urine screening and the recent improvements in its biomarkers, little evidence exists supporting its clinical efficacy in alcohol dependence (Dupouy *et al.* 2014).

In a recent cross-sectional study (Barrio *et al.* 2016), we found that under routine clinical conditions, EtG performed largely better than ethanol, self-report and clinical judgment in the detection of recent drinking. In fact, a solid body of evidence demonstrates that EtG performs largely better than self-reports and ethanol in the detection of recent drinking (Wurst *et al.*, 2004; Junghanns *et al.*, 2009; Dahl *et al.*, 2011; Jatlow *et al.*, 2014; Leickly *et al.*, 2015). Given that both patients and clinicians were unaware of EtG results and that patients were followed-up as part of their usual treatment during the following year, and subsequent urinary assessments were done with ethanol, we had the opportunity to assess the differential, 1-year correlates of a baseline EtG positive urine screening. We believe that this is a relevant issue, since it allows for a more detailed and precise delineation of what is really a positive urine screening with a highly sensible biomarker telling us, when we face an alcohol addicted patient with regard to risk of relapse, risk of hospitalization and what its economic implications are, something that has not been previously studied. It must be noted that subsequent urinary assessments were performed with ethanol instead of EtG because ethanol was the routine marker used in our laboratory, and during the study period, we had not the chance to routinely utilize EtG as a marker of alcohol consumption.

While there is a solid body of evidence assessing the predictive capacity of other variables such as illness severity (Langenbucher *et al.*, 1996), craving (Bottlender and Koyka, 2004), DSM-IV criteria (Fazzino *et al.*, 2014) or other psychological constructs such as persistence and self-efficacy (Cannon *et al.*, 1997) when trying to determine the risk of relapse, there is no such literature related to the predictive capacity of urine screenings. And the same happens when analyzing the risk of hospitalization (Lawder *et al.*, 2011; Hong *et al.*, 2014; Chang *et al.*, 2016). The objective of the present study was to analyze 1-year correlates of a EtG positive urine screening, with special attention to relapse and the need of hospitalization. We also tried to estimate costs related to addiction treatment for both EtG and EtG negative subjects in the following year.

MATERIALS AND METHODS

Subjects

Participants were previously recruited in a study comparing the performance of urinary EtG in routine clinical conditions (Barrio *et al.*, 2016). Subjects were adult alcohol-dependent patients receiving treatment in an outpatient department from a big tertiary urban hospital in Barcelona. In the initial study, in a cross-sectional design, patients were tested for both ethanol and EtG in their urine, incorporating also patients' self-reports and the judgment of the attending nurse. Patients were unaware of EtG testing, and the results obtained were not available to their treating clinicians. For the present study, patients were divided into two cohorts, those who screened positive for EtG and those who screened negative for EtG. Patients that were actively and overtly drinking at baseline were excluded from this study, since they could not be incorporated into the main survival analysis. Ethics approval was granted from the Clinic Hospital of Barcelona IRB (decision number HCB/2015/0984).

Measurements

Basic sociodemographic and clinical data, as well as the baseline value of urinary EtG, were extracted from the previous study. One year after the study was completed, electronic medical records from participants were reviewed for data collection and analysis. The number of total or partial hospitalizations (day hospital) was recorded.

The main outcome of the study was defined as relapse, which was operationalized as meeting any of the following criteria:

(1) Need for total or partial (day hospital) hospitalization, or emergency department attendance, due to alcohol consumption.
(2) Positivity of a urine screening (performed with ethanol).
(3) Clinical detection, according to patient's medical record, of any alcohol consumption. This could be in the form of patient self-report, significant others report or clinician report.

Time until relapse was also recorded. Other collected variables included the number of visits with an addiction professional that patients attended during the following year, the number of urine screenings performed and whether patients were lost to follow-up or not during this time. For economical evaluations, price per day of total or partial hospitalization and price per visit were obtained from the corresponding local agency.

Statistical analysis

To compare the differential rate of relapse between EtG positive and EtG negative subjects, a survival analysis was performed. The

endpoint was defined as relapse, according to the first occurring criteria of the operationalization described above. Kaplan–Meier survival curves were plotted and compared with the log-rank test. A Cox-regression model was further conducted, including age, sex, addictive comorbidities and length of urine testing in order to adjust the contribution of an EtG positive urine screening at baseline as an indicator of relapse risk during the following year.

To compare hospitalizations between EtG positive and negative groups, a multivariate regression analysis was conducted with the mean number of days of hospitalization as the dependent variable. For this purpose, days of complete hospitalization and days of partial hospitalization (day hospital) were added together. Independent variables included EtG status at baseline, sex, age, addictive comorbidities and length of urine testing.

For economical evaluations, a price per day of total and partial hospitalization was gathered from the pertinent local health agency. A price was also fixed for every outpatient visit that patients completed. A mean price for each group (EtG positive vs EtG negative) was calculated. Also, a multivariate regression analysis was conducted with mean price as a dependent variable and EtG status at baseline, sex, age, addictive comorbidities and length of urine testing as independent predictors.

Finally, the rate of patients lost during the next year was compared between EtG groups with binary logistic regression incorporating age, sex, addictive comorbidities and length of urine testing as independent variables.

In order to test whether other factors could replicate the prediction capacity of EtG, all models were performed again substituting EtG results by clinician judgment. Given the outlying few positive self-reports we had in the initial study, the use of this variable for another set of analysis was deemed inappropriate.

Data were analyzed using SPSS 21.0 (SPSS Inc., Chicago, Illinois). Ethanol measurement in urine was performed with molecular absorption spectroscopy.

RESULTS

At baseline, data were extracted from 185 patients, of which 33 were excluded from analysis since they were considered to be actively and overtly drinking. This could be because they had a positive ethanol result at baseline, because their self-report was positive or because the treating clinician had clearly identified the patient was actively drinking in that period of time. Since the main objective of the present paper was the survival analysis, they were excluded because they were considered to have already reached the endpoint before study initiation. Basic sociodemographic characteristics of both groups and clinical data gathered during the 1-year follow-up are compared in Table 1.

The Kaplan–Meier curves comparing EtG positive and negative groups are displayed in Fig. 1. The log-rank test revealed significant differences (chi = 58.382 df = 1; $P < 0.001$). The mean survival time of EtG positive subjects was 163 days, compared to 329 days in those with a negative result. In the Cox-regression model, only EtG positivity yielded significant results, with a hazard ratio of 5:3 (95% CI: 3.1–9.1).

In the comparison between hospitalizations, the multivariate regression analysis confirmed the significance of a positive EtG result at baseline as a predictor of increased number of days hospitalized, with $b = 5.3$ (95% CI: 2.1–8.4). The rest of the covariates were non-significant.

For economical evaluations, the following prices were established according to the local health agency recommendations—day

of total hospitalization: 555 €; day of partial hospitalization (day hospital): 117€; outpatient visit with an addiction professional: 137 €. Calculations yielded a mean cost of 2.167 € for EtG positive patients, and 566 € for EtG negative patients. In the regression analysis, only EtG status was a significant predictor.

Finally, in the binary logistic regression conducted to investigate factors associated with the risk of being lost to follow-up during the year following EtG testing, EtG positivity was significant in the univariate analysis, but only age was a significant predictor in the final model, being older associated with a lesser risk of discontinuing treatment (OR = 0.94, 95% CI: 0.89–0.98).

When substituting EtG for clinician judgment, none of the models found a significant contribution of this variable. The survival curves according to the different clinician judgment (abstinent vs non-abstinent) are displayed in Fig. 2 (log-rank test not significant; chi = 3264 df = 1; $P = 0.071$).

DISCUSSION

In this study, we evaluated 1-year clinical correlates of a positive baseline EtG urine screening, as compared to a negative baseline result. Both patients and clinicians were unaware of baseline EtG results. Also, since we could not incorporate EtG testing as our routine biomarker due to budget and time constraints in the following year, the ongoing urine screenings were performed with ethanol. This in fact allowed the performance of the present study, where the implications of a single EtG testing could be evaluated. The data obtained during the follow-up suggest that patients testing positive in EtG will have a different clinical evolution in the following year, with a significant increase in relapses, hospitalizations and treatment expenses. Given that both patients and clinicians were unaware of EtG status at baseline, one pressing question emerges: could some of this differences have been avoided, was this information made available to them? Although such a question cannot be answered by this study, and needs for prospective, randomized investigations, we believe some clues can be drawn from our data.

Although the need for hospitalization for the whole sample was rather low, with only 10 patients (6.6% of the total sample) requiring it, the differences between groups were both significant and large, with only one patient in the EtG negative arm being hospitalized in the following year. Taking a stepped care approach, hospitalization could be considered as one of the final steps in dealing with a relapse, which might have been initiated much before in the form of lapses. This might be a crucial point in time where the use of sensible alcohol biomarkers such as EtG could help to identify the beginning of the relapse, and so to earlier address it, with the potential impact of avoiding the need for hospitalization and also of reducing treatment expenses.

Though at first glance suggesting that patients who test positive for EtG will relapse at a higher rate than those who do not could seem tautological, this fact deserves further elaboration. First, one should notice that relapse, though widely used as a concept, lacks firm and conclusive criteria (Maisto *et al.*, 2016), a fact that could explain that being EtG positive does not immediately imply a relapse. In fact, a minority of patients tested positive for EtG and were clinically deemed as non-relapsed during the following year. That being said, our data robustly show that an EtG positive dramatically increases the risk of having a clinical correlate in the following year, as shown by the hazard ratio obtained in the survival analysis. In other words, patients testing positive for EtG will, with very high probabilities, ultimately have clinical symptoms of relapse.

Table 1. Sociodemographic and clinical data comparison between groups

Characteristic	EtG negative (*n* = 102)	EtG positive (*n* = 50)	Whole sample
Age: mean (SD)	51.6 (10.3)	50.8 (11.5)	51.2 (10.7)
Gender: % of males	70 (69.3%)	31 (62%)	101 (66.9%)
Addictive comorbidities	36 (35.3%)	15 (30%)	51 (33.6%)
Benzodiacepines	10 (9.8%)	8 (16%)	18 (11.8%)
Cocaine	15 (14.7%)	3 (6%)	18 (11.8%)
Opiates	3 (2.9%)	0 (0%)	3 (2%)
Cannabis	28 (27.5%)	8 (16%)	36 (23.7%)
Length of urine screening (in months)	26.3 (34.6)	57.4 (74.6)	36.4 (53.2)
Number of patients requiring hospitalization: *n* (%)	1 (0.9%)	9 (18%)	10 (6.6%)
Days of hospitalization (adding up the count for all patients)	29	302	331
Number of visits with an addiction professional: mean (SD)	3.81 (2.4)	5.1 (2.7)	4.3 (2.6)
Number of urine screenings: mean (SD)	29.8 (26.4)	50.4 (32.5)	36.6 (30)
Number of patients relapsing: *n* (%)	24 (23.5%)	40 (80%)	64 (42.1%)
Number of patients lost to follow-up: *n* (%)	18 (17.6%)	16 (32%)	34 (22.4%)
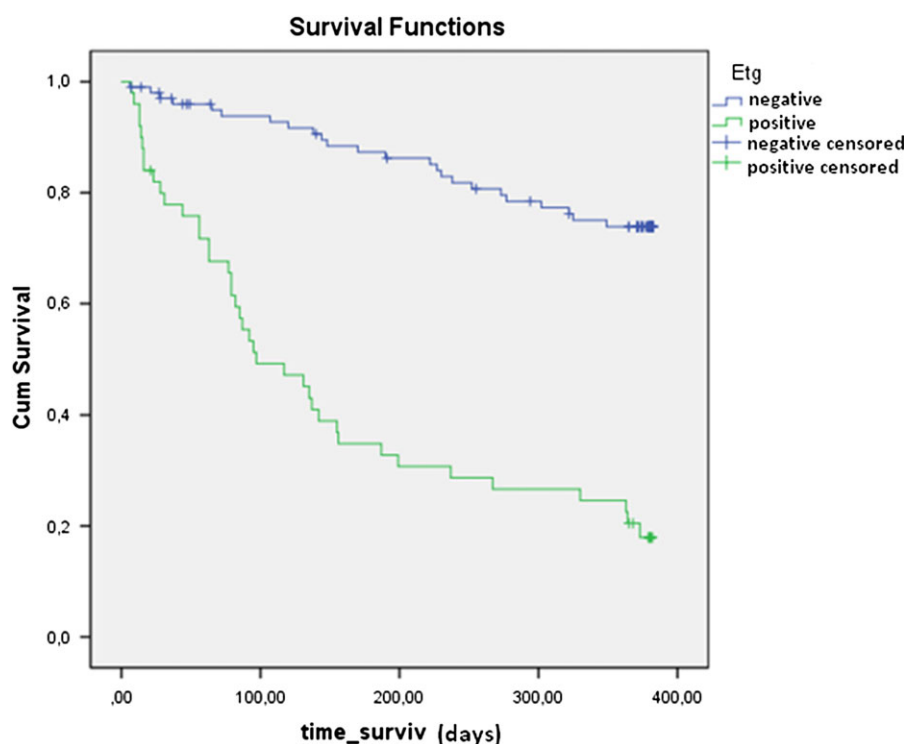
Fig. 1. Survival curves plotted with the Kaplan–Meier method for EtG results.
Survival curves (in days) of both EtG positive (lower curve) and negative (upper curve) patients, with relapse considered the endpoint.

Therefore, an EtG positive screening could be considered as an early relapse sign. But also looked the other way around, it looks like having an EtG negative screening has a strong negative predictive value, that is, it should reassure clinicians regarding patients' favorable evolution, at least in alcohol-related outcomes.

Our results are in line with previous, similar studies. For example, Junghanns et al. (2009), found out that positive EtG urine screening early after discharge significantly increased the rate of subsequent relapse in recently discharged alcohol-dependent patients. Similarly, Dahl *et al.* (2011) found EtG to be a useful and reliable ongoing monitoring tool in alcohol treatment studies, specially suggesting that an initial EtG negative sample is useful to confirm self-reports.

Treatment expenses were clearly different between groups, driven both by the different number of days of hospitalization in both cohorts as well as an increased number of visits in those EtG positive. In fact, it has already been shown that patients actively drinking incur in greater costs (Aldridge *et al.*, 2016; Witkiewitz and Horn, 2016; Miquel et al., 2017). Although it was not included in the cost analysis, it is worth mentioning that EtG positive patients had also much more frequent urine testing during the follow-up. All these data suggest that the implementation of EtG could also have an economic impact in the treatment of alcohol dependence.

Regarding the capacity of predicting the risk of being lost to follow-up, EtG showed significant results in the univariate analysis, which seemed to disappear once age was included in the multivariate
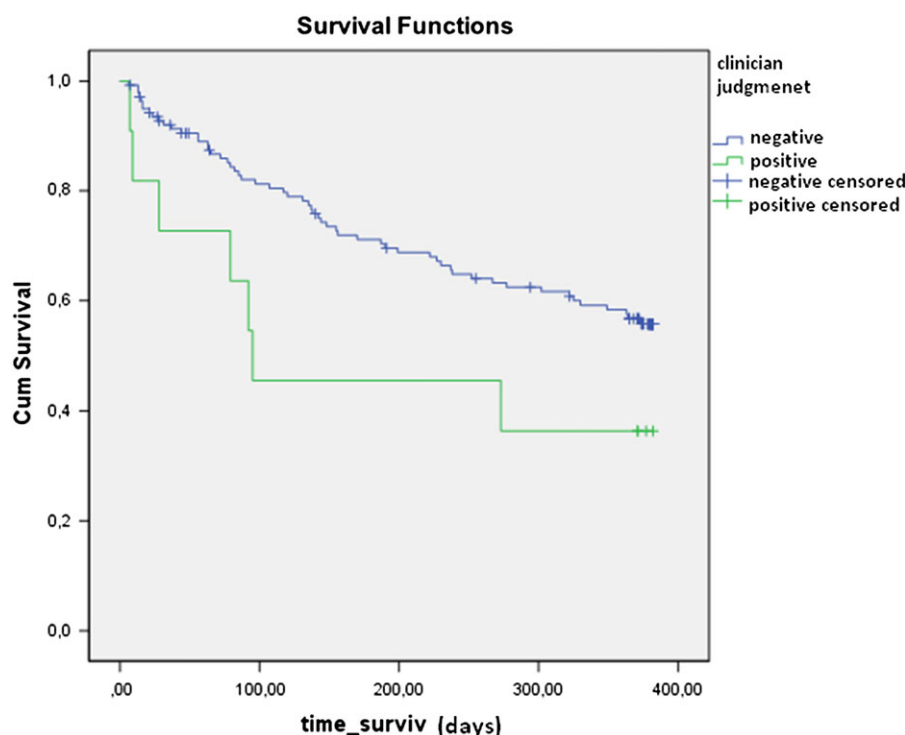
Fig. 2. Survival curves plotted with the Kaplan–Meier method for clinical judgment.
Survival curves (in days) of both patients with positive (lower curve) and negative (upper curve) clinician judgment, with relapse considered the endpoint.

model. In fact, previous literature already pointed out at older age as a predictor of treatment retention (Korte *et al.*, 2011; Haug and Schaub, 2016). That being said, prior literature also consistently shows that patients actively using alcohol or drugs are at a greater risk of becoming non-treatment adherent (White *et al.*, 2014; Campbell *et al.*, 2016; Haug *et al.*, 2016). Also, previous studies with EtG (Junghanns et al., 2009) have found that testing EtG positive increases the risk of being lost to follow-up. Therefore, it would not be unwise to consider EtG as a potentially useful tool in predicting the risk of treatment abandonment.

Taken together, we believe that the data gathered by this study has important implications for real practice. Although, as previously acknowledged, there exist many other variables with a demonstrated predictive capacity in alcohol-dependent patients regarding relapse risk and general outcome, it looks like the implementation of EtG in routine urine screening could improve clinicians capacity to detect early signs of relapse, and therefore it would also allow them to early address it, making the whole process more efficient. Also, it looks like both the positive and negative predictive values of EtG could allow for a better targeting of those patients that are in need of a more urgent, intense intervention. It means that an EtG positive patient should raise clinicians awareness and efforts immediately, while an EtG negative patient could reassure them of a favorable evolution, at least in the following months. Again, it is important to state that urine screening should not be a substitute of other assessments. However, in this study, we found it to be the most accurate, precise predictor, even when controlling for other variables such as age, sex, addictive comorbidities or length of urine testing, and also clearly better than clinical judgment.

Several limitations should be noticed when interpreting our study. First, data were gathered at the end of follow-up, which

means that variables were collected retrospectively. Importantly, there exists the possibility that patients were hospitalized in other centers, which could have biased our data. However, it would be reasonable to consider that in both groups more hospitalizations would have been seen, and probably even more in the EtG positive patients. Therefore, this bias would result in an infraestimation of EtG prediction capacity, which as we showed, turn out to be already significant. Related to this, it is the fact that more EtG positive patients were lost to follow-up. While survival analysis specifically addresses this data, when analyzing days of hospitalization and relapse risk, they had to be considered as missing data. However, as previously mentioned, treatment abandonment has been associated with increased relapse risk; therefore, it is probable that this missing data turned out into an infraestimation of EtG prediction capacity regarding relapse risk and hospitalization risk. Also relevant to mention is the fact that relapse as an outcome was operationalized according to different criteria, a fact that could limit the validity of our results. Finally, it is important to note that psychiatric comorbidities, a frequent phenomenon in alcohol-dependent patients (Flensborg-Madsen *et al.*, 2009; Fein, 2015), were not systematically recorded in this study, and therefore, their contribution to the results obtained could not be evaluated.

All in all, we believe our study increases the available evidence supporting the usefulness and clinical impact of regular urine screening in alcohol treatments. Though no efficacy data could be directly inferred from our data, it looks like a wide implementation of sensible alcohol biomarkers could help to improve the prediction capacity of clinicians, especially in abstinence oriented settings. Further prospective studies will have to examine whether this increased prediction capacity can be translated into a greater treatment efficacy, probably due to a better prevention.

AUTHORS' CONTRIBUTIONS

P.B. designed the study and analyzed the data. He was also responsible for the writing of the first draft. All authors revised the manuscript critically. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

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5

Study 3

Patients' knowledge and attitudes towards regular alcohol urine screening: a survey study

Study 3

Summary

Reference

Aims

Based on hypotheses #3 and #4, we aimed at investigating if regular alcohol urine
screening serves other purposes beyond abstinence monitoring, what attitudes patients display
towards it and patients' technical knowledge about basic screening notions.

Methods

We conducted a cross-sectional survey among adults with alcohol dependence attending
outpatient alcohol dependence treatment. It aimed at investigating patients' attitudes and beliefs
towards regular alcohol urine screening, and technical notions of alcohol urine screening. For
attitudes' assessment, we adapted the Drug Attitude Inventory (DAI-10) to the field of alcohol urine
screening. Internal consistency, test-retest reliability and concurrent validity were evaluated for the
adapted questionnaire. For technical knowledge assessment we used multiple-choice and Likert-
type questions.

Regarding the adapted version of the DAI-10, an internal consistency analysis was carried
out with Cronbach's alpha. Concurrent validity was assessed via correlation between the DAI-10
total score and a 0 to 10 Likert scale measure assessing the overall perceived value of urine
screening as part of patients' treatment.

In order to evaluate if attitudes were influenced by any specific variable, we conducted a
linear regression model with DAI-10 scores as the dependent variable and age, sex, level of

instruction, therapeutic objective, person taking the decision of attending the screening program and length of urine testing as independent variables. A subset of patients was asked to undertake the test again two to four weeks apart, to assess test-retest reliability for the DAI-10 scores. For that purpose we calculated the intraclass correlation coefficient, based on absolute agreement and a 2-way mixed-effects model.

Results

A total of 128 patients completed the questionnaire. Patients rated regular alcohol urine screening high. The DAI-10 mean score was 7,2 (SD=3,6). Internal consistency analysis revealed a Cronbach's alpha of 0,718. Test-retest reliability evaluation yielded an intraclass correlation coefficient of 0,932. The score of a single Likert-type question about overall perceived value was 8,5 (SD=2). Their correlation with mean DAI-10 score was of r=0,254, with p=0,009. Regression analysis could not find any significant predictor for test scores. Besides relapse prevention, patients frequently reported other functions such as showing professionals and family members that they don't drink or having a closer contact with professionals. A majority of patients believed alcohol use goes undetected after 48 hours from last ingestion.

Conclusions

Regular alcohol screening is highly valued by alcohol dependent outpatients. It seems that besides relapse prevention, other functions related to therapeutic alliance building, social desirability and impression management play also a key role. Patients have an incomplete, inaccurate knowledge of EtG kinetics.

Patients' Knowledge and Attitudes Towards Regular Alcohol Urine Screening: A Survey Study

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Background: Despite its wide implementation, there is a paucity of data supporting the effectiveness of regular alcohol urine screening (RAUS) in maintaining abstinence. This study aims at investigating if RAUS serves other purposes, what attitudes patients display towards it, and patients' technical knowledge about basic screening notions.
Method: We conducted a cross-sectional survey among adults with alcohol dependence, attending outpatient alcohol-dependence treatment. It aimed at investigating patients' attitudes and beliefs towards RAUS, and technical notions of alcohol urine screening. For attitude assessment, we adapted the Drug Attitude Inventory (DAI-10) to the field of alcohol urine screening. Internal consistency, test-retest reliability, and concurrent validity were evaluated for the adapted questionnaire.
Results: In all, 128 patients completed the questionnaire. Patients rated RAUS as high. The DAI-10 mean score was 7.2 (SD = 3.6). Internal consistency analysis revealed a Cronbach alpha of 0.718. Test-retest reliability evaluation yielded an intraclass correlation coefficient of 0.932. The score of a single Likert-type question about overall perceived value was 8.5 (SD = 2). Their correlation with mean DAI-10 score was of $r = 0.254$, with $P = 0.009$. Apart from relapse prevention, patients frequently reported other functions such as showing professionals and family members that they do not drink, or having a closer contact with professionals. A majority of patients believed alcohol use goes undetected after 48 hours from last ingestion.
Conclusion: Regular alcohol screening is highly valued by alcohol outpatients. It seems that apart from relapse prevention, other functions related to therapeutic alliance building, social desirability, and impression management also play a key role.

Key Words: alcohol, attitudes, ethylglucuronide, survey, urine screening

(*J Addict Med* 2017;xx: xxx–xxx)

Alcohol remains a first-order global health problem, with 15 million people affected in the European Union (Wittchen et al., 2011). Its consequences to individuals and society are of an enormous dimension, the majority being attributable to the severest form of alcohol use, namely alcohol dependence (Mohapatra et al., 2010). It is currently considered a chronic disease, with a relapsing-remitting nature (Miller et al., 2001; Merkx et al., 2011). Despite some controversies in the field (Gastfriend et al., 2007; Heilig et al., 2011; Luquiens et al., 2011), abstinence has been the prevailing therapeutic goal in most of the existing settings, being considered the safest and most efficient pathway to early recovery (Owen and Marlatt, 2001; Cox et al., 2004). Therefore, for a great majority of professionals dealing with alcohol dependence, monitoring abstinence is a task of paramount importance.

Professionals dispose mainly 2 types of tools to undertake this salient job. First, patients' self-reports. For many years, they were, apart from clinicians' judgment, the only available instrument. Despite all the advances in biological markers, they remain a key component of routine clinical care in many settings (Del Boca and Darkes, 2003). Nonetheless, they suffer from some important pitfalls, especially regarding their sensitivity in detecting alcohol consumption. Some of the reasons underlying this shortcoming might be cognitive deficits, fear of putting treatment in danger, fear of legal consequences, or social desirability (Zemore, 2012). Some of these might be overcome with alcohol biomarkers. They should not be considered substitutes of self-reports, but rather a complementary element that might yield important contributions in different situations, such as outcome measures in research studies, screening for alcohol problems in individuals unable to provide accurate self-reports, or an instrument to monitor abstinence (SAMHSA, 2012).

Alcohol biomarkers can be obtained from a variety of sources. Blood, breath, and urine are the most common. Whereas some of them should be considered markers of heavy use over time, others are better suited for abstinence

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monitoring. For example, traditional markers such as gamma-glutamyl transferase (GGT) or mean corpuscular volume (MCV) need prolonged ingestion of relatively high amounts of alcohol to become elevated (Mihas and Tavassoli, 1992; Conigrave et al., 1995). Even carbohydrate-deficient trasnferrin (CDT), which certainly improves the specificity of traditional biomarkers, requires at least a few drinks a day for 2 weeks to become elevated (Hock et al., 2005). Hence, they do not seem feasible candidates for a proper abstinence monitoring system, since they would be unable to detect single lapses or short-term relapses. Moreover, they are measured in blood, a fact that limits its usefulness as a routine screening method.

In this sense, urine offers some relevant advantages over blood in routine clinical practice, especially when patients have to undergo frequent testing. Regular urine screening for abstinence monitoring is indeed a frequent practice in many abstinence-oriented settings (American Society of Addiction Medicine, 2010). So far, urinary ethanol has been the main marker used. Similar to breath alcohol testing, it only remains positive for a few hours after alcohol ingestion, thus precluding a proper monitoring of abstinence (Helander and Eriksson, 2002). Fortunately, in the field of alcohol biomarkers, some recent advances display promising features, which could allow the overcoming of some of the previously mentioned shortcomings. Especially, ethylglucuronide (EtG), a water-soluble, direct metabolite of alcohol, which remains detectable in urine up to 72 hours after the ingestion of even a single drink (Lowe et al., 2015). In a recent study, Barrio et al. (2016) demonstrated an over-riding superiority of EtG over ethanol in the detection of recent drinking in an abstinence-oriented setting. Despite the intuition that a higher detection capacity would translate into more efficacious and efficient clinical care, there is a paucity of data addressing this question. A recent systematic review (Dupouy et al., 2014) found little evidence in favor of the clinical utility of conducting urine drug screening, outlining that only a few, ill-powered studies have directly addressed this question. Taking our previous research into account, it became also evident that conventional urine screening for alcohol outpatients is far from satisfactory in monitoring abstinence. In assessing this fact, some related questions seemed to emerge: what are the reasons underlying this poor effectiveness? Does urine screening serve other functions besides monitoring abstinence, such as offering ongoing support? What do patients know about urine screening, and what are their attitudes towards it?

In this study, we try to unravel some of the answers to these questions by focusing mainly on 2 aspects: first, patients' knowledge about urine-screening elements and techniques, with a special focus on detection times, aiming at discerning if it could partly explain the low effectiveness of ethanol urine screening previously reported. Second, we aim at investigating patients' attitudes and beliefs about urine screening, to obtain patients' perspectives on the motives and perceived usefulness of such technique. It is important to remember that, in line with the increasing importance of patient-centered care as a central tenet of high-quality healthcare delivery (Institute of Medicine., 2001), also in the field of alcohol dependence (Bradley and Kivlahan, 2014; Barrio and

Gual, in press), patients always have a unique perspective on any service or intervention they receive. Hence, their input becomes an essential component of service evaluation and improvement. Whereas there are multiple surveys among professionals regarding urine drug screening (Reisfield et al., 2007; Pergolizzi et al., 2010; Owen et al., 2012; Starrels et al., 2012; Kirsh et al., 2015), to the best of our knowledge, this is the first time that patients become the target population of the survey.

METHODS

Study Design and Subjects

We performed a cross-sectional survey among adult, alcohol-dependent patients attending the outpatient service of the Addictive Behaviors Unit at the Clinic Hospital of Barcelona. Eligible participants were those who attended regular urine screening as part of their usual treatment. The nurse responsible for receiving patients and storing their urine specimens consecutively offered them to participate in the study. No compensation existed for study completion. The local ethics committee granted study approval.

Instrument

Questionnaires, along with focus groups, semistructured interviews, and patient shadowing, are one of the main instruments to collect patients' views (Domecq Garces et al., 2012). For this study, a specific questionnaire was designed. Four psychiatrists, 1 addiction nurse, 2 psychologists, and 1 social science expert took part in its design. The questionnaire consisted of 3 main parts. The first was devised to gather basic sociodemographic characteristics. The second one was aimed at evaluating patients' knowledge regarding technical aspects of urine drug screening. It consisted of 3 multiple-choice questions related to general concepts of screening, such as basic pharmacokinetic notions, alcohol metabolites, and its detection window. The third part was designed to obtain patients' beliefs and attitudes towards urine screening as part of their treatment. The methodology employed in this section was mainly that of multiple-choice questions and Likert-scale responses to affirmations related to possible patients' attitudes. Also, given the lack of similar research for this specific subject, we took advantage of the extensive literature regarding the Drug Attitude Inventory-10 (DAI-10) (Hogan et al., 1983), which was initially designed to test the attitudes of patients with schizophrenia towards medication to correlate it to medication adherence. It consists of 10 items, each one of which is scored with either 1 or −1, depending on whether the response signals a good attitude towards medication or not. To avoid response bias, half of the items are worded positively, and half negatively. Its score ranges from −10 to 10. We adapted its 10 items to the field of alcohol urine screening, replacing the concept of medication by that of regular alcohol urine screening (RAUS). While this adaptation of the DAI-10 lacks previous validation, a former study with alcoholic patients attending Alcoholic Anonymous performed a similar adaptation, showing good psychometric properties (Terra et al., 2011). Also, we still considered it a good approach

to capture patients' attitudes, given the lack of more specific, validated instruments for our study aims.

In the design of multiple-choice questions, authors initially provided several responses in a brain-storming phase. This initial pooling of possible responses was based both on literature searches from all of the authors, and also their personal expertise in the field. Once all authors agreed that all possible and meaningful responses were present, a consensus process was initiated to narrow the options to the most relevant, keeping in mind the importance of covering all possible responses to avoid biases and at the same time trying to keep the questions short and simple to facilitate questionnaire comprehension and increase response rates. Once all questions with its multiple options were finalized, they were shared with 2 external psychiatrists and 1 psychologist, who suggested minor changes.

Once designed, the authors analyzed the linguistic aspects of the questionnaire, and the necessary amendments were made to improve its understandability. Face and content validity was also evaluated by authors and external experts on the field. The complete questionnaire can be seen in Figure 1.

Procedure

The professional responsible for receiving patients and their urine specimens, an experienced nurse in the addiction field, consecutively in a 2-week period, offered patients the possibility of taking the questionnaire. Patients with cognitive decline (based on the nurse clinical judgment) or any other condition, which, in the opinion of the investigators, could have compromised the validity of responses, were not offered to participate. Patients were reassured that all data provided would be kept totally anonymous. Once completed, questionnaires were kept safe until study end, when they were all analyzed.

Statistical Analysis

A descriptive analysis of sociodemographic data was conducted. The mean and the standard deviation (SD) were used for continuous variables; percentages were used for qualitative variables. Regarding the adapted version of the DAI-10, an internal consistency analysis was carried out with Cronbach alpha. Concurrent validity was assessed via bivariate correlations between the DAI-10 total score and a 0 to 10 Likert scale measure assessing the overall perceived value of urine screening as part of patients' treatment. These 2 measures were also compared between patients attending twice per week and those with less frequent attendance to the screening program, with independent *t* test calculation, to evaluate if a more regular attendance could influence patients attitudes and overall perceived value. Finally, to evaluate if attitudes were influenced by any specific variable, we conducted univariate correlations between DAI-10 scores and age, sex, level of instruction, therapeutic objective, person taking the decision of attending the screening program, and length of urine testing. Finally, all variables were introduced into a lineal regression model. A subset of patients was asked to undertake the test again 2 to 4 weeks apart, to assess test-retest reliability for the DAI-10 scores. For that purpose, we calculated the intraclass correlation coefficient, based on absolute agreement and a 2-way mixed-effects model.

RESULTS

During the study period, 160 patients were approached, of which 128 accepted and completed the questionnaire. The mean age of the sample was 54 years (SD = 10.9). The majority (67.5%) were men, and 41.7% of the sample was currently employed. Regarding education status, 15% had primary studies, 28% secondary studies, 19% technical studies, and 37% university studies. Most of the patients (70%) underwent screening twice a week, 27.7% once a week, and 2.5% less than once a week.

The main functions attributed to urine screening by patients and their frequencies can be seen in Table 1. Most of the patients (82%) reported abstinence to be their therapeutic objective. Only a small minority (14%) reported drinking reduction as their aim. Half of the sample reported the decision of undergoing regular urine screening was their own, whereas 40% attributed it to their therapist and 4% to a legal requirement. Almost half of the sample (44.3%) believed people undergoing regular urine screening cheat or try to cheat, whereas only 22% of the sample reported having drunk small quantities of alcohol that have gone undetected in the screening.

Regarding the adapted DAI-10 questionnaire, the mean score was 7.2 (SD = 3.6). Internal consistency, measured with Cronbach alpha, was 0.718, indicating fair reliability. Test-retest reliability, measured from 20 subjects taking the questionnaire 2 to 4 weeks apart, revealed an intraclass correlation coefficient of 0.932 (95% confidence interval [CI] 0.828–0.973), indicating excellent test-retest reliability. The question about the overall perceived value of urine screening showed a mean of 8.46 (SD = 1.96). The correlation between this and the DAI-10 score, as a mean to investigate concurrent validity, was $r = 0.254$, with $P = 0.009$. No significant differences were observed in these 2 measures between twice-per-week attendants and less frequent attendants. Univariate correlations did not show any significant difference in DAI-10 scores for any of the variables evaluated. Similarly, the regression model revealed no significant predictor of DAI-10 scores.

Regarding technical aspects of urine screening, the majority of patients (78%) believed alcohol was the substance detected in urine, whereas 11% thought it was other sub-products of alcohol. Also, a majority (69%) believed a single drink was enough to get a positive urine screening, 22% believed 2 drinks were needed, 5% reported 3 drinks, and 4% reported 4 or more drinks. Regarding the detection window of urine screening, findings are displayed in Figure 2.

DISCUSSION

In this study, we aimed at investigating the beliefs and attitudes that patients have towards RAUS. Globally, we believe the results suggest that alcohol patients perceive routine urine screening as a highly valuable part of their treatment.

The adapted version of the DAI-10 scored high among our sample. Importantly, its internal reliability, with a Cronbach alpha of 0.718, was fair. Also, its correlation with a single Likert-type question about the global perceived value that patients give to regular urine screening, despite being

We would like to thank you for your time in answering this completely anonymous questionnaire about alcohol urine screening. We hope we will be able to improve our services due to your participation.

- The decision of undertaking regular alcohol urine screening was taken by:

☐ me   ☐ my therapist   ☐ a court or a judge   ☐ others (specify):

-My therapeutic goal is:

☐ not to drink at all   ☐ to reduce/control my drinking   ☐ other (specify):

-To me, the main function of regular alcohol urine screening is (please select as many as you wish):

☐ to accomplish my objectives regarding alcohol

☐ to prevent relapse

☐ to demonstrate to professionals that I do not drink

☐ to demonstrate to my family that I do not drink

☐ to have a closer contact with professionals/to feel better cared for

☐ to remind myself that I am in treatment because of alcohol

☐ to comply with a court requirement

☐ others (specify):

-Please select what is the overall value you give to regular urine screening (0 being the lowest, 10 being the highest).

0 - 1 - 2 - 3 - 4 - 5 - 6 - 7 - 8 - 9 - 10

-I believe that, frequently, patients undergoing regular alcohol urine screening cheat or try to cheat. ☐ true   ☐ false

-Sometimes I have drunk small amounts of alcohol and it has not been detected in the urine screening. ☐ true   ☐ false

-Please indicate if the following statements in your case are true (mark T) or false (mark F):

1. For me, the good things about regular alcohol urine screening outweigh the bad T / F
2. I feel strange undergoing regular alcohol urine screening T / F
3. I undergo regular alcohol urine screening the days I decide, not the days I am supposed to T/ F

FIGURE 1. Questionnaire for the evaluation of patients' attitudes and knowledge towards regular alcohol urine screening.

mild in intensity, was clearly significant. It all leads to the tentative conclusion that the results of the adapted DAI-10 questionnaire could be considered reasonably valid. Interestingly, the high perceived value and positive attitude is in sharp contrast with the lack of evidence regarding the efficacy of regular urine drug screening (Dupouy et al., 2014). Whereas the lack of evidence should not be interpreted as evidence of no efficacy, if we take into account the previous results of a

4. Undergoing regular alcohol urine screening makes me feel more safe and confident T/F
5. Undergoing regular alcohol urine screening makes me feel tired and sluggish T / F
6. I only undergo alcohol urine screening when I have used alcohol T / F
7. I find it normal to undergo regular alcohol urine screening T / F
8. It is unnatural for me to undergo regular alcohol urine screening T / F
9. Undergoing regular alcohol urine screening allows me to think and act more clearly T/ F
10. Undergoing regular alcohol urine screening helps me not to get worse T / F

-What do you think is looked for or tried to detect in the urine when undergoing alcohol use screening?

☐ alcohol   ☐ some byproduct of alcohol breakdown   ☐ I don't know

-What would you say is the minimum amount of alcohol units that need to be ingested in order to have a positive urine screening? (one alcohol unit is equivalent to one beer, one glass of wine, one small shot of spirits or half long shot of spirits)

☐ 1   ☐ 2   ☐ 3   ☐ 4   ☐ more than 4

-How long do you think it takes since someone last drinks until alcohol urine screening becomes negative?

☐ 0-4h
☐ 5-10h
☐ 10-24h
☐ 24-48h
☐ 48-72h
☐ longer than 72 h

-Your age: ☐ years

-Your sex: ☐ Male   ☐ Female

-Are you employed?   ☐ no   ☐ yes

-Your level of instruction is:
☐ primary studies ☐ secondary studies ☐ technical studies ☐ university

-How long have you been undergoing regular alcohol urine screening? _____

-You undergo regular alcohol urine screening:
☐ twice or more a week ☐ once a week ☐ less than once a week

FIGURE 1. *(Continued).*

study conducted in the same population, in which self-reports and routine ethanol screening performed clearly poor in detecting alcohol use (Barrio et al., 2016), one is compelled to think that there must be other reasons, apart from alcohol use detection, why patients keep attending the urine screening program.

Looking at patients' responses, the majority stated that preventing relapse and accomplishing their therapeutic goals

TABLE 1. Main Functions of Regular Urine Screening

| Function	Percentage of Patients Reporting the Function
To accomplish my therapeutic objectives regarding alcohol	75
To prevent relapse	53.1
To show to professionals that I do not drink	39.8
To show to my family that I do not drink	35.9
To have closer contact with professionals/to feel better cared of	39.8
To remind myself that I am in treatment because of alcohol	42.2
To comply with a legal requirement	0.8
Others	0.8

regarding alcohol were the main functions of regular urine screening. Notwithstanding, a high proportion of patients did also report that having a closer contact with professionals, feeling better cared for, and reminding themselves that they were in treatment were also relevant functions of screening. Taken together with the positive DAI-10 scores, we believe these results point out to a human relational factor of notable importance in the dynamics of regular urine screening. Indeed, it should not be surprising, because it has long been noted that the therapeutic relationship between patients and professionals is of over-riding importance in the field of alcoholism (Ritter et al., 2002; Ilgen et al., 2006). Although to the best of our knowledge, there are no similar previous studies regarding urine screening, a previous survey about preferences of users in addiction services revealed that patients clearly preferred help that involved human contact compared with computerized help or self-help, irrespective of personalized help being dispensed by professional or lay providers (Tucker et al., 2009). Similarly, a recent study about the needs of addiction patients in primary care highlighted the importance of feeling cared for as a major characteristic for a successful therapeutic relationship with their primary care provider (Press et al., 2016). It should be taken into account that in our study, patients were always received by the same professional, a fact that might have facilitated an ongoing, positive therapeutic interaction that might help explain our results.

Regarding patients' technical knowledge, as it could have been expected, only a minority thought it was a breakdown product of ethanol that was detected in urine, suggesting that ethylglucuronide and other subproducts of ethanol such as ethylsulphate or phosphatidylethanol are big unknowns to alcohol patients. What remains more interesting, however, are the detection windows reported by patients. Although findings are mixed, taken together, more than 75% of patients believe alcohol use cannot be detected beyond 48 hours after consumption. This might partly explain the high discrepancies that studies comparing ethanol with ethylglucuronide have consistently shown (Skipper et al., 2004; Wojcik and Hawthorne, 2007; Böttcher et al., 2008; Dahl et al., 2011; Jatlow et al., 2014; Barrio et al., 2016), since ethylglucuronide might be a reasonably valid metabolite to detect alcohol use beyond 48 hours of last alcohol consumption (Helander et al., 2009). In trying to find other reasons explaining these consistently

reported discrepancies, it should be noted that more than 1 in 5 patients admitted to have drunk small quantities of alcohol that have gone undetected by routine urinary ethanol detection, a proportion that could be even higher, since almost half of the patients believed others might try to cheat while undergoing urine screening. Taken together, all these data suggest that, although patients do not have a fully accurate knowledge of ethanol pharmacokinetics, they do have some notions that could allow them to self-regulate their drinking to avoid positive urine screenings. Be it because they do not know about ethylglucuronide pharmacokinetics or because its detection window expands beyond their self-regulatory capacity, what becomes clear is that when urine screening is performed with ethylglucuronide, the number of positive screens dramatically increases. What remains to be investigated is whether once patients become aware of ethylglucuronide kinetics, they will somehow regulate their drinking again so as to reduce the number of positive urine samples.

A key issue in interpreting all studies using questionnaires is social desirability (Van De Mortel and Van De Mortel, 2008). In fact, addiction is especially prone to such bias (Davis et al., 2010; Zemore, 2012). Although questionnaires were completely anonymous, it cannot be totally ruled out. In this sense, it is interesting to note the high proportion of respondents that reported "*showing professionals or their family that they do not drink*" as a main function of screening. It suggests regular urine screening plays an important role in patients' interaction with both professionals and their social network.

Other relevant limitations should also be taken into account when interpreting our findings. First, we developed a new questionnaire. Although it was based on an extensively validated one such as the DAI-10, it must be acknowledged that our study was not focused on questionnaire validation; therefore, more measures could have been obtained to better validate it. That being said, internal reliability and concurrent validity were fair. It would have been interesting to correlate the DAI-10 scores with adherence to urine screening by assessing the rate of prescribed versus attended appointments. However, we preferred to keep the questionnaires anonymous to increase response validity. Another important limitation
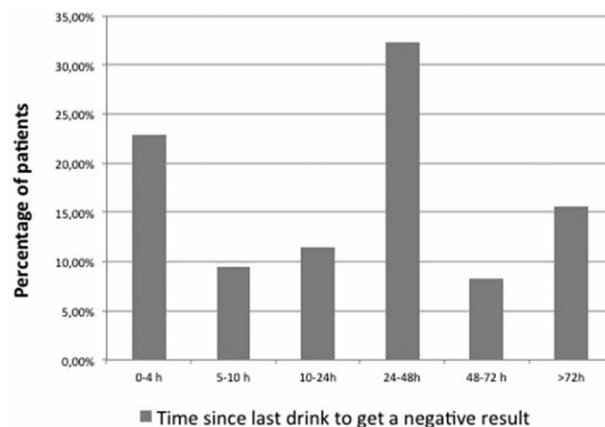
FIGURE 2. Patients' beliefs about detection windows for alcohol urine screening.

stems from the fact that all patients belonged to a single outpatient center, a fact that might diminish external validity. In this sense, for example, only a minority of patients underwent urine screening due to legal requirements. It would be reasonable to expect different results in settings where this proportion is higher. It is also important to mention that the nature of this study was mainly descriptive. However, we tried to find some predictors of patients' attitudes towards RAUS, but found no significant predictors, a fact that could partly be due to insufficient statistical power. Finally, a few questionnaires were not fully completed and therefore we had a minor proportion of missing data.

CONCLUSIONS

We believe the results obtained in this study suggest regular urine screening plays a significant role in abstinence-oriented treatments. The lack of evidence regarding its efficacy contrasts with the highly perceived value and attitudes that patients display towards it. It looks like apart from the more traditional therapeutic and relapse prevention function, other more patient-centered or humanistic functions such as a closer contact with professionals are also relevant. Also, social desirability and impression management seem to be key ingredients for a relevant portion of patients attending the screening program. In consonance with the complexity of addiction, this study also suggests that some patients try to self-regulate their drinking to avoid positive urine screenings. Further research should elucidate what the consequences are of widely and routinely implementing more sensitive alcohol biomarkers such as ethylglucuronide.

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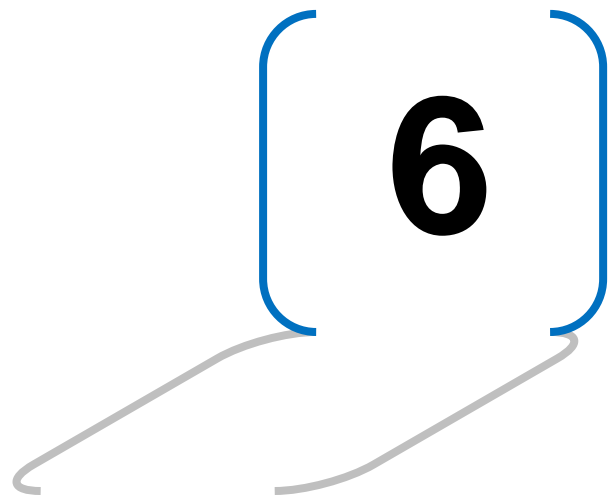
General discussion

Main Findings

The present thesis expands the current knowledge about the clinical implications of routinely screening alcohol dependent outpatients with urine ethyl glucuronide and thus adds extra value to this technique as a management strategy for alcohol dependent outpatients.

Study 1 clearly signals that the increased detection capacity of recent drinking shown in previous experimental designs and small sample size studies is fully transferable to "real world" and "real practice settings". It also demonstrates that urine ethyl glucuronide displays an overriding superior detection performance of recent drinking when compared to self-reports and clinician judgment.

Study 2 provides new and useful information about the differential predictive capacity of positive and negative urine ethyl glucuronide regarding relapse and hospitalization risk in the following year, thus increasing the value and significance of routine urine screening in the management of alcohol dependence, both when a negative and a positive result is obtained. As shown by the results of the study, an EtG positive patient should raise clinicians' awareness immediately, while an EtG negative patient could reassure clinicians of a favorable evolution, at least in the following months. Study 2 also suggests that ethyl glucuronide might have economical predictive implications as positive patients incur in more treatment expenses. All in all, Study 2 opens the possibility of improved relapse prevention for alcohol dependent outpatients, suggesting relapse could be much earlier detected and therefore also earlier addressed.

Finally, Study 3 provides insight into patients' perspectives and technical knowledge regarding urine screening, demonstrating that a majority of patients highly value frequent urine testing as part of their alcohol treatment. Important reasons supporting this appreciation are relapse prevention, a closer contact with professionals and impression management. Study 3 also shows that patients have a low level of knowledge about ethyl glucuronide kinetics, a fact that could partly explain its highly superior detection capacity regarding recent drinking.

Ethyl glucuronide in routine, real clinical conditions

Ethyl glucuronide signaling of alcohol use has been known for several years. The first demonstration of ethanol conjugation with glucuronic acid was seen in rabbits back in 1953 (87). It was not, however, until late 90s that ethyl glucuronide started to emerge in the field of alcohol research in humans (88–90). All studies conducted onwards have consistently shown that urine ethyl glucuronide behaves radically different from ethanol, especially when it comes to its wider detection window after alcohol ingestion. This means that ethyl glucuronide has persistently detected a higher number of positive samples when compared to ethanol. And the difference has been consistently high.

While experimental assessments are clearly indispensable, they suffer from various caveats, such as assessment reactivity, Hawthorne's effect, or even social desirability, all well known biases to scientific research (48,91). Therefore, what lacked to the existing literature (mostly based on experimental or highly controlled designs), was the confirmation that this different detection performance was to be sustained in routine, clinical settings under real circumstances.

Study 1 provides data that suggest this is indeed the case. We found a large discrepancy between ethanol and ethyl glucuronide, one yielding only 1,5% of positive samples, the other 22,2%. These results are in line with previous studies. For example, Mutschler et al. (92) found in a group of 51 outpatients under supervised disulfiram a 59% discrepancy between EtG and breath alcohol testing. Similarly, Junhagams et al. (66) found a 28% discrepancy between EtG and self reports in 139 outpatients. The studies by Wurst et al.(76) and Skipper et al. (93), in which EtG was compared to urinary alcohol, reported a discrepancy of 9% and 7%, respectively.

Beyond numbers, the relevant point of Study 1 is that the large discrepancy found between ethanol and ethyl glucuronide could be seen as the two metabolites depicting totally different realities. If we were to rely only on urinary ethanol, it would look like the great majority of our outpatients do exceedingly well in an abstinence oriented program, with less than 5% of patients drinking alcohol. On the other hand, if we consider the data provided by EtG assessment, the picture is radically different. We no longer have a big population of alcohol patients who cope with their alcohol problems in a way that they are able to maintain abstinence. We indeed have almost a 40%

of patients who are not fully abstinent. And, importantly, were it not for EtG, we would not be aware of this huge proportion.

Self reports were, in Study 1, even less reliable than ethanol. It is indeed well known that self-reports tend to underestimate patients' consumption rates (94–97). The rate of positives suspected by the nurse was halfway between those of EtG and urinary ethanol, suggesting up to 10,5% of urine samples came from not abstinent patients. In fact, previous studies suggest clinicians are ill-equipped when it comes to assess substance intake in their patients (98).

All in all, Study 1 suggests that ethyl glucuronide is an indispensable, and probably one of the best tools in order to assess the reality of alcohol dependent outpatients when it comes to determine their drinking status. It follows that in clinical settings where it is not implemented, and where routine urinary or breath ethanol screening is conducted aiming at relapse prevention, such performance might be rather poor, even if incorporating professionals' expertise and judgment into the equation. Given the high impact alcohol use imposes on individuals and societies, it seems reasonable to believe that an effort to expand the implementation of urine ethyl glucuronide is warranted.

As a conclusion, the data displayed by this and other studies clearly suggest that a wide implementation of EtG in real settings would yield relevant improvements in the monitoring of abstinence in outpatient populations, therefore offering a better relapse prevention.

Ethyl glucuronide prediction of clinical evolution

Following participants of Study 1, Study 2 evaluated one-year clinical correlates of positive baseline EtG urine screening, as compared to a negative baseline result. Both patients and clinicians were unaware of baseline EtG results. Since we could not incorporate EtG testing as our routine biomarker due to budget and time constraints in the following year, the ongoing urine screenings were performed with ethanol. This in fact allowed the performance of Study 2, where the implications of a single EtG testing could be evaluated.

The data obtained during the follow-up suggest that patients testing positive in EtG will have a different clinical evolution in the following year, with a significant increase in relapses, hospitalizations and treatment expenses. Given that both patients and clinicians were unaware of EtG status at baseline, one pressing question emerges: could some of this differences have been avoided, was this information made available to them? Although such a question cannot be directly answered by Study 2, and needs for prospective, randomized investigations, we believe some clues can be drawn from its data.

Although the need for hospitalization for the whole sample was rather low, with only 10 patients (6,6% of the total sample) requiring it, the differences between groups were both significant and large, with only one patient in the EtG negative arm being hospitalized in the following year. Taking a stepped care approach, hospitalization could be considered as one of the final steps in dealing with a relapse, which might have been initiated much before in the form of lapses (99,100). This might be a crucial point in time where the use of sensible alcohol biomarkers such as EtG could help to identify the beginning of the relapse, and so to earlier address it, with the potential impact of avoiding the need for hospitalization and also of reducing treatment expenses.

Though at first glance suggesting that patients who test positive for EtG will relapse at a higher rate than those who don't could seem tautological, this fact deserves further elaboration. First, one should notice that relapse, though widely used as a concept, lacks firm and conclusive criteria (101), a fact that could explain that being EtG positive does not immediately imply a relapse. In fact, a minority of patients tested positive for EtG and were clinically deemed as non-relapsed during the following year. That being said, our data robustly show that an EtG positive result dramatically increases the risk of having a clinical correlate in the following year, as shown by the hazard ratio obtained in the survival analysis. In other words, patients testing positive for EtG will, with very high probabilities, ultimately have clinical symptoms of relapse. Therefore, an EtG positive screening could be considered as an early relapse sign. But also, looked the other way around, it looks like having an EtG negative screening has a strong negative predictive value, that is, it should reassure clinicians of patients' favorable evolution, at least in alcohol related outcomes.

Results of study 2 are in line with previous, similar studies. For example, Junghans et al. (66), found out that positive EtG urine screening early after discharge significantly increased the rate of

subsequent relapse in recently discharged alcohol dependent patients. Similarly, Dahl et al. (102) found EtG to be a useful and reliable ongoing monitoring tool in alcohol treatment studies, specially suggesting that an initial EtG negative sample is useful to confirm self-reports.

Treatment expenses were clearly different between groups, driven both by the different number of days of hospitalization in both cohorts as well as an increased number of visits in those EtG positive. In fact, it has already been shown that patients actively drinking incur in greater costs (103–105). All these data suggest that the implementation of EtG could also have an economic impact in the treatment of alcohol dependence.

Regarding the capacity of predicting the risk of being lost to follow-up, EtG showed significant results in the univariate analysis, which seemed to disappear once age was included in the multivariate model. In fact, previous literature already pointed out at older age as a predictor of treatment retention (106,107). That being said, prior literature also consistently shows that patients actively using alcohol or drugs are at a greater risk of becoming non-treatment adherent (106,108,109). Also, previous studies with EtG (66) have found that testing EtG positive increases the risk of being lost to follow-up. Therefore, it would not be unwise to consider EtG as a potentially useful tool in predicting the risk of treatment abandonment.

Taken together, we believe that the data gathered by study 2 has important implications for real practice: namely, the implementation of ethyl glucuronide in routine urine screening could improve clinicians' capacity to detect early signs of relapse, and therefore it would also allow them to early address it, increasing the efficiency of the process. Also, it looks like both the positive and negative predictive value of EtG could allow for a better targeting of those patients that are in need of a more urgent, intense intervention. Given the high rate of relapse displayed by EtG positive patients, it seems that a positive testing for EtG should raise clinicians' awareness immediately, while an EtG negative result could reassure them of a favorable evolution, at least in the following months.

While there is a solid body of evidence assessing the predictive capacity of other variables such as illness severity (107), craving (111), DSM-IV criteria (112), or other psychological constructs such as persistence and self-efficacy (113) when trying to determine the risk of relapse, there is no such literature related to the predictive capacity of urine screenings. And the same happens when

analyzing the risk of hospitalization (114–116). In fact, in study 2, we found EtG to be the most accurate, precise predictor, even when controlling for other variables such as age, sex, addictive comorbidities or length of urine testing, and also clearly better than clinician judgment. Therefore, EtG status should not be seen as a substitute of other important variables, but it clearly increases the global assessment and prediction capacity of clinicians treating alcohol dependent outpatients.

All in all, we believe Study 2 increases the available evidence supporting the usefulness and clinical impact of regular urine screening with sensible biomarkers in alcohol treatments. Though no efficacy data could be directly inferred from our data, it looks like a wide implementation such sensible alcohol biomarkers could help to improve the prediction capacity of clinicians, especially in abstinence oriented settings. Further prospective studies will have to examine whether this increased prediction capacity can be translated into a greater treatment efficacy, probably due to a better prevention.

Patients' Perspectives

The appearance of new alcohol biomarkers with overriding superior sensibilities in the detection of drinking has made clear that routine urine screening has been far from satisfactory when it comes to abstinence monitoring. The huge discrepancy found in Study 1 and all other studies comparing new biomarkers with traditional ones lead to a pressing question: what is the real purpose of regular urine screening? Is it about regular control, relapse prevention and contingency management? Or is it about education, habit changing routines and continuous support? Or is it both? That was partly what we tried to answer in Study 3, aimed at investigating the beliefs and attitudes patients have towards regular alcohol urine screening.

Globally, the results of Study 3 show that alcohol patients perceive routine urine screening as a highly valuable part of their treatment. The adapted version of the DAI-10 scored high among our sample. Importantly, its internal reliability, with a Cronbach's alpha of 0,718, was fair. Also, its correlation with a single Likert-type question about the global perceived value patients give to regular urine screening, despite being mild in intensity, was clearly significant. It all leads to the tentative conclusion that the results of the adapted DAI-10 questionnaire could be considered reasonably valid.

Interestingly, the high perceived value and positive attitude is in sharp contrast with the lack of evidence regarding the efficacy of regular urine drug screening. While the lack of evidence should not be interpreted as evidence of no efficacy, if we take into account the results of Study 1, where self-reports and routine ethanol screening performed clearly poor in detecting alcohol use, one is compelled to think that there must be other reasons, besides alcohol use detection, why patients keep attending the urine screening program.

Looking at patients' responses, the majority stated that preventing relapse and accomplishing their therapeutic goals regarding alcohol were the main functions attributed to regular urine screening. Notwithstanding, a high proportion of patients did also report that having a closer contact with professionals, feeling better cared for and reminding themselves that they were in treatment were also main functions of screening. Taken together with the positive DAI-10 scores, we believe these results point out to a human relational factor of notable importance in the dynamics of regular urine screening. Indeed, it should not be surprising, since it has long been noted that the therapeutic relationship between patients and professionals is of overriding importance in the field of alcohol dependence (117,118). While to the best of our knowledge there are no similar previous studies regarding urine screening, a previous survey about preferences of users in addiction services revealed that patients clearly preferred help that involved human contact compared to computerized help or self-help, irrespective of personalized help being dispensed by professional or lay providers (119). Similarly, a recent study about addiction patients' needs in primary care did also highlight the importance of feeling cared for as a major characteristic for a successful therapeutic relationship with their primary care provider (120). It should be taken into account that in our study, patients were always received by the same professional, a fact that might have facilitated an ongoing, positive therapeutic interaction that might help explain our results.

Regarding patients' technical knowledge, as it could have been expected, only a minority thought it was a breakdown product of ethanol that was detected in urine, suggesting that ethylglucuronide and other subproducts of ethanol such as ethylsulphate or posphatidylethanol are big unknowns to alcohol patients. What remains more interesting, however, are the detection windows reported by patients. While findings are mixed, taken together, more than 75% of patients believe alcohol use cannot be detected beyond 48 h after consumption. This might partly explain the high

discrepancies that studies comparing ethanol with ethylglucuronide have consistently shown (61,63,65,76,121), since ethylglucuronide might be a reasonably valid metabolite to detect alcohol use beyond 48 hours of last alcohol consumption (54). In trying to find other reasons explaining these consistently reported discrepancies, it should be noted that more than one in five patients in Study 3 admitted to have drunk small quantities of alcohol that had gone undetected by routine urinary ethanol detection, a proportion that could be even higher, since almost half of the patients believed others might try to cheat while undergoing urine screening. Taken together, all these data suggest that although patients have not a fully accurate knowledge of ethanol pharmacokinetics, they do have some notions that could allow them to self-regulate their drinking in order to avoid positive urine screenings. Be it because they do not know about ethylglucuronide pharmacokinetics or because its detection window expands beyond their self-regulatory capacity, what becomes clear is that when urine screening is performed with ethylglucuronide the number of positive screens dramatically increases. What remains to be investigated is whether once patients become aware of ethylglucuronide kinetics, they will somehow regulate their drinking again so as to reduce the number of positive urine samples.

We believe the results obtained in Study 3 suggest that regular urine screening plays a significant role in abstinence oriented treatments. The lack of evidence regarding its efficacy contrasts with the highly perceived value and attitudes that patients display towards it. It looks like besides the more traditional therapeutic and relapse prevention function, other more patient-centered or humanistic functions such as a closer contact with professionals are also relevant. Social desirability and impression management seem also to be key ingredients for a relevant portion of patients attending the screening program. In consonance with the complexity of addiction, Study 3 also suggests that some patients try to self-regulate their drinking in order to avoid positive urine screenings.

Limitations

Several limitations must be taken into account when interpreting the findings of the present thesis. Regarding Study 1, and related to EtG measurement, it is important to note that EtG false positives are known to occur after the ingestion of mouthwashes or the use of alcohol-containing hand sanitizers. However, this might account only for a residual number of positives. Moreover, with a cut-off of 500 ng/ml, the specificity of EtG remains quite high (122). In fact, previous studies suggests that a cut-off of 500 mg/nl reliably prevents these false positives from occurring (123–125). Also, EtG/creatinine ratios and EtG-LC-MS/MS confirmation tests were not conducted. Nonetheless, recent studies (61,64,126) suggest that this is not necessary. Also, despite being an observational study with an expected high external validity, the results belong to a single center, a fact that might limit the generalization of the results.

Turning to Study 2, it should be noted that data were gathered at the end of follow-up, which means that variables were collected retrospectively. Taking into account that we also collected the hospitalization rate of patients, it should be considered that there exists the possibility of patients being hospitalized in other centers, which could have biased our data. However, it would be reasonable to consider that in both groups more hospitalizations would have been seen, and probably even more in the EtG positive patients. Therefore this bias would result in an infraestimation of EtG prediction capacity, which, as it has been shown, turned out to be already significant. Related to this, is the fact that more EtG positive patients were lost to follow-up. While survival analysis specifically addresses this data, when analyzing days of hospitalization and relapse risk, they had to be considered as missing data. However, as previously mentioned, treatment abandonment has been associated with increased relapse risk, therefore, it is probable that this missing data turned out into an infraestimation of EtG prediction capacity regarding relapse risk and hospitalization risk. Also relevant to mention is the fact that relapse as an outcome was operationalized according to different criteria, a fact that could limit the validity of our results. That being said, composite endpoints are now frequently used and reasonably valid if well and appropriately designed (127,128). Finally, it is important to note that psychiatric comorbidities, a frequent phenomenon in alcohol dependent patients (129,130) were not systematically recorded in this study, and therefore, their contribution to the results obtained could not be evaluated.

Finally, in Study 3, a key issue, as in all studies using questionnaires, is social desirability (131). In fact, addiction is especially prone to such bias (132,133). Although questionnaires were completely anonymous, it cannot be totally ruled out. Also relevant is the fact that we developed a new questionnaire. Although it was based on an extensively validated one such as the DAI-10, it must be acknowledged that our study was not focused on questionnaire validation, therefore more measures could have been obtained in order to better validate it. However, internal reliability and concurrent validity were fair. Another important limitation stems from the fact that all patients belonged to a single outpatient center, a fact that might diminish external validity. In this sense, for example, only a minority of patients underwent urine screening because of legal requirements. It would be reasonable to expect different results in settings where this proportion is higher.

Connecting the dots: what is this thesis showing us?

We believe that with the evidence provided by this thesis, it is reasonable to argue that regular alcohol urine screening with biomarkers such as EtG is a relevant component in the management of alcohol dependent outpatients, and that it seems to have an effect on patients' clinical evolution. It is also reasonable to argue that this effect stems from two separate mechanisms: one would be EtG's excellent internal validity and extended detection times as well as high predictive values. The second one would be independent of the biomarker characteristics, and would be related to the opportunity that regular alcohol urine screening offers to both patients and professionals for therapeutic alliance building and an improved, better perceived, patient care.

This, in fact, reminds us that medicine is not all about technique, and that scientific progress should always furnish the framework for a stronger humanistic, value-based medicine (134). Though EtG is merely a molecule, we believe that it can indeed bring both scientific and humanistic progress. Clearly, EtG will help clinicians to better assess and comprehend patients' reality, opening new possibilities for a more accurate and compassionate care. Where clinicians were blind before, they will now have the opportunity to discuss with patients what their difficulties are in achieving and maintaining abstinence. We also expect that the improved, more accurate feedback that patients will

get from EtG will, in the end, help them through the arduous, but so many times enlightening, process of recovery.

Future directions and challenges

Patients' assessment and correct evaluation are essential in all medical branches and diseases. When it comes to addiction patients, it is key to accurately know whether patients are abstinent or not. Though probably not a single tool fits all patients and settings, it looks like good biomarkers, with high sensitivity and specificity, and with extended detection window, are essential components in abstinence oriented treatments.

In this sense, the emergence of new alcohol biomarkers has clearly opened new and promising possibilities, taking the field closer to a better and more accurate appreciation of reality. However, both evidence based medicine and patient complexity and heterogeneity require that all new treatments, assessment tools or whatever elements, undergo a rigorous research process aimed at demonstrating their efficacy. We hope this thesis has added relevant evidence into the field. However, we are aware that more efforts are needed in this direction.

Throughout this thesis we have mentioned several times the potential relapse prevention improvement that EtG might yield if widely implemented in outpatient settings. However, 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 (135– 137). Comparing sensitivity and specificity of diagnostic techniques in a transversal design, as it is usually the case when developing new diagnostic strategies, precludes drawing firm conclusions about their clinical effectiveness. Just as drug-therapies and behavioral interventions ultimately rely on randomized trials to establish their clinical significance, so should diagnostic techniques.

The lack of randomization when assessing the effectiveness of a diagnostic test used in alcohol screening is especially worrisome for at least two reasons. First, it is reasonable to believe that the screening workup of alcohol use disorders has a therapeutic effect via feedback to the patient, thus it is of crucial relevance that the performance of the screening tools is assessed using a

randomized design. Second, unlike in other diseases where a positive diagnostic test is expected to be followed by a highly standardized intervention , there is no such standardization in the addiction field, and the gap between a positive screening and the related clinical consequences should be elucidated.

Thus, in order to fully and firmly discern the ultimate contribution of EtG to alcohol use disorders' management, its well established superior diagnostic performance in urine screening is not enough. That is the reason why we are currently conducting a randomized study where 160 patients have been randomized to 24 weeks of ongoing urine screening with ethanol or ethyl glucuronide, in order to assess the differential impact EtG could have in alcohol related outcomes, with special emphasis on relapse prevention.

Finally, it is important to note that despite EtG being probably the most studied new biomarker of alcohol use, many others might follow in the coming years. We believe special attention is deserved by posphatidylethanol, especially now that its measurement in dried blood spots is available (138–140), and that specific antibodies have been produced (141), facts that could accelerate its routine, seriated implementation.

In this sense, the expanding science of proteomics displays also promising features for alcohol biomarkers (142–144). That being said, it is important to understand that the development of a new biomarker is a long, arduous journey, departing from discovery and arriving at clinical validation and implementation. Thus, we believe it is important to mention that this thesis has served as the final destination for urine ethyl glucuronide in our site, where it has now been implemented as the routine screening method of alcohol dependent outpatients.

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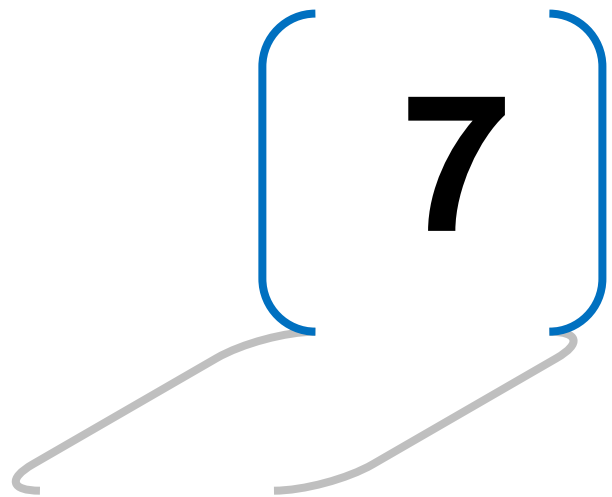
Conclusions

Conclusions

1. Urine ethyl glucuronide detection capacity of recent drinking is clearly superior to that of ethanol, self-report or clinician judgment in routine clinical settings, under real circumstances.

2. Urine ethyl glucuronide has a relevant prediction capacity regarding relapse risk, with patients screening positive having a higher rate of clinical significant relapse in the following 12 months.

3. Urine ethyl glucuronide has a relevant prediction capacity of need of hospitalization, with patients screening positive spending more days hospitalized during the following 12 months.

4. Urine ethyl glucuronide has a relevant prediction capacity regarding treatment expenses, with patients screening positive incurring in higher costs.

5. Patients have a low level of knowledge regarding urine ethyl glucuronide as well as other concepts related to urine screening, including the detection window of EtG.

6. Patients highly value regular alcohol urine screening as part of their treatment. The main functions they attribute to it are improved relapse prevention, a closer contact with professionals and impression management.

Resumen en castellano

Reemplazo de etanol por etilglucurónido en el cribado rutinario de pacientes ambulatorios dependientes al alcohol: implicaciones clínicas.

Introducción

El consumo de alcohol es una de las tres primeras causas de carga de enfermedad a nivel mundial (1). En Estados Unidos representa la tercera causa prevenible de muerte (4), mientras que Europa, con más de 15 millones de individuos afectos por un trastorno por uso de alcohol, posee el mayor número de muertes atribuibles al alcohol (5). Se añade además el problema del gran número de pacientes que no reciben tratamiento (6–8), todo ello implicando grandes repercusiones tanto a nivel individual como social (9), convirtiendo al alcohol en una prioridad de salud pública.

La forma más severa de trastorno por uso de alcohol, la dependencia al alcohol (10), es una enfermedad crónica recurrente, donde las recaídas son un fenómeno frecuente (12–14). Las consecuencias que supone para los pacientes afectos son muchas y diversas, tanto a nivel orgánico como psiquiátrico, incluyendo trastornos depresivos, ansiosos, accidentes, enfermedades gastrointestinales, cirrosis hepática, problemas sociales y legales, entre muchas otras más (18,19).

El tratamiento más eficaz para los tratarnos por uso de alcohol es aquel que combina estrategias psicosociales y farmacológicas (24). Dentro de estas dos modalidades, existen múltiples opciones que han demostrado ser eficaces en multitud de estudios previos, tales como la terapia cognitivo-conductual, la entrevista motivacional, el manejo de contingencias (25–32), la naltrexona, el acomprosat, el disfulfiram, el baclofeno o el topiramato (33–37).

En relación al objetivo del tratamiento, aunque ha sido siempre un tema debatido y es bien sabido que la reducción de daños junto a la reducción de consumos es una estrategia válida y frecuente en el mundo de los trastornos adictivos (40–42), la abstinencia es en general el objetivo de elección para una gran mayoría de pacientes y profesionales, puesto que, conceptualizando la adicción como una incapacidad de control sobre una sustancia, es considerada la vía más eficiente y segura hacia la total recuperación, tanto a nivel médico como psicosocial (43,44).

Por tanto, la monitorización de la abstinencia es una tarea indispensable para los profesionales que tratan pacientes dependientes al alcohol. En este sentido, y para realizar dicha tarea, los profesionales cuentan con varios métodos. Cabe comentar primeramente el autoinforme de los pacientes, que si bien es un elemento importante (47), son conocidos también todos sus sesgos y su baja fiabilidad cuando se compara con métodos más sensibles (48). Los biomarcadores son otra herramienta que puede complementar y mejorar el uso de autoinformes, pudiendo además ser claves para la monitorización de la abstinencia (49). Los marcadores tradicionales obtenidos en sangre (volumen corpuscular medio, gamma-glutamil transferasa, transferrina deficiente en carbohidratos) son poco sensibles a la hora de detectar pequeños consumos, por lo que no son buenos candidatos para una correcta monitorización de la abstinencia (46-48). Lo mismo le sucede al etanol en orina, que sólo permanece positivo unas pocas horas tras el último consumo de alcohol (54).

Afortunadamente durante la última década se han producido avances importantes en el campo de los biomarcadores del consumo de alcohol, siendo especialmente relevante el caso del etilglucurónido (EtG). Aunque sólo una pequeña parte del etanol ingerido se degrada mediante la conjugación con ácido glucurónico, esta molécula hidrosoluble puede permanecer detectable en orina hasta 72 horas después del último consumo de alcohol, por lo que hace posible una mayor ventana de detección del consumo de alcohol y posibilita una detección temprana de consumos y una mejor prevención de recaídas, al menos desde un punto de vista teórico.

Hasta la fecha se han realizado diversos estudios sobre EtG. No obstante, muchos han sido realizados bajo paradigmas de consumo controlado para estudiar su farmacocinética,(60–63), otros han sido estudios imbuidos en otros ensayos clínicos experimentales, (61,64–67), y otros han sido estudios con pequeño tamaño muestral o realizados con pacientes hospitalizados (74–77). Es por todo esto que es necesario estudiar el rendimiento diagnostico del EtG bajo condiciones reales de elevada validez externa, un criterio que frecuentemente es marginado en los estudios experimentales y que supone importantes sesgos (64-69). Por todo esto, el **Estudio 1** se realizó para comparar el rendimiento diagnostico del EtG con el del etanol, el juicio clínico y el autoinforme bajo condiciones reales de elevada validez externa, en un diseño transversal.

Otro interrogante en el cribado de alcohol es cuán eficaz es dicha técnica en el tratamiento de los pacientes. En este sentido una revisión sistemática reciente señala que existen escasos datos

al respecto (78). De hecho, ningún estudio con anterioridad ha evaluado las implicaciones clínicas que supone un resultado EtG positivo en cuanto a riesgo de recaída, riesgo de hospitalización y costes de tratamiento. Esta es la pregunta que intentó resolver el **Estudio 2**, donde los pacientes del estudio 1 fueron evaluados durante los siguientes 12 meses mediante un análisis de supervivencia con el fin de investigar la evolución clínica diferencial entre los pacientes EtG positivo y EtG negativo

Finalmente, teniendo en cuenta que hasta la fecha los datos sugieren que la detección del consumo de alcohol en pacientes ambulatorios dista de ser adecuada, parece razonable preguntarse si existen otras razones por las cuales los pacientes acuden regularmente al cribado de orina para monitorizar la abstinencia. Esto es lo que trató de evaluar el **Estudio 3**, donde a través de un cuestionario se evaluaron también los conocimientos técnicos de los pacientes respecto al cribado de alcohol.

Objetivos e hipótesis

El objetivo primordial de la presente tesis es ampliar el conocimiento existente sobre las implicaciones clínicas del cribado regular de alcohol en orina mediante métodos de alta sensibilidad y especificidad, como es el caso del EtG. Ello implica establecer su rendimiento en condiciones de rutina y elevada validez externa, así como investigar qué diferencias existen entre los pacientes positivos y negativos en los meses siguientes, en relación a riesgo de recaída, hospitalización y costes sanitarios. Finalmente es un objetivo también primordial conocer las actitudes y conocimientos de los pacientes en relación al cribado regular de alcohol. Estos objetivos se articulan en las siguientes hipótesis:

1. El uso de etilglucurónido resultará en un mayor número de muestras positivas en relación al uso de etanol, juicio clínico y autoinformes, debido a su mayor ventana de detección y su mayor sensibilidad.
2. Debido a que las recaídas se inician frecuentemente en forma de consumes encubiertos, el etilglucurónido identificará pacientes en fases iniciales de recaída, lo que supone que aquellos

pacientes EtG positivo presentarán en los siguientes meses mayor riesgo de recaída y hospitalización, así como un mayor gasto sanitario.

3. Debido a su relativa novedad, es esperable que los pacientes tengan un bajo nivel de conocimiento sobre el EtG y su farmacocinética.

4. Asumiendo que los pacientes tienen razones y expectativas diversas en relación al cribado rutinario de alcohol en orina, hipotetizamos que se obtendrán resultados mixtos en relación a sus actitudes respecto a dicha estrategia. Se espera que algunos pacientes la vean como una ayuda en su camino hacia la abstinencia, mientras que otros la experimenten como una obligación y presenten actitudes negativas.

Métodos

El **Estudio 1** consistió en una comparación transversal de todas las muestras de orina recogidas consecutivamente durante 14 días, analizándose todas para EtG, etanol, juicio clínico y autoinforme. El etilglucurónido fue analizado mediante un ensayo inmunoenzimático basado en un anticuerpo monoclonal (DRI Ethyl Glucuronide Enzyme Immunoassay , DRI-EtG EIA, Thermo Fisher Scientific Diagnostics, Hemel Hempstead, UK). Otras variables recogidas fueron las comorbilidades adictivas, la antigüedad en el cribado de alcohol y los datos sociodemográficos básicos. Se comparó la tasa de positivos entre etanol y EtG, así como el rendimiento diagnóstico del juicio clínico considerando el EtG como patrón oro. Se realizó un análisis de regresión en busca de predictores de un resultado EtG positivo.

El **Estudio 2** analizó un año después la presencia de recaídas, hospitalizaciones y costes sanitarios en los participantes del Estudio 1. Dichas variables fueron recogidas de manera retrospectiva y se llevó a cabo un análisis de supervivencia (junto a una regresión de Cox), comparando los grupos según su fueron EtG positivo o EtG negativo en relación al riesgo de recaída. Se utilizaron modelos de regresión lineal para comparar entre grupos el número medio de días de hospitalización y los costes sanitarios en que incurrieron, con la finalidad de encontrar predictores significativos de las posibles diferencias existentes entre grupos. También se comparó el número de pacientes que abandonaron tratamiento entre ambos grupos mediante análisis de regresión logística.

Todos los modelos fueron repetidos de nuevo sustituyendo el EtG por el juicio clínico, con el fin de comparar su poder predictivo.

En el **Estudio 3** se llevó a cabo de manera transversal, la realización de un cuestionario por parte de los pacientes ambulatorios dependientes al alcohol de la misma población que los estudios previos. Para evaluar sus actitudes se adaptó el Drug Attiude Inventory (DAI-10) al campo del cribado rutinario de alcohol, analizándose su consistencia interna, su fiabilidad test-retest y su validez concurrente. Para la evaluación de conocimientos se llevaron a cabo preguntas de respuesta múltiple. Se llevaron a cabo análisis de regresión lineal con la finalidad de encontrar predictores de las puntuaciones del cuestionario.

Resultados

En el **Estudio 1** un total de 188 pacientes proporcionaron 613 muestras consecutivas de orina durante 14 días. El etanol identificó 9 muestras como positivas, pertenecientes a 8 pacientes. El etilglucurónido identificó 136 muestras positivas, pertenecientes a 74 pacientes. Un 28,1% (172/613) de muestras fueron cribadas para otras drogas, principalmente cannabis (125 sobre 613 muestras), resultando positivas un 9,6% de las mismas en el cómputo global de muestras (59/613). En el modelo de regresión logística, solo el juicio clínico y la presencia de medicación aversiva fueron predictores significativos del resultado de EtG. El juicio clínico de la enfermera encargada de recibir a los pacientes y sus muestras, clasificó un 89,7% de las muestras (550/613) pertenecientes a 178 pacientes, como abstinentes. Juzgó un 7,8% (48/613) de las muestras, pertenecientes a 26 pacientes, como no abstinentes, dudando en 15 muestras de 15 pacientes. Usando el EtG como patrón oro, se obtuvo un área bajo la curva de 0,592.

En el **Estudio 2** se incluyeron 152 pacientes para el análisis de supervivencia. Las curvas de Kaplan-Meier mostraron una clara diferencia entre sujetos EtG positivo y EtG negativo (Log-Rank test significativo; chi=58,382 df=1; p<0,001). El promedio de tiempo hasta la recaída fue de 163 días en los sujetos EtG positivo y de 329 días en los EtG negativo. La regresión de Cox estableció el EtG como el único predictor significativo de dicha diferencia (hazard ratio = 5,3; IC 95% de 3,1 a 9,1). Lo mismo sucedió en los análisis de regresión lineal en relación al número medio de días de

hospitalización y el coste medio del tratamiento durante los siguientes 12 meses, donde el EtG fue el único predictor significativo. En este sentido, los pacientes EtG positivo presentaron mayor número medio de días de hospitalización (6,04 frente a 0,28 días) y mayores costes sanitarios promedio (2167 € frente a 566 €). El único factor predictor de riesgo de abandonar tratamiento fue la edad, asociándose una mayor edad a un menor riesgo (OR= 0,94; IC95% de 0,88 a 0,98). Al sustituir el EtG por el juicio clínico, en ninguno de los modelos previamente explicados obtuvo esta variable la significación estadística.

En el **Estudio 3**, se obtuvieron cuestionarios de 128 pacientes. Se observó una valoración muy positiva por parte de estos en relación al cribado rutinario de alcohol en orina, obteniéndose una puntuación media del cuestionario adaptado DAI-10 de 7,2 puntos (DE= 3,6). La alfa de Cronbach fue de 0,718. El coeficiente de correlación intraclase, utilizado para medir la fiabilidad test-retest fue de 0,932. La correlación entre la puntuación del cuestionario y la puntuación de una pregunta tipo Likert sobre cuánto valoran globalmente los pacientes el cribado rutinario de alcohol del 0 al 10 obtuvo un coeficiente de correlación de 0,254, con una p de 0,009. A parte de la prevención de recaídas, otras funciones importantes reportadas por los pacientes fueron demostrar a la familia y los profesionales que no beben y tener un contacto más cercano con los profesionales. La mayoría de pacientes refirió creer que el consumo de alcohol no se puede detectar pasadas 48 horas desde la última ingesta.

Discusión

Etilglucurónido en condiciones rutinarias de alta validez externa

El Estudio 1 sugiere que la elevada sensibilidad y especificidad del etilglucurónido para la detección de consumos recientes que se ha observado en estudios previos de tipo experimental, es claramente transferible a las condiciones clínicas rutinarias donde los pacientes dependientes del alcohol son monitorizados con el fin de preservar la abstinencia. Además, este estudio sugiere que si no fuera por la incorporación de un biomarcador de las características del EtG, nuestra percepción de la realidad sería claramente sesgada. Sin ir más lejos, si usamos los datos proporcionados por el etanol, parece que menos del 5% de nuestros pacientes no están abstinentes, mientras que si

utilizamos los datos que aporta el EtG, esta proporción asciende hasta casi el 40%. Los autoinformes fueron incluso menos fiables que el etanol. De hecho existe literatura previa señalando la tendencia de los autoinformes a infravalorar los consumos de los pacientes (94–97). El juicio clínico estimó que un 10,5% de las muestras pertenecían a pacientes no abstinentes. Este número está a medio camino entre el etanol y el etilglucurónido. De hecho, estudios previos sugieren que los profesionales no poseen una buena capacidad de detección de consumo de sustancias en sus pacientes (98).

En su conjunto, el Estudio 1 sugiere que el EtG es una de las mejores herramientas que existen en la actualidad para determinar la abstinencia de los pacientes dependientes al alcohol. Esto sugiere que se debería tratar de implementar de la manera más extensiva posible en los diversos ámbitos clínicos donde esta monitorización es importante, puesto que de no hacerlo, se corre un elevado riesgo de interpretar la realidad de una manera altamente sesgada. El estudio sugiere también que el uso de etilglucurónido podría mejorar significativamente la prevención de recaídas, permitiendo su detección de forma más temprana y por tanto también permitiría un abordaje más temprano y eficiente.

Etilglucurónido y predicción de la evolución clínica

El hecho que tanto los pacientes como los profesionales no dispusieran de los resultados obtenidos en el Estudio 1, y que los controles posteriores se realizaron, como es habitual en nuestro centro, con etanol, permitió la evaluación longitudinal de los pacientes haciendo posible el estudio de la capacidad predictiva de un resultado positivo a EtG en relación a diversos parámetros clínicos y económicos.

Los datos obtenidos sugieren que efectivamente, los pacientes con un resultado positivo tendrán una evolución clínicamente distinta a aquellos con un resultado negativo, presentando un mayor riesgo de recaída, un mayor número medio de días de hospitalización y un mayor coste en su tratamiento. Es importante remarcar que, aunque se necesitan estudios prospectivos para confirmar este hecho, los datos del Estudio 2 sugieren que el etilglucurónido es en efecto una herramienta potencialmente útil en la mejora de la prevención de recaídas, pues permitiría a los profesionales conocer con mucha antelación el estado clínico de los pacientes. Los datos apuntan a que un EtG positivo debería alertar rápidamente a los profesionales responsables en cuanto a la necesidad de

abordar el consumo y el riesgo de recaída. Por el contrario, un resultado negativo sugeriría que en los siguientes meses el paciente es capaz de mantener la abstinencia. Por tanto, el EtG presenta un elevado poder predictivo tanto positivo como negativo, un hecho relevante de cara a la práctica clínica habitual. Estudios previos apuntaban conclusiones similares a las obtenidas en el Estudio 2 (62,98).

En cuanto a los costes de tratamiento, cabe destacar que el mayor gasto de los pacientes EtG positivo vino dado por un mayor número de hospitalizaciones y un mayor número de visitas con los profesionales pertinentes. Estos datos están en línea con múltiples evidencias previas que sugieren que los pacientes no abstinentes incurren en mayores gastos sanitarios (103–105). Este hecho sugiere que la implementación del EtG podría tener también importantes implicaciones económicas.

Finalmente, aunque los resultado no fueron significativos para EtG en cuanto al riesgo de abandonar tratamiento, estudios previos señalan que, en efecto, el consumo activo de drogas es un factor de riesgo para abandonar tratamiento (106,108,109), por lo que, pese a la falta de significación estadística, cabe la posibilidad de que el EtG también posea cierto poder predictivo en cuanto a la retención de los pacientes en el tratamiento de su dependencia, hecho ya señalado por estudios previos (62).

Aunque existen muchas otras variables de poder predictivo demostrando en el campo del alcohol (106-112), ninguna de ellas en nuestro estudio obtuvo resultados similares a los del EtG, ni si quiera el juicio clínico. Esto no implica que el EtG deba sustituir a muchas de estas variables, pero parece evidente que de tener en cuenta su resultado en la valoración global de los pacientes, las conclusiones a las que se puedan llegar serán mucho más cercanas a la realidad y por tanto de una mayor validez.

La perspectiva de los pacientes

La aparición de nuevos biomarcadores con elevada sensibilidad y especificidad ha hecho patente el bajo rendimiento del cribado rutinario de alcohol con marcadores tradicionales. Muestra de

ello son los resultados del Estudio 1, así como todos los estudios previos llevados a cabo con etilglucurónido. Esto sugiere diversos interrogantes, en relación a qué función cumple realmente el cribado de orina en los pacientes dependientes del alcohol. ¿Se trata de una función de control, un manejo de contingencias, una prevención de recaídas? ¿O existen otras funciones como ofrecer soporte continuado y el fomento de hábitos regulares? ¿O son ambas cosas? Esto es en parte lo que se trató de desvelar en el Estudio 3.

En su global, los resultados de dicho estudio sugieren que los pacientes valoran muy positivamente el cribado rutinario de alcohol como parte de su tratamiento. De las respuestas de los pacientes se desprende que la prevención de recaídas es una función primordial para la mayoría. No obstante, una parte importante de los mismos también refiere que tener un contacto más cercano con los profesionales y sentirse más atendido son también funciones relevantes, sugiriendo que el factor humano juega un papel importante en la dinámica del cribado regular de alcohol en orina. Este hecho no es sorprendente, pues estudios previos ya demuestran la importancia de la relación terapéutica en el campo del alcoholismo (117,118). También estudios previos apuntan a que los pacientes prefieren tratamientos que implican contacto humano frente a tratamientos computarizados (119), y que es primordial para los pacientes afectos de un trastorno adictivo percibir que sus profesionales se preocupan por ellos (120). Cabe destacar también el elevado número de participantes que respondieron como función el demostrar a su familia y sus profesionales que no beben, apuntando también a la importancia de la conveniencia social y el manejo de impresiones.

Respecto a los conocimientos técnicos de los pacientes, se hizo patente que el etilglucurónido es un gran desconocido para ellos. En especial en lo que a su ventana de detección concierne, hecho que podría ayudar a explicar las grandes discrepancias que se encuentran cuando se compara con el etanol (61,63,65,76,121). Los datos en su conjunto apuntan a la posibilidad de que muchos pacientes, teniendo conocimientos suficientes sobre la farmacocinética del etanol, podrían tratar de autorregular sus consumos para evitar cribados positivos. La pregunta que aparece rápidamente es si podrán, una vez implementado el EtG y conocidas sus características, readaptar su consumo para seguir evitando cribados positivos o si la prolongada ventana de detección del EtG será demasiado amplia para que puedan ejercer dicho autocontrol.

Conclusiones

En su global, esta tesis enriquece la evidencia disponible en relación al cribado rutinario de alcohol en orina en pacientes dependientes al alcohol. Los datos aportados confirman que el etilglucurónido presenta en condiciones rutinarias de práctica clínica habitual, una elevada sensibilidad para la detección del consumo reciente, convirtiéndose así en una herramienta idónea para la monitorización de la abstinencia.

Además, sus resultados tienen un elevado poder predictivo en relación al riesgo de recaída y el riesgo de hospitalización en los siguientes 12 meses, así como también en cuestiones de costes de tratamiento. Por otro lado, los pacientes tienen un bajo conocimiento de las características farmacocinéticas del etilglucurónido, siendo especialmente importante el desconocimiento de su amplia ventana de detección. No obstante, los pacientes valoran muy favorablemente el cribado rutinario de alcohol en orina como parte de su tratamiento, destacando como funciones importantes la prevención de recaídas, una relación terapéutica más cercana y el manejo de impresiones en relación a sus familiares y a los propios profesionales.

List of abbreviations

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AUC	area under the curve
AUD	alcohol use disorder
CDT	carbohydrate deficient transferring
DAI	drug attitude inventory
DRI-EtG EIA	diagnostic reagents incorporated ethyl glucuronide enzymatic immuno assay
DSM-IV	diagnostic and statistical manual of mental disorders, 4ht edition
EtG	ethyl glucuronide
EtS	ethyl sulfate
GGT	gamma glutamyl transferase
GWAS	genomic wide association study
LC-MS/MS	liquid chromatography- mass spectrometry
MCV	mean corpuscular volume
PEth	phosphatidylethanol
ROC	receiving operator curve
SD	standard deviation

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Acknowledgements

Acknowledgements

Cuando uno termina algo como un doctorado, es imposible no pensar en la cantidad de gente que te ha ayudado, de manera directa o indirecta, a conseguir dicha meta. Y te invade una cierta ola de gratitud.

En primer lugar no puedo dejar de mencionar a mis padres. Su dedicación, amor y generosidad han sido fundamentales a lo largo de mi vida. Temo no ser capaz de agradecerles cómo se merecen todo lo que han hecho (y hacen) por mí.

Tampoco puedo dejar de mencionar a mis hermanos. Mi hermano Fermín, un ejemplo de lucha, superación y generosidad. Mi hermana María, que me enseñó a leer y a escribir, y también el teorema de Pitágoras y a atarme los zapatos, y que tanto cariño me ha dado en lo que llevo en esta vida. Y mi hermano Diego, con el que comparto muchas más cosas de lo que seguramente ambos pensamos, y de quién mi identidad y cómo se ha forjado no se pueden desligar.

Y mis amigos, aquellos que me escuchan sin juzgarme y me hacen entender qué bonito es poder experimentar la amistad en esta vida.

Dentro de este, nuestro Hospital, hay también mucha gente a la que estoy sinceramente agradecido. Començant pels meus directors de tesi, l'Eduard Vieta i el Toni Gual. A l'Eduard, a part de tota l'ajuda proporcionada per a tirar endavant aquesta tesi li estic agraït per donar-me l'oportunitat de treballar a prop d'una persona del seu nivell. Al Toni Gual de la mateixa manera li haig d'agraïr l'oportunitat d'aprendre al seu costat. No només és una persona amb una ment brillant, sinó que té una qualitat humana també brillant. Crec que mai vaig arribar a dir-li gràcies per com em va tractar quan era R4 i vaig atravessar una petita crisi existencial amb la Psiquiatria. Em va ensenyar què significa ser motivacional de veritat. Gràcies.

La meva gratitud va també cap a tota la Unitat de Conductes Addictives de l'Hospital Clínic, per fer-me sentir part de la mateixa i per haver-me acollit desde que era resident d'una manera tan amable, sincera i real. I la Lídia, la nostra infermera, que s'enfada amb mi quan anomeno en públic

com d'indispensable és per a nosaltres i de quina manera tan excel·lent fa la seva feina…espero que no s'enfadi gaire amb mi per aquestes línies, però de veritat que sense ella i la seva feina i la seva dediació als pacients, aquesta tesi hagués estat impossible. I la Lluisa, que a la seva manera es preocupa i s'ocupa de mi aquí abaix a l'ambulatori. Gràcies Lluisa. Estic segur que ben aviat tornaràs a somriure. I la Mercè, i la Neus, i la Presen, i la Nayara, i l'Hugo, i la Laia, i l'Anna, I l'Ana, i el Miquel, i el Pol…i com no, la Sílvia Mondon, a estones companya, a estones amiga, a estones confessora i a estones mestre i mirall d'on intentar aprendre continuament, no només sobre addiccions. Em sobren motius per dir-li gràcies, però crec que en un momento com aquest cal remarcar com em va fer possible continuar dins la unitat quan no vaig obtenir la beca fi de residencia. Amb tota sinceritat, gràcies Sílvia!

I sense sortir de les parets de l'Hospital, no puc deixar de pensar en les grans persones que vaig descobrir mentres feia la residència. A l'Àlex González m'agradiria donar-li les gràcies per donar-me l'oportunitat de descubrir que es poden fer amics de veritat a qualsevol edat, i per fer-me sentir sempre que tinc algú a prop que em cuida i em protegeix si cal. Al Diego Hidalgo també haig d'agraïr-li no només la seva amistat, sinó també la seva generositat amb mi desde que érem residents de primer any. Els qui el coneixen ja ho saben: és una persona gran de ment, cor i esperit.

I moltíssima altra gent que he anat trobant pel camí i que d'alguna manera o d'altra tenen una petita part de l'explicació de qui sóc i què faig avui en dia. Encara que no us esmenti a tots i cadascun, voldria donar-vos les gràcies.

I finalment, no per ser menys importants, sino tot el contrari. Perquè són els dos pilars fonamentals de la meva vida. La Maria i el Martí. A tu Maria vull dir-te gràcies per fer-me sentir estimat tal i com sóc, per fer-me perdre la por tants cops i per haver-me regalat les millors coses d'aquesta vida. I a tu Martí, que avui quan escric aquestes línies encara no t'ho puc explicar, però espero poder-te transmetre algun dia tot el que signifiques per a mi. Us estimo amb tot el meu cor.