Ethyl Glucuronide (EtG): Better than Breathalyser or Self-Reports to Detect Covert Short-Term Relapses into Drinking

T. Wetterling1,2, L. Dibbelt3, G. Wetterling1, R. Göder4, F. Wurst5, M. Margraf6 and K. Junghanns1,6,*

1Department of Psychiatry and Psychotherapy, University of Luebeck, Luebeck, Germany, 2Vivantes Klinikum Hellersdorf, Berlin, Germany, 3Department of Clinical Chemistry, University Hospital Schleswig-Holstein, Campus Luebeck, Luebeck, Germany, 4Department of Psychiatry and Psychotherapy, University of Kiel, Kiel, Germany, 5Department of Psychiatry and Psychotherapy II, Christian-Doppler-Clinic, Paracelsus Medical University, Salzburg, Austria and 6AHG Klinik Luebeck, Luebeck, Germany

*Corresponding author: Department of Psychiatry and Psychotherapy, University of Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany. Tel.: +49-451-5002920; Fax: +49-451-5004957; E-mail: klaus.junghanns@uksh.de

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Abstract — Aims: The assessment of relapses is widely used as an outcome measure of alcohol dependence treatment. However, the methods of assessing relapses range from questionnaires to biological markers of alcohol for different time spans. The aim of this study was to compare the relapse rates of weekend home stays during long-term alcohol dependence treatment, assessed by ethyl glucuronide (EtG), breath alcohol tests and self-reports. Methods: Two hundred and ninety-seven alcohol-dependent patients receiving a long-term inpatient treatment programme participated. After a weekend at home (Friday to Sunday) they were evaluated for relapse by personal interviews and with breath alcohol tests. A concomitantly collected urine sample was later assessed for EtG with liquid chromatography-tandem mass spectrometry (LC-MS/MS analysis). Results: Of the total, 37.7% of the patients were positive for EtG at least once. Breath alcohol tests had been positive in only 4.4% and in personal interviews only 5.7% of the patients had admitted relapse. 15.6% of EtG tests were positive, but breath alcohol tests were negative (Cohen’s kappa = 0.056). Ninety-three per cent of the relapses were only detected by EtG. Conclusion: In addition to breath alcohol tests and interviews, urinary EtG can clearly improve the verification of relapse in inpatient treatment programmes allowing for weekend stays at home. Without EtG testing, a high amount of relapses will stay undetected.

INTRODUCTION

If abstinence from alcohol is an outcome criterion, the reliable assessment of abstinence is a prerequisite for the evaluation of treatment effects in treatment programmes. This accounts for psychosocial treatments (i.e. Feuerlein and Küfner, 1989; Project MATCH, 1997), pharmacotherapies (i.e. Mann et al., 2004) and the combination of both (COMBINE-study, Anton et al., 2006; PREDICT-study, Mann et al., 2012) as well as for abstinence surveillances after drunk driving.

However, there are some methodological problems to assess recent alcohol ingestion. First, the definition of relapse varies (i.e. ‘any drink’ or ‘first heavy drinking day’). Furthermore, besides a personal interview or questionnaires several biological markers to assess alcohol consumption can be used. For instance, studies like Project MATCH or the COMBINE-study used carbohydrate deficient transferrin (CDT) as marker for alcohol consumption (Anton and Youngblood, 2006; Anton et al., 2006). CDT, however, is only a sensitive measure for alcohol consumption if the proband has drunk at least 1000 g of alcohol within the last 14 days. Short-term relapses into drinking therefore cannot be detected with CDT. In the setting of this study, only relapse markers sensitive for alcohol drinking during the last 3 days made sense.

More recently, ethyl glucuronide (EtG) has been proved to be a better marker for drinking during the last days preceding assessment (Wurst et al., 2003; Høiseth et al., 2008; Helander et al., 2012). Prior to the introduction of EtG into clinical use, recent alcohol consumption was commonly assessed by breath alcohol tests. We therefore compared reported drinking of alcohol with breath alcohol tests and with urinary EtG measurement. CDT was not assessed.

Some studies (Wurst et al., 1999, 2000, 2003, 2008a,b; Junghanns et al., 2009; Mutschler et al., 2010; Dahl et al., 2011a,b; Lahmek et al., 2012) have shown that the measurement of urinary EtG allows an identification of covert relapse during treatment programmes. But most of these studies have only small numbers of participants. Furthermore, they were performed in different settings, i.e. under disulfiram (Mutschler et al., 2010) or acamprosate medication (Dahl et al., 2011b) or psychotherapeutic treatment of alcoholism or methadone maintenance programmes (Wurst et al., 2008a,b).

EtG is directly produced during the biotransformation of alcohol (glucuronidation). This pathway accounts for about 0.5–1.5% of alcohol degradation in humans. Depending on the drunken amount of alcohol EtG is detectable up to 70 h after the elimination from blood (Helander et al., 2009). Several studies showed a good sensitivity of EtG for detecting the consumption of small amounts of alcohol (Wurst et al., 2004, 2005; Tierauf et al., 2009; Albermann et al., 2012a,b). The sensitivity of EtG was high, but it can be influenced by several factors (Wurst et al., 2004), e.g. renal diseases (Høiseth et al., 2012). In contrast, EtG values are not influenced by liver diseases (Stewart et al., 2013).

In Germany, alcohol-dependent patients have the possibility to take part in a long-term psychotherapeutic inpatient treatment of several months’ duration. Only for some weekends, patients are allowed to spend two nights at home. Drinking any amount of alcohol is strictly prohibited during the whole programme and a repeated consumption results in a discharge. Abstinence is usually controlled by repeated breathalyser tests and interviews. But how reliable are these measures after a weekend stay at home? In order to answer this question, we compared the relapse rates detected by the highly sensitive EtG measurement to alcohol breathing tests and self-reports of patients participating in a long-term alcohol dependence treatment.

METHODS

The study was executed in accordance with the Declaration of Helsinki and was approved by the local ethics committee,
under the local authorization number 06-099. All patients gave their written informed consent before entering the study. They were informed that the urinary sample would not be analysed for EtG before the end of the study and the result would have no consequences on their treatment. No patient refused participation and there were no dropouts.

The study was performed at the AHG Klinik Luebeck, Germany in cooperation with the Department of Psychiatry and Psychotherapy and the Institute for Clinical Chemistry of the University of Luebeck, Germany. The AHG Klinik Luebeck is specialized in the treatment of patients with substance disorders, particularly alcohol dependence. The concept for alcohol dependence inpatient treatment includes cognitive behavioural therapy for alcoholism, social skills training, anti-anxiety training, as well as a relapse prevention programme. The primary aim of treatment was achieving long-term abstinence.

**SAMPLE**

Two hundred and ninety-seven patients consecutively admitted to the AHG Klinik Luebeck were included in this study. All had a diagnosis of alcohol dependence (according to the ICD-10 criteria for alcohol dependence F10.2 (WHO, 1992)). They participated in a long-term alcohol dependence treatment (2–20 weeks). None of them received drugs for relapse prevention like acamprosate, disulfiram or naltrexone.

The sample is characterized in Table 1. Mean age was 43.0 ± 9.8 years. Forty-nine patients (16.5%) were females. No gender differences concerning the sociodemographic data could be found.

All patients were asked to deliver a urine sample immediately after return from the weekend. The sample was collected in presence of a staff member. The samples were then frozen at −25°C until LC/MS measurement. The EtG concentration in the urinary samples was measured by liquid chromatography combined with mass spectroscopy (LC/MS; 500-MS Ion Trap (Varian, Darmstadt, Germany)) according to the method published by Stephanson (2002). The detection limit is 0.1 mg/l, and in clinical practice a cut-off of 0.5 mg/l EtG was used. The breath alcohol concentration was measured by Breathalyzer (Dräger, Lübeck). In personal interviews the patients were then asked about alcohol use during the home stay and the answer was registered.

The statistical calculations were conducted with IBM-SPSS program, version 19.0G. Since many variables were not normally distributed, predominately non-parametric statistical methods were performed.

**RESULTS**

The data analysis showed some gender differences (Table 2). The reported duration of alcohol dependence and mean alcohol consumption was assessed in personal interviews including a Timeline-Follow-Back method for drinking during the last month before treatment. Mean alcohol consumption was 261 ± 156 g/drinking day in males and 207 ± 175 g/drinking day in females (U-test: z = −2.73, P = 0.006). Of the males, 68.3% and of the women, 53.2% were smoking daily (χ² = 4.00, df = 1, P = 0.045). Females more often had an additional abuse of other substances, mainly benzodiazepines (21.3% vs. 10.4%, χ² = 4.33, df = 1, P = 0.037). No gender differences were found concerning the rate of at least one EtG positive urinary sample or positive alcohol breathing test (Table 2).

The mean duration of alcohol dependence treatment was 13.0 ± 3.8 (range 3–20) weeks. The individual number of home stays varied due to individual reasons (distance to home, etc.): 5.7 ± 3.5 (range 1–16). Every home stay was calculated as one case. The total number of analysed urine samples was 1697 (Table 2).

Only in 18 of the 1697 self-reports (1.1%) alcohol consumption on the preceding days was admitted before urine sampling. No patient reported more than one relapse at his weekends. Only 13 of these patients (4.4% of all patients) could be identified as relapers by the alcohol breath tests (range: 0.06–2.60 g alcohol/l).

In 112 of the 297 patients (37.7%) the urine samples were positive for EtG at least once (concentration range = 0.2–1220 mg/l, mean = 47.2 mg/l). In 62 patients (21.3%) more than one urine sample was positive on EtG with a maximum of 12 positive samples. The total number of EtG positive samples was 275 (16.2%). The proportion of EtG positive samples among the patients with a weekend at home was very similar during all weekends (χ² = 8.33, df = 16, P = .938).

The comparison of the self-reports with the alcohol breathalyser test yielded a good agreement (Cohen’s kappa 0.790).

### Table 1. Sociodemographic data of the sample

<table>
<thead>
<tr>
<th>n</th>
<th>Sample</th>
<th>Males</th>
<th>Females</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43.0 ± 9.8</td>
<td>42.8 ± 9.5</td>
<td>44.6 ± 10.6</td>
<td>U-test, n.s.</td>
</tr>
<tr>
<td>Education (years)</td>
<td>9.4 ± 1.5</td>
<td>9.4 ± 1.4</td>
<td>9.5 ± 1.7</td>
<td>U-test, n.s.</td>
</tr>
<tr>
<td>Living alone</td>
<td>242 (81.5%)</td>
<td>203 (81.9%)</td>
<td>39 (79.6%)</td>
<td>χ² test, n.s.</td>
</tr>
<tr>
<td>Without job</td>
<td>226 (76.1%)</td>
<td>191 (77.0%)</td>
<td>35 (71.4%)</td>
<td>χ² test, n.s.</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>114 (38.4%)</td>
<td>94 (37.9%)</td>
<td>20 (40.8%)</td>
<td>χ² test, n.s.</td>
</tr>
</tbody>
</table>

### Table 2. Alcohol dependence or treatment-related data

<table>
<thead>
<tr>
<th>n</th>
<th>Sample</th>
<th>Males</th>
<th>Females</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>189 (65.9%)</td>
<td>164 (68.3%)</td>
<td>25 (53.2%)</td>
<td>χ² = 4.00, df = 1, P = 0.045</td>
</tr>
<tr>
<td>Other substances</td>
<td>35 (12.2%)</td>
<td>25 (10.4%)</td>
<td>10 (21.3%)</td>
<td>χ² = 4.33, df = 1, P = 0.037</td>
</tr>
<tr>
<td>Duration of alcohol dependence (years)</td>
<td>13.2 ± 12.7</td>
<td>13.8 ± 13.4</td>
<td>10.1 ± 7.0</td>
<td>U-test, z = −1.88, P = 0.030</td>
</tr>
<tr>
<td>Mean alcohol consumption (g/day)</td>
<td>252 ± 160</td>
<td>261 ± 156</td>
<td>207 ± 175</td>
<td>U-test, z = −2.73, P = 0.006</td>
</tr>
<tr>
<td>Weeks in therapy</td>
<td>13.0 ± 3.7</td>
<td>13.2 ± 3.7</td>
<td>12.0 ± 3.8</td>
<td>U-test, z = −2.19, P = 0.030</td>
</tr>
<tr>
<td>Home stays during treatment</td>
<td>5.7 ± 3.5</td>
<td>5.8 ± 3.6</td>
<td>5.2 ± 3.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>At least one positive self-report</td>
<td>17 (5.7%)</td>
<td>11 (4.4%)</td>
<td>6 (12.2%)</td>
<td>χ² = 4.62, df = 1, P = 0.032</td>
</tr>
<tr>
<td>At least one positive EtG measurement</td>
<td>111 (37.4%)</td>
<td>95 (38.3%)</td>
<td>16 (32.7%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>At least one positive breathing test</td>
<td>13 (4.4%)</td>
<td>10 (4.0%)</td>
<td>3 (6.1%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Most patients admitting relapse into drinking also had a positive breathalyser test (12/17). The comparison of self-reports with EtG measurement in urine showed poor agreement (both positive and both negative 84.3%). Cohen's kappa was 0.070 indicating discrepancy. And, indeed, in 262 cases (15.6%), the EtG test was positive, but patients denied drinking alcohol at weekend. Five patients (0.4%) admitted alcohol drinking during home stay but had negative EtG results. Three of these also had a positive alcohol breathing test.

The comparison of breath alcohol test with urinary EtG measurement revealed good agreement (both positive and both negative 84.2%). But, again, a Cohen's kappa of 0.056 indicated discrepancy. In 265 cases (15.6%) EtG test was positive, but breath alcohol test negative. In three cases (0.2%) only the alcohol breathing test was positive. These cases had rather high alcohol concentrations (mean 1.24 g/l), which was probably due to very recent alcohol consumption.

93.2% of the relapses were only detected by EtG and not by self-reports or breathalyser. Cohen's kappa consequently was 0.076 indicating no agreement.

DISCUSSION

The assessment of relapses is widely used as the most important outcome measure of alcohol dependence treatment. However, the definition of relapse varies in the literature (i.e. first consumption of any alcohol after therapy, several days of drinking a certain amount of alcohol, etc.).

Our data clearly demonstrate that (a) a considerable percentage of inpatients in an abstinence training programme have relapses during short-term home stays and (b) most of them would remain undetected if only breathalyser tests and personal interviews were used for detection.

This result is in accordance with some other studies (Wurst et al., 1999, 2000, 2003, 2008a; Junghanns et al., 2009; Mutschler et al., 2010; Dahl et al., 2011a,b; Lahmek et al., 2012) that also have shown that the measurement of urinary EtG allows an identification of covert relapse during treatment programmes. To our best knowledge our data are the first on a complete sample of inpatients attending a long-term treatment programme for abstinence on a voluntary basis.

In a previous study (Junghanns et al., 2009) of newly detoxified alcohol-dependent patients 13.5% of the first sample were already EtG positive before being discharged from hospital after a 3-week motivation enhancement training. At the follow-ups 3, 6 and 12 weeks after discharge, 12.2, 19.4 and 28.0%, respectively, of the patients coming to the follow-up and denying relapse were positive on urinary EtG. In a second sample, of those patients showing up for follow-up after 1 week and denying relapse, EtG was positive in four cases (17.4%). In contrast to these participants of an outpatient follow-up the rate of positive EtG tests in this study did not correlate with the time in treatment. This might be due to the very restricted availability of alcohol and the external control of abstinence during inpatient training.

In a study with a design comparable with ours (Lahmek et al., 2012) EtG was screened in 75 patients during a hospital-based treatment for an alcohol use disorder in France. During follow-up, EtG was detected in 14.6% of the 239 urine samples. Of the 22 patients with positive EtG, five (22%) also gave a positive breath alcohol test and 10 (45.5%) reported recent alcohol consumption; 12 (54.5%) had a negative breath alcohol test and declared no relapse. Apart from a higher rate of positive self-reports these results were similar to ours demonstrating that such data on hidden relapse might point to a more universal character of addictive patients' behaviour and not just be due to differences in treatment settings.

Dahl et al. (2011a) measured urinary EtG in outpatient treatment programmes for alcohol and drug dependence (n = 24). In 87% of the cases, the self-report information agreed with the EtG results (i.e. true positives and true negatives).

In our sample the agreement between the different measures was in the same range, but Cohen's kappa was low due to a considerable number of positive EtG cases without self-reporting of drinking.

Dahl et al. (2011b) compared urinary EtG measurement with self-reports for detection of drinking during outpatient treatment with acamprosate or placebo (n = 56). They found a reduction of positive EtG samples during treatment. But at the final day when drinking was denied, still 28% of the sample was EtG positive. In our sample there was also a relevant, but smaller proportion (15.5%) of patients having positive EtG tests while denying drinking of alcohol.

In two studies alcohol use among methadone maintenance patients was evaluated by direct ethanol metabolites and self-reports. Of the 14 participants reporting no alcohol intake during the previous week, four (28.5%) were urinary EtG positive (Wurst et al., 2008a). In another sample of 8 of 19 EtG positives (42.1%) had not reported any ethanol intake in the week prior to the study (Wurst et al., 2008b). Like in our sample in these samples of methadone maintenance patients a considerable proportion of patients denying to drink alcohol showed positive EtG test in urinary samples.

In two studies (Wurst et al., 2000, 2003) comparing the potential of several alcohol markers (i.e. MCV, CDT, EtG, PEth and breath ethanol) for detecting recent alcohol intake 14 of the 146 urine samples (9.6%) examined were positive for EtG, but breath ethanol in only one case (0.7%) (Wurst et al., 2003). These results revealing a higher rate of EtG positive cases than of breath alcohol positive cases agreed well with our data. In one study 6 of 107 patients (5.6%) without any clinical impression or routine laboratory findings indicating a relapse, urinary EtG test was positive (Wurst et al., 2000). In yet another study 6 of 106 patients (5.7%) were EtG positive (Wurst et al., 1999).

In sum, these studies and ours show that urinary EtG testing is a useful tool for objective identification of recent drinking in patients treated for alcohol dependence. However, the limitations of EtG as a marker of recent alcohol consumption have to be considered, i.e. the short period of detection after alcohol consumption (Wurst et al., 2004; Albermann et al., 2012a). In our sample four cases were not identified by the EtG test. Three of them had rather high alcohol concentrations (mean 1.24 g/l) in alcohol breathing test. This data may be interpreted as due to very recent alcohol consumption, which could not yet be assessed by EtG measurement. Another reason might be that the threshold for assessment of EtG in our sample was too high to give positive results in these cases.

In conclusion, we could demonstrate that urinary EtG monitoring significantly improved verification of abstinence in patients participating in long-term alcohol dependence treatment programmes. Without EtG assessment these patients could spend 3 days at home and return without evidence of
relapse in interviews or breathalyser tests thereby probably making treatment an utter failure. A routine assessment of urinary EtG immediately after return from outside activities might be a good ground for improvement of long-term abstinence rates as the early detection of relapse could allow modification of treatment in the interest of the patient such as increasing efforts for motivational change. A treatment aiming at abstinence of a patient who is pretending to be abstinent while drinking secretly certainly is counterproductive.

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Conflict of interest statement. None declared.

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