TREATMENT
Comparison of Two Oral Symptom-triggered Pharmacological Inpatient Treatments of Acute Alcohol Withdrawal: Clomethiazole vs. Clonazepam

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Abstract — Aims: To compare two inpatient symptom-triggered pharmacological treatments of acute alcohol withdrawal (AWS) (clomethiazole vs. clonazepam). Methods: Prospective observational comparison within a quality improvement project. Because of a need for extra precautions against complications such as seizures and severe respiratory complaints, patients with a history of withdrawal seizures or complications with clomethiazole in their history were automatically assigned to the clonazepam group. The remaining patients were alternately assigned either to the clonazepam group (n = 38 altogether) or the clomethiazole group (n = 36). Rescue medication could consist of adding either extra clonazepam or clomethiazole. Effectiveness was measured by Clinical Global Impression Scale, Revised Clinical Institute Withdrawal Assessment for Alcohol Scale, Mainz Alcohol Withdrawal Scale, Essen Self-Assessment-Alcohol Withdrawal and attrition rate. Safety and tolerability was estimated from adverse clinical events. Secondary outcome values were heart rate, blood and pulse pressure. Results: There were no significant differences between the treatments with respect to primary and secondary effectiveness measures, safety or tolerability or duration of medication treatment. Both reduced the severity of initial withdrawal symptoms below 20% up to the end of withdrawal medications. No withdrawal seizure or delirium occurred. Conclusion: Both score-driven treatments were equally effective, safe and well tolerated in this setting. This is the first study demonstrating the utility of clonazepam in the treatment of AWS syndrome.

INTRODUCTION
Acute alcohol withdrawal (AWS) of at least moderate severity requires pharmacological treatment to avoid severe complications such as epileptic seizures or delirium. Most effective treatments used benzodiazepines (Kosten and O’Connor, 2003) and in Europe also clomethiazole (Majumdar, 1991; Morgan, 1995). Approved strategies were ‘loading with diazepam’ and ‘fixed-dosing’ or ‘symptom-triggered’ treatments with highly potent benzodiazepines (Hall and Zador, 1997; Kosten and O’Connor, 2003; Kumar et al., 2009).

Symptom-triggered treatments reduced both withdrawal medication and duration of treatment when compared with fixed-dose regimes in two studies (Daeppen et al., 2002; Mayo-Smith, 1997). Symptom-triggered treatments were usually driven by withdrawal scores (Kosten and O’Connor, 2003). Most detoxification units have specially trained nurses who administer medication when the score builds up to at least moderate severity (e.g. ‘Revised Clinical Institute Withdrawal Assessment for Alcohol Scale’ (CIWA-Ar) >10 or ‘Score-Driven Treatment of Alcohol Withdrawal by Nurse Staff’ (SAB-P) >4 points), the score being used to determine an individual initial amount of withdrawal medication over the span of the first 24 or 48 h of treatment followed tapering off (‘score-driven treatment’) (Banger et al., 1997; McKay et al., 2004; Sullivan et al., 1989).

There are pros and cons regarding the usual benzodiazepines diazepam, chlordiazepoxide, lorazepam and oxazepam (Daeppen et al., 2002; Holbrook et al., 1999; Kumar et al., 2009; Mayo-Smith, 1997; Ntais et al., 2005). We have used clonazepam as an alternative over many years as it has a relatively long biological half-life, which is important in the prevention of withdrawal seizures. It also has several advantages for the management of AWS: its mainly renal elimination, no pharmacologically active metabolites, no capacity to induce cytochrome P-450, and no sequestration in brain tissue (Greenblatt et al., 1987; Pachecka et al., 1990).

Alcohol detoxification in Germany is traditionally managed with oral clomethiazole in symptom-triggered regimes, whenever possible, score-driven (Mundle et al., 2006). This study compares the effectiveness and tolerability of clonazepam to clomethiazole. We hypothesized that both score-driven pharmacological treatments are equally potent, safe and tolerable when simple precautions are taken.

MATERIALS AND METHODS
This was a prospective open study to compare the effectiveness, safety and tolerability of score-driven clomethiazole and clonazepam in the treatment of acute AWS. In order to avoid foreseeable complications (Booth and Blow, 1993; Duka et al., 2004; Majumdar, 1991), patients who reported prior withdrawal seizures or prior complications with clomethiazole were automatically assigned to the clonazepam group. The remaining patients were alternately assigned either to the clonazepam group or to the clomethiazole group. Subjects were inpatients suffering from alcohol-dependence (ICD-10: F10.25) who displayed at baseline a moderate AWS according to SAB-P >4 points (Banger et al., 1997). Further inclusion criteria were: age between 18 and 70, no relevant psychiatric and somatic co-morbid disorders requiring an acute intervention and stabilization including liver disease, no pregnancy, no delirium tremens, no severe cognitive deficits, no other substance-use disorders excluding tobacco, and breath alcohol concentration (BAC) ≤0.2%. Current use of the following medications was not allowed: benzodiazepines, clomethiazole, lithium, disulfiram, β-blockers, neuroleptics, anticonvulsants, antidepressants or...
z-drugs (e.g. zopiclone). Patients who were delirious, urine-screened positive for other substance use or were having moderate-to-severe respiratory complaints were excluded.

One capsule of clomethiazole (192 mg) was taken to be equivalent to 0.5 mg oral clonazepam. During the initial 24 h of the pharmacological treatment, the items tachycardia, hypertension, tremor, hyperhidrosis and anxiety were rated hourly by the nurse and added to a sum-score (SAB-P; Banger et al., 1997): patients had to reach 4–6 points in order to receive one capsule of clomethiazole (or 0.5 mg clonazepam), 7–9 points for two capsules (or 1 mg clonazepam) (Banger et al., 1997; Bonnet et al., 2003). The amount of medication required according to the sum-score within the first day (‘score-driven’ part) was given again on the next day but evenly distributed every 4–6 h. Thereafter, medication was reduced daily by two capsules of clomethiazole or 0.5 mg clonazepam (‘tapering-off’ part). The ‘tapering-off’ part was also characterized by: (i) three times daily checks of blood pressure and heart rate and (ii) sleeplessness, moderate mood-instability or restlessness was treated with the butyrophenone pipamperon (20–40 mg), if necessary, before resorting to rescue medication. In this case, rescue medication could consist of an additional dose of clomethiazole or clonazepam.

Data on demographics and alcohol history were recorded, and changes in CIWA-Ar (Sullivan et al., 1989), Mainz Alcohol Withdrawal Scale (MAWS; Banger et al., 1992), Clinical Global Impression Scale (CGI), Essen Self-Assessment-Alcohol Withdrawal (ESA; Banger et al., 2001), Hamilton Depression Scale (HAMD21item, Hamilton, 1960) and Hamilton Anxiety Scale (HAMA14item, Hamilton, 1959).

Primary effectiveness measures were effects on CIWA-Ar, MAWS and ESA. Measurements were made at baseline, Day 2, in the middle and at the end of the pharmacological treatment. Change of CGI was estimated from baseline to end. Furthermore, during the first 24 h of treatment, heart rate and blood- and pulse-pressure were frequently measured (secondarily effectiveness measures). Tolerability and safety was estimated by listing all adverse clinical events (ACEs). Routine laboratory results and electrocardiogram were carried out at baseline and at the end of the study.

Abstinence was verified due to a 24-h observation by the nursing staff and random breath alcohol checks. Nearly complete medication compliance was assured by ensuring that the medication was taken under observation and with a subsequent talk of at least 2 min with the investigators or staff. All patients received oral thiamine. They all had given informed consent. The project has been carried out in accordance with the Declaration of Helsinki and was approved by the local Ethics Commission.

Effectiveness was analyzed for the intention-to-treat sample, which consists of all included subjects. Missing data were substituted by carrying the last observation forward. Statistical tests on the outcome measures were performed using repeated measured analysis of variance with multivariate criteria. Results of between group comparisons at the respective time points will be displayed for illustrative purposes. Between-group comparisons were made using t-tests (Welch tests in case of significantly different variances), Fisher’s exact test (see secondary analysis) or χ² tests. Statistical software was SPSS Vers. 16. The significance level for all tests was 0.05.

RESULTS

The study was conducted in a detoxification unit of the Essen Department of Addictive Behaviour and Addiction Medicine between 2005 and 2007. A total of 74 patients were included (intention-to-treat sample). All were Germans with 31% (n = 23) females. Mean ± SD age was 42.5 ± 10.4 years. According to the protocol, 12 patients with withdrawal seizures in their history had to be automatically assigned to the clonazepam group. There were no patients reporting previous complications with clomethiazole. The remaining patients were assigned either to the clonazepam group (n = 38) or to the clomethiazole group (n = 36). There were no statistically significant differences in baseline characteristics between groups with the expected exception of seizure-and-related treatment history (Table 1, see Discussion).

Pharmacological treatment duration was 3.9 ± 2.8 days in the clomethiazole and 4.3 ± 2.6 days in the clonazepam group (P = 0.55). The entire inpatient treatment duration was 11.5 ± 9.0 days in the clomethiazole and 10.2 ± 7.8 days in the clonazepam group (P = 0.51). The dosage within the first 24 h after starting medication was 7.5 ± 5.1 capsules of clomethiazole and 2.8 ± 1.5 mg of clonazepam. One patient in each group did not need any medication.

Both treatments significantly reduced the severity of withdrawal symptoms, which was below 20% of the initial severity at the end of the treatments (Fig. 1, P < 0.001). There were no statistically significant differences in baseline characteristics (Table 1).

Table 1. Baseline characteristics and alcohol history data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clomethiazole</th>
<th>Clonazepam</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>36</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>41.3 ± 10.5</td>
<td>44.5 ± 10.4</td>
<td>0.38</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>9/27</td>
<td>14/24</td>
<td>0.37</td>
</tr>
<tr>
<td>ICD-10 criteria of alcohol-dependence (eight item)</td>
<td>7.4 ± 1.9</td>
<td>7.7 ± 1.7</td>
<td>0.46</td>
</tr>
<tr>
<td>BAC at baseline (%)</td>
<td>0.13 ± 0.11</td>
<td>0.18 ± 0.13</td>
<td>0.52</td>
</tr>
<tr>
<td>Daily alcohol consumption (g)</td>
<td>303 ± 140</td>
<td>326 ± 176</td>
<td>0.52</td>
</tr>
<tr>
<td>Years of drinking</td>
<td>14.8 ± 12.0</td>
<td>17.9 ± 10.7</td>
<td>0.25</td>
</tr>
<tr>
<td>Family history positive for alcoholism (yes/no)</td>
<td>13/23</td>
<td>18/20</td>
<td>0.33</td>
</tr>
<tr>
<td>Daily number of cigarettes</td>
<td>23 ± 14</td>
<td>26 ± 15</td>
<td>0.41</td>
</tr>
<tr>
<td>Prior delirium (yes/no)</td>
<td>1/35</td>
<td>2/36</td>
<td>&gt;0.9</td>
</tr>
</tbody>
</table>
| Prior epileptic seizures (yes/no)             | 0/33         | 12/26      | <0.001*
| Number of prior inpatient withdrawal treatments| 2.2 ± 2.5    | 12.5 ± 15.9| <0.001*
| Number of prior weaning therapies             | 0.5 ± 1.1    | 1.4 ± 1.5  | 0.01*
| Visiting self-helping groups (yes/no)         | 5/31         | 14/24      | 0.024*
| Compensated co-morbid mental diseases (yes/no) | 10/26        | 4/34       | 0.058|
| Compensated co-morbid somatic diseases (yes/no)| 5/31         | 2/36       | 0.21|
| MCV (fl)                                      | 93 ± 12      | 91 ± 10    | 0.28|
| GGT (U/l)                                     | 331 ± 488    | 186 ± 392  | 0.17|
| GPT (U/l)                                     | 74 ± 65      | 100 ± 123  | 0.26|
| Cholesterol (mg/dl)                           | 216 ± 47     | 216 ± 68   | >0.9|
| Triglycerides (mg/dl)                         | 153 ± 102    | 158 ± 118  | 0.87|
| Magnesium (mM)                                | 0.80 ± 0.2   | 0.81 ± 0.22| 0.82|

*Significant differences between the treatment groups according to t-test (Welch test in case of unequal variances) or χ² test (P < 0.05).

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were no significant differences between the treatments according to primary effectiveness measures (no significant group * time interaction for MAWS, P = 0.67; CIWA-Ar, P = 0.83; ESA, P = 0.37; CGI, P = 0.73; see Fig. 1) or to secondary effectiveness measures (Fig. 2). Additionally required pipamperon did also not differ significantly between the groups (P = 0.51). No ‘rescue’ clomethiazole or clonazepam was required in either group.

In the clomethiazole group, HAMA and HAMD-scores improved from 16.4 ± 9.2 and 15.2 ± 6.9 points at baseline to 3.9 ± 5.2 (P < 0.001) and 3.2 ± 3.7 (P < 0.001) points at the end of the study, respectively. Similarly in the clonazepam group, HAMA and HAMD-scores improved from 18.1 ± 9.7 and 17.8 ± 8.4 points at baseline to 3.2 ± 3.6 (P < 0.001) and 2.8 ± 3.3 (P < 0.001) points at the end of the study, respectively. There were no significant time * group interactions for either measure (P = 0.25 for HAMA and P = 0.093 for HAMD).

No withdrawal seizure or delirium occurred. Two (5.5%) and four (10.5%) patients (P = 0.36) dropped out in the clonazepam and clomethiazole group, respectively, due to withdrawal of consent (clonazepam) or moderate but increasing nasal irritation (clomethiazole).

A secondary analysis was carried out for those patients without epileptic seizures in their history: 26 patients from the clonazepam group and all 36 patients from the clomethiazole group. Statistical differences according to alcohol history data (c.f. Table 1) disappeared: numbers of patients with prior detoxification treatments and attendance at self-help groups now did not differ between the groups (P = 0.19 and P = 0.11). The average inpatient treatment duration was 10.5 ± 8.7 days for the clonazepam group and 11.5 ± 9.0 days for the clomethiazole group (P = 0.67). Mean length of

Thirteen patients (36.1%) in the clomethiazole and 15 patients (35.4%) in the clonazepam group had new-onset ACEs throughout the whole study: primarily dizziness, vertigo, insomnia and mood instability, all homogeneously distributed between the groups (Table 2). Seven and nine patients had more than three complaints in the clomethiazole- and clonazepam group, respectively. Nasal irritation appeared only in the clomethiazole group. All other ACE were judged to be mild, and were transient with the exception of the four moderate nasal irritations leading to drop outs. No serious ACE occurred, and laboratory results as well as electrocardiogram were not significantly different between the groups.

Fig. 1. Primary effectiveness measures. From baseline to the end of the pharmacological treatment, both treatments reduced the scores to all times of measure (P<0.001). There were no statistically significant differences between the groups (P>0.05). Pharmacological treatment duration was 3.9 ± 2.8 days in the clomethiazole and 4.3 ± 2.6 days in the clonazepam group (day end). Day mid was at 2.3 ± 1.5 (clomethiazole) and 2.4 ± 1.2 days (clonazepam group) (both P>0.5). The study also used the MAWS used in Germany so that a comparison with the international standard scale (CIWA-Ar) was possible.
medication was 3.7 ± 2.0 days in the clonazepam group and 3.9 ± 2.8 days in the clomethiazole group (P = 0.75). A premature treatment termination was seen in two patients treated with clonazepam (7.7%) compared with four (11.1%) in the clomethiazole group (P = 1.0, Fisher’s exact test). Regarding the primary outcome parameters, the symptom reduction was similar in both groups (no significant time *group interaction; MAWS, P = 0.33; CIWA-Ar, P = 0.2; ESA, P = 0.19; CGI, P = 0.56).

### DISCUSSION

This prospective comparative study shows that score-driven clomethiazole and clonazepam were (i) equally effective in the treatment of acute AWS and (ii) safe and well tolerated under simple precautions. If those patients with epileptic seizures under clomethiazole in their history were excluded in a second analysis, there are still no differences between the treatment groups.

Benzodiazepines have not been often compared directly with clomethiazole in the treatment of acute AWS, and no score-driven comparison of both first-line withdrawal medications exists so far (Bonnet et al., 2009; Ntais et al., 2005). A few previous fixed- or flexible-dosing regimes demonstrated an equal efficacy and safety of clomethiazole and the benzodiazepines chlordiazepoxide (Burroughs et al., 1985; Lapierre et al., 1983; McGrath, 1975), alprazolam (Tubridy, 1988) and diazepam (Lucht et al., 2003), which was confirmed in a recent meta-analysis (Minozzi et al., 2010). These drugs have several pharmacological limitations that could reduce their flexibility in modern symptom-triggered withdrawal management, such as induction of cytochrome P-450, psychoactive metabolites and greater hepatic elimination (Greenblatt et al., 1987; Pachecka et al., 1990). We have used clonazepam as an alternative for many years as it is free of these limitations (Greenblatt et al., 1987; Pachecka et al., 1990). The biological half-life of 22–32 h is suited to

Table 2. ACE throughout the whole study

<table>
<thead>
<tr>
<th></th>
<th>Clomethiazole (n = 36)</th>
<th>Clonazepam (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ACEa</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Dizziness/somnolence</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Vertigo/ataxia</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Dysphoria/mood instability</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Nasal irritation (tingling in the nose/ sneezing)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Restlessness/anxiety</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Seizure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Delirium</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Several complaints at one patient are recorded in most cases.
prevent withdrawal seizures (Ahmed et al., 2000; Hillbom et al., 2003; Ntais et al., 2005). In a previous observational study, we saw with clomethiazole, which has a much shorter biological half-life (3–6 h), 11 (7.5%) withdrawal seizures within 146 score-driven treatments (Banger et al., 1997). This seizure rate might have been based upon clomethiazole’s shorter biological half-life. Additionally, it is possible that it could have resulted from inadequate compensation of the AWS due to the symptom-triggered regimen. Although seizure rates near 10% were not the exception even with the AWS, because such a history has been consistently related to complications in recurring withdrawals (Booth and Blow, 1993; Duka et al., 2004). This resulted in the clonazepam group having more patients who had reported previous detoxifications and attendance at self-help groups (Table 1) which would seem to suggest that these patients were more severely dependent on alcohol than the typical patient allocated to the clomethiazole group. However, laboratory results and the number of fulfilled dependence criteria according to ICD-10 did not support this assumption (Table 1). Taking into account that the reported number of previous detoxifications and attendance at self-help groups was found to be related to seizure-history in our secondary analysis one might speculate on more intense openness or motivational state in the clonazepam group due to the experience of withdrawal seizures.

Another precaution was established in connection with adverse events due to clomethiazole with respect to putative fatal respiratory complaints (Majumdar, 1991; Morgan, 1995). We had already excluded patients from the study when even moderate irritations developed in the respiratory tract because such nasal irritations sometimes culminate in allergic tracheobronchial hypersecretion (Spies et al., 1995).

In the clomethiazole group, four (10.5%) patients were withdrawn because of worsening sneezing and tingling in their noses. No patient developed a severe respiratory complaint. Nearly 36% of patients in each group had unspecific adverse events. The great majority (96.6%) were mild and transient. In the clomethiazole group, four (10.5%) patients were withdrawn because of worsening sneezing and tingling in their noses. No patient developed a severe respiratory complaint. Nearly 36% of patients in each group had unspecific adverse events. The great majority (96.6%) were mild and transient. Safety of both score-driven treatments was further confirmed by the absence of withdrawal seizures and deliria. However, it should be noted that the average withdrawal severity of the investigated population was moderate even at baseline (CIWA-Ar: 12.1 ± 7.6 points) and so the probability of complications would be expected to be less (Hillbom et al., 2003; Kosten and O’Connor, 2003).

As stated in the Materials and Methods section, sleeplessness, moderate mood-instability or restlessness occurring in the ‘tapering off-part’ of the study was treated first with pipamperon. Although not validated for the treatment of AWS so far, in our hands pipamperon seemed helpful in avoiding additional rescue medication with clomethiazole or clonazepam.

Regarding the general applicability of our findings it should be mentioned that symptom-triggered regimens are usually only used in settings where there is the 24-h clinical coverage and not used in the out-patient or home setting. Likewise, clomethiazole and clonazepam would not be ideal for use in these settings because of possible serious side effects when taken together with alcohol and because of their addictive potential especially in less tightly controlled intake (Daeppen et al., 2002; Kosten and O’Connor, 2003; Mayo-Smith, 1997).

This study is limited by its small size which presumably did not allow for finding any patient with prior or current severe complications with clomethiazole. The open and not blinded design might have biased effectiveness outcome due to expectations e.g. resulting from the establishment of precautions. Nevertheless, this is the first study demonstrating the utility of clonazepam in the treatment of acute AWS.

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