TREATMENT

Alcohol Withdrawal Syndrome: Symptom-Triggered versus Fixed-Schedule Treatment in an Outpatient Setting

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Abstract — Aims: To investigate whether, in the treatment with chlordiazepoxide for outpatient alcohol withdrawal, there are advantages of symptom-triggered self-medication over a fixed-schedule regimen. Methods: A randomized controlled trial in outpatient clinics for people suffering from alcohol dependence (AD) and alcohol-related problems; 165 adult patients in an outpatient setting in a specialized alcohol treatment unit were randomized 1:1 to either a symptom-triggered self-medication or tapered dose, using chlordiazepoxide. Alcohol withdrawal symptoms, amount of medication, duration of symptoms, time to relapse and patient satisfaction were measured. Patients assessed their symptoms using the Short Alcohol Withdrawal Scale (SAWS). Patient satisfaction was monitored by the Diabetes Treatment Satisfaction Questionnaire. We used the Well-Being Index and the European addiction severity index for the 1-year follow-up. Results: We found no differences in the quantity of medication consumed, time to relapse, well being or treatment satisfaction. Conclusion: Symptom-triggered self-medication was as safe as fixed-schedule medication in treating outpatients with AD and mild to moderate symptoms of AWS. The SAWS is a powerful monitoring tool, because it is brief and permits the subject to log the withdrawal symptoms.

INTRODUCTION

Ninety-three percent of the Danish population above the age of 15 consumes alcohol on a regular basis and 860,000 Danish citizens have an alcohol intake exceeding the sensible drinking limits set to 14 drinks per week for women and 21 drinks per week for men (one drink equals 12 g of pure alcohol), according to the National Board of Health. A total of 585,000 adults fulfill diagnostic criteria for hazardous alcohol consumption and 140,000 adults for alcohol dependence (AD), and these individuals are especially at risk of developing the alcohol withdrawal syndrome (AWS).

There is general agreement that AWS is a condition that occurs after shorter or longer periods of heavy alcohol intake and is caused by neurophysiologic changes in the brain (McKeon et al., 2008). The AWS consists of a cluster of symptoms developing within 1–3 days after the last drink. In the mild form of the syndrome tremor, hyperactivity, anxiety, tachycardia, sweating and sleep disturbances are seen (Table 1). Without treatment, patients may develop more severe symptoms like hallucinations, seizures and delirium tremens, which is a potentially lethal condition with a mortality rate of 1–5% (Becker, 1998) even when treated. Adequate treatment of AWS is important for the adherence of patients with alcohol addiction to treatment as patients’ fear of getting symptoms can be an obstacle to seeking alcohol treatment (Becker, 1998; Gossop et al., 2002; Malcolm et al., 2000). A sufficient treatment programme for detoxification and withdrawal can reduce the severity of future attacks of AWS (reduce kindling: Becker, 1998; Erwin et al., 1998) and motivate the patients’ determination to move on to continuous alcohol treatment and a period of abstinence.

Pharmaceutical treatment is important (Whitfield et al., 1978) and benzodiazepines have been proved efficient in treating AWS in several studies; benzodiazepines can prevent seizures and delirium tremens (Holbrook et al., 1999; Ntais et al., 2005). Furthermore, an antidote is available and has made benzodiazepines the drugs of choice for treatment of AWS (National Board of Health, 2006; National Board of Health, 2006 2729 /id). In Denmark, most patients with AWS are treated on an outpatient basis either in alcohol treatment units or by their general practitioner, while patients with more severe symptoms are treated as inpatients in medical or psychiatric hospitals or departments.

In the Alcohol Unit at Hvidovre Hospital, we used chlordiazepoxide according to a fixed-dosage schedule, tapering the dose to zero over 8–10 days. No monitoring or systematic documentation of symptoms was used unless the patient complained of continuing clinical symptoms causing the dose to be changed. A fixed-dosage scheme suffers from the lack of individualized treatment, lack of monitoring and documentation of symptoms, and a paternalistic view hampering the patients’ motivation for continued adherence to treatment. Studies from abroad (Jaeger et al., 2001) indicate successful inpatient treatment of AWS using a symptom-triggered schedule rather than a fixed-schedule medication. Some studies suggest that even outpatients may profit from a symptom-triggered medication therapy in terms of motivating patients for enrolment in alcohol treatment (Holbrook et al., 1999; Ntais et al., 2005). Therefore, it is important to implement a monitoring instrument in the treatment of AWS in outpatient settings. A number of scales have been developed to monitor the AWS in inpatient settings but only the Short Alcohol Withdrawal Scale (SAWS) developed by Gossop et al. 2002 has been used and validated in an outpatient setting. No consensus exists regarding a standardized monitoring of AWS (Saitz and O’Malley, 1997). The aims of this study were to test the hypotheses that a symptom-triggered self-medication and self-monitoring of...
Table 1. The SAWS

<table>
<thead>
<tr>
<th>Item</th>
<th>None (0)</th>
<th>Mild (1)</th>
<th>Moderate (2)</th>
<th>Severe (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxious</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling confused</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Miserable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems with memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor (shakes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart pounding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td></td>
<td></td>
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</tbody>
</table>

The patients fill in the SAWS by ticking the appropriate box that best describes each of the 10 symptoms in the previous 24 h. Each item is scored on a four-point scale: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms. The scores are summed up to give a total score.

AWS in outpatients would reduce the intake of medication and the duration of symptoms, prevent relapse and increase patient satisfaction compared with a fixed-schedule medication.

METHODS

This study took place in public outpatient services in five Copenhagen hospitals with affiliation to the medical and psychiatric emergency rooms with 10–15 patients admitted per day with alcohol-related problems. The patient population and design of the study have previously been described in detail (Elholm et al., 2010).

In brief, consecutive outpatients aged 18 years or more were consecutively assessed for inclusion. All patients fulfilling ICD-10 diagnostic criteria for AD and the AWS were evaluated by means of the European addiction severity index (EuropASI). Patients were included if abstinence from alcohol had lasted for <72 h prior to inclusion. Patients who had been treated for AWS within the last week, who had a history of three or more attempts of outpatient detoxification within the last month, allergy towards chlordiazepoxide or using drugs with known interaction with chlordiazepoxide were excluded. Furthermore, patients were excluded if they had known severe psychiatric illness including the Wernicke/Korsakoff Syndrome, suicidal behaviour, severe cardiac or liver disease, type 1 diabetes, as well as pregnant or breastfeeding women and fertile women without safe contraception. Finally, patients were excluded if the breath alcohol concentration was >10 mg%.

After informed consent included, patients were randomized to fixed-schedule treatment or symptom-triggered treatment with chlordiazepoxide. Randomization was performed as block randomization, stratified according to the SAWS score at the baseline (score < 12 or score ≥ 12). Sealed envelopes were administered by a secretary instructed to hand out the envelope with the lowest number from the block indicated.

Fixed-schedule treatment
In the fixed-schedule group, 200 mg chlordiazepoxide was prescribed as a starting dose with daily tapering of the dose with 25 mg for patients with a SAWS score ≥ 12 at the baseline. For patients scoring SAWS <12 at the baseline, the starting dose of chlordiazepoxide was 80 mg with daily tapering of the dose with 10 mg. Patients were instructed to take the medication in fixed daily doses as prescribed and offered an extra dose if necessary.

Symptom-triggered treatment
In the symptom-triggered group, patients scoring ≥ 12 at the baseline were prescribed a maximum daily dose of chlordiazepoxide of 300 mg for 10 days. For patients scoring SAWS <12, the maximum daily dose was 120 mg for 10 days. These patients administered the medication according to their symptoms with the possibility of taking extra doses if necessary. All patients were instructed to bring back any unused tablets.

Follow-up
Patients attended the outpatient clinic daily preferably for 10 days. To support abstinence, patients in both arms were offered concurrent treatment with disulphiram and/or acamprosate, and monitored by breath alcohol levels. All patients filled in the SAWS daily until they terminated treatment. SAWS contains the 10 items shown in Table 1. Each symptom was scored 0–3 points retrospectively for the last 24 h (0 = no symptoms, 3 = severe symptoms). Patients were instructed to fill in the SAWS every day, preferably when they woke up and to bring the SAWS to the outpatient clinic. The points were transferred to their medical record. Treatment was to be continued for at least 5 days and symptoms were monitored for 10 days.

The primary trial endpoints were time to SAWS score <12 and time to SAWS score <6.

Secondary endpoints were time to relapse, defined as time to interview or questionnaire-monitored first drink.

Patients were followed for 1 year after randomization. Patients self-monitored their experience with adverse reactions from chlordiazepoxide on Day 10 on a 12 cm Visual Analogue Scale; 12 cm, 0–4 cm indicated light discomfort, 4–8 cm some discomfort and 8–12 cm massive discomfort. This scale was supplemented with the nurses’ clinical evaluation on Day 10.

EuropASI was used to monitor the impact of alcohol on daily life (baseline, 3, 6 and 12 months) (Scheirich et al., 2000). We used the Well-Being Index (WHO-5) well-being scale to monitor patients’ well-being during Days 1–14 and every 3rd month until 1 year after randomization (Bonsignore et al., 2001). The scale contains five questions about patients’ well-being graduated from 0 to 5. The scores were added and multiplied by 4. The scale ranges from a minimum of 0 to a maximum of 100 with scores <50 indicating low well-being.

Patient satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ; Bech et al., 2003). The scale contains six questions and each question was scored from 0 to 6, where 0 indicates ‘very unsatisfied with treatment’ and 6 indicates ‘very satisfied with treatment’.
**Ethical approval**

All patients gave their informed consent to their participation, and the study was performed in accordance with The Declaration of Helsinki. The project was approved by The Danish National Committee on Biomedical Research Ethics, (ref. no.01–063/03), The Danish Medicines Agency (ref. no. 2612–2264) and the Danish Data Protection Agency (ref. no. 2003–41–2937).

**Statistical methods**

Data were analysed according to the principles of intention to treat. Non-parametric statistics were used in comparing continuous data, and the \( \chi^2 \) test was used for bivariate statistics. The level of significance was set to 0.05.

The primary endpoint was defined from the questionnaire data as a time-to-event endpoint. An event time was defined as a time-to-event endpoint. An event time was defined for the patient as the first day he or she had a SAWS of less than or equal to a pre-specified cut-point. If the patient experienced a SAWS score below the cut-points at one of the days, the patient was registered as having had an event. If not, the patient was censored, and the number of days the patient had been in the trial was registered. Five variables were subsequently used as covariates in a survival analysis, and the log-rank test was used to evaluate the significance of the effect of the covariates on the endpoint. Likelihood ratio tests for different treatment effects in subgroups were also carried out.

Mann–Whitney’s non-parametric test was used to compare the accumulated use of tablets, side effects and quality of life endpoints between the two treatment groups.

**RESULTS**

One hundred and fifty-three randomized patients completed the study (Fig. 1). We excluded eight patients due to the use of concurrent medication or illicit drugs. Two patients wished to be anonymous. One patient had trouble understanding the SAWs and one had major depression.

Patient characteristics did not differ significantly across the two treatment groups as seen from Table 2 although a slightly more number of patients in the symptom-triggered group lived alone (\( P < 0.05 \)).

Time to SAWs score \( \leq 12 \) (\( P = 0.924 \)) and 6 (\( P = 0.091 \)), respectively, did not differ between the two treatment groups as displayed in Fig. 2. In men, the time to reach SAWs score \( \leq 12 \) was significantly longer than in women (\( P = 0.043; \) data not shown), and in patients with an alcohol intake \( <20 \) drinks/day the time to SAWs \( \leq 12 \) (\( P = 0.017 \)) and \( \leq 6 \) (\( P = 0.034 \)) were significantly shorter compared with those with an alcohol intake \( >20 \) drinks/day (Fig. 3).

The median cumulated dose of chlordiazepoxide was 725 mg in the symptom-triggered group and 875 mg in the fixed-schedule group. This difference was minimal and not statistically significant (Table 3). Likewise, median side-effect scores did not differ significantly between the treatment groups (Table 3).

According to the WHO-5 well-being scale, most individuals scored \( <50 \) at inclusion, which is a well-known experience. At Day 14, most individuals scored \( >50 \), and the median increase in the WHO-5 score was 32 and 16 in the symptom-triggered and fixed-schedule group, respectively, and these differences were not significant (Table 3).

Furthermore, patient satisfaction (DTSQ score) did not differ significantly between groups (Table 3). We tested for different treatment effects in men and women (interaction) and found a slightly better effect of symptom-triggered treatment in men compared with men for time to SAWs score \( <12 \) (likelihood ratio test; \( P < 0.043 \)) and time to SAWs score \( <6 \) (likelihood ratio test; \( P < 0.078 \)), while there was no significant interaction between treatment and age, number of drinking days or amount of alcohol intake (\( P > 0.05 \)).

Forty six patients in the symptom-triggered group and 45 patients in the fixed-schedule group relapsed within the first year. No difference in time to relapse was observed (Table 3), and no statistical differences were observed.

Table 2. Demographic and data on alcohol variables including ASI alcohol score

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Symptom-triggered (( n = 78 ))</th>
<th>Fixed-schedule (( n = 75 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>87.2</td>
<td>80</td>
</tr>
<tr>
<td>Age, years median (range)</td>
<td>49 (20–68)</td>
<td>49 (20–68)</td>
</tr>
<tr>
<td>Civil status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living together</td>
<td>51</td>
<td>70</td>
</tr>
<tr>
<td>Living alone</td>
<td>49</td>
<td>30</td>
</tr>
<tr>
<td>Job situation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Job last 30 days</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Other income</td>
<td>55</td>
<td>52</td>
</tr>
<tr>
<td>Mild AWS (SAWS ( &lt;12 ) (%)</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>Moderate AWS (SAWS ( \geq 12 ) (%)</td>
<td>76</td>
<td>73</td>
</tr>
<tr>
<td>Alcohol history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Units per day (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 20 )</td>
<td>68.9</td>
<td>54.8</td>
</tr>
<tr>
<td>( &gt;20 \leq 30 )</td>
<td>20.3</td>
<td>23.3</td>
</tr>
<tr>
<td>( &gt;30 )</td>
<td>10.8</td>
<td>21.9</td>
</tr>
<tr>
<td>Alcohol intake continuously (days) median (range)</td>
<td>30 (1–365)</td>
<td>25 (2–365)</td>
</tr>
<tr>
<td>Money used on alcohol last 30 days; DKK median (range)</td>
<td>2547 (0–10,000)</td>
<td>2948 (0–30,000)</td>
</tr>
<tr>
<td>ASI composite score alcohol median (inter-quartile range)</td>
<td>0.65 (0.49–0.79)</td>
<td>0.68 (0.51–0.79)</td>
</tr>
<tr>
<td>Years of alcohol dependency, median (range)</td>
<td>8 (1–34)</td>
<td>6 (1–37)</td>
</tr>
<tr>
<td>( \leq 5 ) years of alcohol dependency (%)</td>
<td>47.9</td>
<td>46.7</td>
</tr>
</tbody>
</table>

Only significant difference between groups was civil status (\( P < 0.05 \)). Otherwise none of the observed differences were significant (\( \chi^2 \) test or Mann–Whitney test whenever applicable).

*\( P < 0.05 \).

DKK, Danish kroner.
between groups when time to relapse was plotted in a Kaplan–Meier plot (Fig. 4). One year after inclusion, 16 and 25%, respectively, of the symptom-triggered and fixed-dose groups were still under disulphiram treatment and 26 and 19%, respectively, received selective serotonin reuptake inhibitor (SSRI) treatment. None of the patients were still under treatment with acamprosate or naltrexone.

**DISCUSSION**

We did not find any difference in time to relapse between symptom-triggered and fixed-schedule treatment groups, and patients were equally satisfied.

Patients with an alcohol consumption >20 units on a daily basis were at a greater risk of having withdrawal symptoms for a longer period than those with a lower consumption. Males are at greater risk for experiencing AWS. The fact that women constituted only 20 per cent of our study population may partly explain this finding. A recent study has shown that women more easily develop alcohol dependency with a lower consumption of alcohol compared with men. Other explanations could be that the duration of alcohol consumption prior to inclusion was shorter in women.

Benzodiazepines are the drugs of choice for the treatment of AWS as shown in numerous randomized controlled trials (RCT), systematic reviews and meta-analyses (Holbrook et al., 1999; Mayo-Smith et al., 2004; Ntais et al., 2005).

In inpatients, an RCT showed that symptom-triggered administration of benzodiazepines was better than fixed-dose administration with regard to the total administered dose as well as the duration of treatment (Saitz et al., 1994). In
This generally positive result of symptom-triggered treatment could not be confirmed in the present study, as we did not observe any significant difference in the total consumption of chlordiazepoxide between the two groups. One of four patients had mild AWS, defined as a SAWS score <12 when they were included in the study. The severity of AWS was equally distributed in the two treatment groups. Some patients may have had treatment for alcohol withdrawal from an outpatient clinic or from a hospital stay prior to inclusion into the study. This may have influenced our results. However, from an ethical point of view, we found it of importance that patients be sober when receiving the information about the study and the SAWS and giving their informed consent.

The WHO-5 well-being scale was easy to administer for the staff and patients. We used the DTSQ on Day 10 for the measurement of patient satisfaction. A repetition of the DTSQ after 4 weeks illustrating the development in patient satisfaction would have strengthened our study. The DTSQ was developed for patients with a chronic disease as type 1 diabetes. The results are used to calculate how well patients cope with their disease. We chose DTSQ because it was easy and quick to administer, and because diabetes and alcohol dependency share the elements of chronic disease and issues of self-control. There were no significant differences between the two treatment groups in DTSQ scores. The high scores may indicate a ceiling effect as has been described in other studies (Bradley et al., 2007). Therefore, we are sceptical as to the future use of this questionnaire in patients with alcohol addiction. DTSQ should be supplemented with other measures of patient satisfaction with treatment, something we discovered in the literature. On several meetings with the nurses in the five alcohol units, we had reports that patients were satisfied with the implication of their treatment. They also appreciated the self-assessment of their symptoms using the SAWS, and the nurses found that the SAWS was a valuable tool for educating the patients in taking care of their health and symptoms during the treatment. These data were not picked up by the formal DTSQ. Modern treatment of AD and its consequences is a prolonged process, while treatment of AWS is short but important because sufficient treatment in the acute phase will motivate the patients’ decision to stay sober much easier as well as sufficient treatment of AWS may reduce future complications. Many patients have experienced several episodes of AWS, and the SAWS provides an easy and safe way of self-monitoring and a good basis for administration of AWS medication focusing on the individual. While the SAWS and symptom-triggered treatment did not prove to have an advantage, the use of SAWS helps in documenting AWS and its treatment.

This is the first time that the SAWS has been tested in an outpatient setting.

Outpatient medical detoxification is an effective, safe and low-cost treatment for patients suffering from mild-to-moderate AWS which can have a wide reach, although rating procedures cannot replace medical staff evaluation.

**CONCLUSION**

This study showed high patient and staff satisfaction and high compliance with self-monitoring of symptoms using the
SAWS. Symptom-triggered medication is as effective and safe as the standard fixed-schedule treatment we use today.

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