INTRODUCTION

The alcohol withdrawal syndrome (AWS) involves a range of neurotransmitter circuits that are implicated in alcohol tolerance reflecting a homeostatic readjustment of the central nervous system (CNS) (De Witte et al., 2003; Nutt, 1999), involving reduced brain γ-aminobutyric acid (GABA) levels, GABA-receptor sensitivity (Dodd et al., 2000; Gilman et al., 1996) and activation of glutamate systems (Glue and Nutt, 1990; Sanna et al., 2004; Tsai et al., 1995; Tsai and Coyle, 1998). These alterations are believed to be mainly responsible for the occurrence of withdrawal seizures (WS) and/or delirium tremens (DT) and have considerable impact on morbidity and mortality of AWS (Ferguson et al., 1996; Mayo-Smith et al., 2004; Saiz, 1995; Victor, 1966).

Both benzodiazepines (BZD) and clomethiazole (CMZ) have proved to be effective in ameliorating AWS symptoms, preventing seizures and forestalling progression to DT, and therefore, are considered first-line agents in the treatment for AWS (Brewer, 1995; Mayo-Smith, 1997; Schuckit et al., 1995). While effectiveness is supported by extensive literature, their use is limited by their potential for abuse, psychomotor sedation, cognitive impairment and pharmacological interaction with alcohol (Ait-Daoud et al., 2006; Lum et al., 2006). In the light of these limitations, antiepileptic drugs (AEDs) have attracted attention in the past two decades, and lamotrigine, topiramate, gabapentin, pregabalin, vigabatrin, oxcarbazepine, levetiracetam, carbamazepine (CBZ) and valproate (VPA) have emerged as possible alternatives or adjuncts to BZD or CMZ (Ait-Daoud et al., 2006; Bonnet et al., 2009; Croissant et al., 2009; De Sousa, 2010; Krebs et al., 2006; Lum et al., 2006; Malcolm et al., 2001; Muller et al., 2010). CBZ and VPA have the advantage that they have been in widespread clinical use for the treatment of AWS for around three decades (Bastie, 1970; Brune and Busch, 1971) and because their clinical effectiveness in ameliorating AWS has been shown in controlled studies (Lucht et al., 2003; Lum et al., 2006; Malcolm et al., 2001; Reoux et al., 2001). Both of these drugs may be as effective as BZD or CMZ in reducing the severity of AWS (at least in mild-to-moderate forms) and are even more potent regarding their anti-seizure property (Lambie et al., 1980; Stuppaack et al., 1992; Wilbur and Kulik, 1981).

Treatment of moderate-to-severe AWS in our department has traditionally been performed using a symptom-triggered detoxification protocol (see METHODS section) with the adjunctive use of CBZ to prevent WS, even if the evidence of using AEDs during AWS is inconsistent (Brathen et al., 2005; Minozzi et al., 2010; Polycarpou et al., 2005). However, increasing data from the literature suggested that additional CBZ treatment may be more frequently related to intolerable side effects and may be less effective compared with VPA to prevent WS or progression of AWS to DT (Bayard et al., 2004; Hillbom et al., 1989; Longo et al., 2002; Lum et al., 2006; Malcolm et al., 2001; Reoux et al., 2001). This led us to adapt our established treatment protocol in 2006, replacing CBZ with VPA but using an otherwise unchanged treatment regimen.

The objective of this study was to compare two historical cohorts of inpatients suffering from moderate-to-severe AWS who received either CBZ or VPA in addition to a standardized symptom-triggered therapy. This investigation mainly focuses on the incidence of complications (WS, DT) and acceptability of these drugs as well as some clinical parameters characterizing the course of AWS.

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METHODS

Patient selection

A retrospective chart review was performed including all patients admitted to our department for alcohol detoxification from January 2000 until December 2009. Patients were identified through a computerized search of discharge diagnoses (International Classification of Diseases [ICD]-10) with the code for alcohol intoxication (F10.0), withdrawal syndrome (F10.3) or alcoholic DT (F10.4). All patients included fulfilled the ICD-10 criteria of alcohol dependence (F10.2).

Patients with alcohol intoxication who did not experience AWS severe enough to be treated pharmacologically were excluded. The severity of AWS was determined in analogy to the revised Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) scale (Sullivan et al., 1989) by a validated and standardized 11-item withdrawal score (AWS score) including six somatic and five mental items with a maximum score of 33. A mild AWS (correspondingly CIWA-Ar <8) is defined as a score <6; a moderate AWS (correspondingly CIWA-Ar 8–15) is defined as a score between 6 and 9; and a severe AWS (correspondingly CIWA-Ar >15) is defined as a score >9 (Wetterling et al., 1997).

Other reasons for exclusion were dependence on BZD (according to ICD-10 criteria), positive screening results for opiates, amphetamines and cocaine (occasional urine drug screening at admission), incomplete or inaccessibility of physical charts and lack of adequate documentation to support the diagnosis of AWS or related complications.

A review was made of 2691 charts. On the basis of the above criteria, we excluded 97 patients due to co-dependence on illegal drugs, BZD or other substances; 228 patients who experienced only mild AWS (e.g. AWS score <6); 966 patients with uncomplicated alcohol intoxication; 82 patients with prematurely discontinued therapy (e.g. the patient left hospital against medical advice); 310 patients who did not receive therapy as defined in the detoxification protocol; and 181 patients whose charts were incomplete or not adequately documented. The pattern of reasons for exclusion did not differ in any relevant way between the two treatment groups. This resulted in 827 patients (n = 374 in the CBZ group; n = 453 in the VPA group) who were finally included in the study. Given the retrospective nature of this study, it was exempt from assessment by the institutional ethics committee.

Detoxification protocol

All patients received score-guided pharmacological treatment with orally administered CMZ (up to 4725 mg/day) to achieve a minimum of withdrawal symptoms as evaluated with the AWS score (usually every 2–4 h). Clonidine (up to 600 µg/day) was administered in the presence of noradrenergic hyperactivity and haloperidol (up to 15 mg/day) was given to treat significant hallucinations. Treatment with an AED started simultaneously with CMZ. Specifically, sustained-release CBZ was administered three times a day (200 mg, each) or twice daily (400 mg, each) and sustained-release VPA was given three to four times a day (300 mg, each). Every patient received 100 mg oral thiamin thrice daily. The decision to start AWS treatment was score-guided (AWS score ≥6) and independent of the breath alcohol concentration at this time. The criteria definition for both AWS and DT, the treatment protocol (except for the given AED), as well as the standard of care did not change during the period of the study.

Intensive care unit (ICU) transfer and intensive care treatment were initiated in cases of DT with massive vegetative dysfunction, severe agitation requiring restraints and sedation as well as other life-threatening complications (e.g. sepsis, need for mechanical ventilation, etc.) commencing during AWS. In these cases, given the inability to swallow tablets, for safety reasons, treatment consisted of symptom-triggered intravenous midazolam, clonidine, haloperidol and thiamin. Due to the potent anti-seizure activity of intravenous midazolam, treatment with CBZ or VPA was discontinued. The onset of DT with the need for ICU therapy was defined as a major complication of AWS. Consequently, consecutive complications (e.g. WS) were no longer considered, as the medication used at the ICU would have influenced these outcome variables.

Data collection

The charts were reviewed to obtain data on demographics, withdrawal history, alcohol or drug use and laboratory data on admission, blood pressure and heart rate, both on admission and during the course of AWS, as well as medical and psychiatric co-morbidities. For patients with liver cirrhosis, the severity of liver disease was coded according to Child’s classification. The amount of daily alcohol consumption reported by the patient (if recorded) was calculated as follows: grams ethanol = volume of the drink (ml) × 0.8 × alcohol content (%) × 100. Complications (WS, DT), length and quantity of medical treatment (CMZ, clonidine, haloperidol and CBZ/VPA) and the need for ICU therapy as well as AWS score upon admission and during AWS treatment were recorded. Possible side effects of AED treatment were logged and considered related only if symptoms could not be sufficiently explained otherwise.

Daily serum drug concentrations of CBZ and VPA determined prospectively in randomly selected individuals in 2010

Drug monitoring had been performed only occasionally (in <5%) of the study population. Thus, to get an impression of the presumed day-to-day concentration of CBZ and VPA in the dose as used in the majority of patients of our retrospective cohort, we prospectively measured CBZ and VPA in serum in six randomly selected individuals (all gave prior written consent) who were treated electively for AWS in our department in 2010. Sustained-release formulations of the drugs were administered orally in a dose of 200 mg three times daily (CBZ) and 300 mg four times daily (VPA). Blood was drawn every morning at the same time on Day 0 (before administration of the AED) and on Days 1, 2, 3 and 4. Serum CBZ and VPA were determined by a standardized fluorescence polarization immunoassay (TDx assay; Abbott Laboratories) at the hospital’s Institute of Clinical Chemistry.
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 827)</th>
<th>Carbamazepine (n = 374)</th>
<th>Valproic acid (n = 453)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45 (10)</td>
<td>43 (10)</td>
<td>47 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>606 (73%)</td>
<td>283 (76%)</td>
<td>323 (71%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Pre-existing co-morbid conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>21 (2%)</td>
<td>11 (3%)</td>
<td>10 (2%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>99 (12%)</td>
<td>47 (13%)</td>
<td>52 (12%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Not available</td>
<td>518 (63%)</td>
<td>243 (65%)</td>
<td>275 (61%)</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>429 (52%)</td>
<td>185 (49%)</td>
<td>244 (54%)</td>
<td></td>
</tr>
<tr>
<td>Addiction-related historyb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous seizures</td>
<td>350 (42%)</td>
<td>202 (54%)</td>
<td>148 (33%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delirium</td>
<td>112 (13%)</td>
<td>48 (13%)</td>
<td>64 (14%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Previous withdrawal</td>
<td>589 (71%)</td>
<td>261 (70%)</td>
<td>328 (72%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Structural cerebral lesions</td>
<td>42 (5%)</td>
<td>21 (6%)</td>
<td>21 (5%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Cause of admittance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manifest withdrawal</td>
<td>122 (15%)</td>
<td>54 (14%)</td>
<td>68 (15%)</td>
<td>0.75</td>
</tr>
<tr>
<td>Elective for withdrawal</td>
<td>257 (31%)</td>
<td>104 (28%)</td>
<td>153 (34%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ethanol intoxicationa</td>
<td>318 (38%)</td>
<td>142 (38%)</td>
<td>176 (39%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Seizuresa</td>
<td>130 (16%)</td>
<td>74 (20%)</td>
<td>56 (12%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) for continuous variables and as frequency (n, %) for categorical variables. Variables that were not normally distributed were expressed as median and [IQR]. Significant P-values (P < 0.05) are indicated in italics.

aThe amount of daily alcohol consumption reported by the patient (if recorded) was calculated according to the formula: grams ethanol = volume of the drink (ml) x 0.8 x alcohol content (%) / 100.

bAddiction-related history was derived from the patients themselves either at admission or during inpatient course.

cPatients developed subsequently alcohol withdrawal syndrome and were treated according to our detoxification protocol.

**Statistical analysis**

Data were entered and analyzed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). The mean and the standard deviation (±SD) were used to describe quantitative data meeting normal distribution according to the Kolmogorov–Smirnov test. Variables that were not normally distributed were expressed as the median and the interquartile range (IQR). As appropriate, the χ² or Fisher exact test was used to compare categorical data between independent groups. Student’s t-test or Mann–Whitney U test was used to compare continuous data distribution between two independent samples.

For multivariate analysis of binary frequency data, multiple logistic regression analysis was employed and confounder-adjusted estimates of odds ratios (OR) reported with 95% confidence intervals (CI). All statistical tests were conducted at a two-sided 0.05 level of significance.

**RESULTS**

We studied episodes of hospitalization for AWS in 827 patients, of whom 606 were men (73%). The mean age was 45 ± 10 with a tendency to younger age in the CBZ group compared with the VPA group (43 ± 10 vs. 47 ± 11; P < 0.001). Despite the majority of baseline characteristics and pre-existing co-morbid conditions being equally distributed between the two groups, we found some significant differences; in the CBZ group there was a longer duration of addiction (15 vs. 10 years; P = 0.04), a higher reported approximated daily ethanol intake (196 vs. 152 g; P = 0.04) and a higher prevalence of reported seizures during previous AWS episodes (54 vs. 33%; P < 0.0001). Regarding the cause of admittance, both groups (CBZ vs. VPA) were otherwise balanced. Seeking admission electively for AWS was the cause of admittance in 28 vs. 34% (P = 0.07); admittance with ethanol intoxication as the cause as 38 vs. 39% (P = 0.82); and patients presented with a manifest withdrawal syndrome at admission in 14 vs. 15% (P = 0.75). Of note, we found a significantly higher incidence of seizures as the cause of admittance in the CBZ group compared with the VPA group (20 vs. 12%; P = 0.003; for details Table 1).

Clinical and analytical findings were essentially balanced between the treatment groups except for lower diastolic blood pressure at the start of therapy (88 vs. 90 mmHg; P = 0.03), higher serum sodium (141 mmol/l; IQR [137–143] vs. 140 mmol/l; IQR [136–143]; P = 0.02), lower serum potassium (4.1 mmol/l; IQR [3.8–4.4] vs. 4.2 mmol/l; IQR [3.9–4.5]; P = 0.001) and lower blood urea nitrogen levels (8 mg/dl; IQR [6–11] vs. 10 mg/dl; IQR [7–13]; P < 0.001) in the CBZ group. In ~20% of the patients, BZD in urine was positive on admission (21% CBZ vs. 22% VPA; P = 0.67), and negative in 28 vs. 22% (CBZ vs. VPA; P = 0.08). (As we did not test for BZD in urine routinely, this result was not available in ~54% of the patients [51% in the CBZ group vs. 56% in the VPA group; P = 0.78]; Table 2; parts of laboratory data not shown).

The severity of AWS did not differentiate the groups. In patients who had a WS, the median AWS score in the 4 h before WS occurred was significantly higher in the VPA group than in the CBZ group (6; IQR 4–10 vs. 4; IQR 0–6; P = 0.04). Conversely, the AWS score in the 4 h before DT was apparent was higher in the CBZ group, although this was not a significant difference.

Duration of medical treatment of AWS (91 vs. 76 h; P < 0.001) as well as the median length of stay in hospital (8 vs. 6 days; P < 0.001) was significantly longer in the CBZ group. Concomitantly, both higher single (data not shown) and higher cumulative doses of CMZ were needed to
For details, see Table 3. 

**Table 3. Withdrawal-associated treatment**

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 827)</th>
<th>Carbamazepine (n = 374)</th>
<th>Valproic acid (n = 453)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWS Score Maximal</td>
<td>8 [6–10]</td>
<td>8 [6–11]</td>
<td>8 [6–10]</td>
<td>0.54</td>
</tr>
<tr>
<td>AWS Score Maximal Since Admission (Hours)</td>
<td>14 [6–23]</td>
<td>15 [6–25]</td>
<td>13 [6–22]</td>
<td>0.11</td>
</tr>
<tr>
<td>Length of Alcohol Withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Treatment (Hours)</td>
<td>82 [52–118]</td>
<td>91 [56–133]</td>
<td>76 [48–105]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of Stay (Days)</td>
<td>7.0 [5–9]</td>
<td>8.0 [6–11]</td>
<td>6.0 [5–8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clomethiazole Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest Single Dose Needed (mg)</td>
<td>315 [315–473]</td>
<td>394 [315–472]</td>
<td>315 [315–473]</td>
<td>0.001</td>
</tr>
<tr>
<td>Cumulative Dose Administered (g)</td>
<td>4.9 [2.7–7.9]</td>
<td>5.6 [2.9–9.1]</td>
<td>4.6 [2.7–7.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional Therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neureptics (haloperidol)</td>
<td>55 (7%)</td>
<td>21 (6%)</td>
<td>34 (7%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Sympatholytics (clonidine)</td>
<td>348 (42%)</td>
<td>134 (36%)</td>
<td>214 (47%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Need for Intensive Care Treatment</td>
<td>37 (4%)</td>
<td>28 (7%)</td>
<td>9 (2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Length of Stay in ICU (Days)</td>
<td>2 [1–3]</td>
<td>2 [1–4]</td>
<td>1 [1–2]</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD) for continuous variables and as frequency (n, %) for categorical variables. Variables that were not normally distributed were expressed as median and [IQR].

AWS: Alcohol Withdrawal Syndrome; CBZ: Carbamazepine; VPA: Valproate; ICU: Intensive Care Unit.

In the multivariate analysis, considering age, gender, a positive history of previous seizures during AWS and seizures as the cause of admittance as confounder variables, the odds ratio (CBZ vs. VPA) of WS was estimated to be 1.58 (95% CI: 0.91–2.74; P = 0.107). Thus, after adjustment, the significant difference in the incidence of WS in the univariate analysis (9.6 vs. 5.5%; P = 0.02) was not seen. The only significant predictor for WS in the multivariate analysis was WS as the cause of admittance, with an odds ratio of 2.61 (95% CI: 1.43–4.78; P = 0.002).

To better understand the incidence of DT in the multivariate analysis, the potential confounders age, gender and a history of DT in previous episodes of AWS were considered simultaneously. The tendency for a higher risk in patients treated with CBZ did not reach statistical significance (OR: 1.84; 95% CI: 0.99–3.42; P = 0.053). However, a significant increment of the risk of developing DT was apparent for older people (OR per 1 year increment of age: 1.043; 95% CI: 1.013–1.07; P = 0.004).
The time of onset of side effects after treatment with the clinically irrelevant thrombocytopenia in the VPA group. Effects were equally balanced between the treatment groups.

Complications during AWS

- Withdrawal seizures: 61 (7.4%) for Carbamazepine, 36 (9.6%) for Valproic acid, 25 (5.5%) for CBZ. P-value = 0.02.
- Serioes of seizures: 17 (2.1%) for Carbamazepine, 11 (2.9%) for Valproic acid, 6 (1.3%) for CBZ. P-value = 0.14.
- Delirium tremens: 46 (5.6%) for Carbamazepine, 26 (6.6%) for Valproic acid, 20 (4.4%) for CBZ. P-value = 0.52.
- Delirium and seizures both: 5 (<1%) for Carbamazepine, 5 (1.3%) for Valproic acid, 0 for CBZ. P-value = 0.02.

Seizures

- Total CMZ dose before first seizure (mg): 630 [0–5000] for Carbamazepine, 2308 [0–5650] for Valproic acid, 487 [0–1890] for CBZ. P-value = 0.14.
- Within presumable therapeutic AED level: 27 (3.3%) for Carbamazepine, 19 (5.1%) for Valproic acid, 8 (1.8%) for CBZ. P-value = 0.12.

AED therapy

- Mean daily dose (mg): NM for Carbamazepine, 684 (143) for Valproic acid, 1062 (176) for CBZ. P-value = 0.14.
- AED therapy prematurely withdrawn: 43 (5.2%) for Carbamazepine, 31 (8.3%) for Valproic acid, 12 (2.6%) for CBZ. P-value = <0.001.
- AED dose reduced: 13 (1.6%) for Carbamazepine, 11 (2.9%) for Valproic acid, 2 (<1%) for CBZ. P-value = 0.004.
- Delay after start of treatment (hours): 70 [49] for Carbamazepine, 70 [46] for Valproic acid, 67 (62) for CBZ. P-value = 0.12.

Compressions

- CNS: 26 (3.1%) for Carbamazepine, 26 (7.0%) for Valproic acid, 0 for CBZ. P-value = <0.001.
- Gastrointestinal: 5 (<1%) for Carbamazepine, 4 (1.1%) for Valproic acid, 1 (<1%) for CBZ. P-value = 0.18.
- Dermatological: 7 (<1%) for Carbamazepine, 4 (1.1%) for Valproic acid, 3 (<1%) for CBZ. P-value = 0.71.
- Hematological: 6 (<1%) for Carbamazepine, 6 (<1%) for Valproic acid, 5 (1.1%) for CBZ. P-value = 0.23.

Data are expressed as mean (SD) for continuous variables and as frequency (n, %) for categorical variables. Variables that were not normally distributed were expressed as median and [IQR]. Significant P-values (P < 0.05) are indicated in italics.

CMZ, clomethiazole; N.M., not meaningful.

aSeverity score of AWS within the previous 4 h before complication (WS or DT) occurred.

bA presumably therapeutic AED level was anticipated according to the post hoc concentration-time profile of both CBZ and VPA (Fig. 1).

cWithdrawal seizures were considered if the AED was withdrawn in more severe side effects or the dose reduced in mild side effects of both CBZ and VPA.

dWithin presumable therapeutic AED level was the period after therapeutic drug concentrations of both CBZ and VPA have presumably been achieved (interpolated or DT occurred after this time point (after 10 h for CBZ; after 37 h for VPA).

If we assume that serum drug concentrations in the patients in the retrospective study resembled those determined prospectively in randomly selected subjects in 2010 (receiving the same dose of each AED) and if we focus on the period after therapeutic drug concentrations of both CBZ and VPA have presumably been achieved (interpolated values for CBZ: 10 h and for VPA: 37 h; see dotted lines in Fig. 1), then we can consider a subset of patients where theoretically therapeutic anticonvulsant concentrations of the AEDs have been reached. The occurrence of complications (WS, DT) in that subset of patients was less frequent than in the whole sample. However, there was no non-significant trend for more frequent complications in this CBZ subgroup compared with the VPA subgroup, both for WS (5.1 vs. 1.8%; P = 0.12) as well as for DT (2.9 vs. 1.3%; P = 0.14; Table 4).

In our retrospective cohort study, adverse reactions of the prescribed AEDs were significantly more frequent in the CBZ group compared with the VPA group (7.6 vs. 2.0%; P < 0.001). Specifically, CNS side effects (e.g. vertigo, diplopia) occurred quite often in the CBZ group (7%) and did not occur in the VPA group (P < 0.001). Other clusters of side effects were equally balanced between the treatment groups with an insignificant trend toward a higher incidence of (clinically irrelevant) thrombocytopenia in the VPA group. The time of onset of side effects after treatment with the AED was started did not differ between groups (CBZ: 70 ± 46 h; VPA: 67 ± 62 h; P = 0.12; Table 4).

As the frequency of patients’ reported history of WS was higher in the CBZ group compared with the VPA group (54 vs. 33%; P < 0.001) and accounting for the known higher risk of developing WS or DT with a positive history of these complications in prior withdrawal episodes, we performed a subgroup analysis. We differentiated between the occurrence of WS or DT in those patients with positive or negative history of these complications during AWS for both CBZ and VPA. Patients with a positive history of WS experienced this complication equally often (CBZ: 9.9%; VPA: 10.9%; P = 0.766). However, of those patients with a negative history of WS, significantly more patients experienced WS during therapy with CBZ compared with VPA (9.3 vs. 2.9%; P = 0.003), whereas the incidence of DT with a negative history was fairly equal in both groups (6.1 vs. 4.3%; P = 0.504). Although the incidence of DT in patients with a positive withdrawal history in the CBZ group was more frequent compared with the VPA group, the difference was not significant (12.5 vs. 4.7%; P = 0.168).

Accounting for the unbalanced higher proportion of patients where WS was the cause of admittance in the CBZ group compared with the VPA group (19.8 vs. 12.4%; P = 0.003; Table 1) and knowing WS as the cause of admittance to be a significant predictor for developing WS in the further course, we analyzed the incidence of WS in these subgroup.
The proportion of patients who were admitted with WS and subsequently developed another WS during AWS was identical both in the CBZ group and in the VPA group (16.2 vs. 16.1%; \( P = 0.982 \)). However, WS occurred significantly more often in those patients where WS was not the cause of admittance in the CBZ group compared with the VPA group (8 vs. 4%; \( P = 0.026 \)).

Because some patients who were drug tested on admission tested positive for BZD in urine (~20% of patients), we analyzed the subgroup of patients who had explicitly tested negative regarding the occurrence of WS and DT in the course of AWS. Interestingly, both WS (10 vs. 4%; \( P = 0.052 \)) and DT (7 vs. 1%; \( P = 0.036 \)) in this subgroup were more frequent in the CBZ group compared with the VPA group, although difference regarding WS only reached borderline significance.

**DISCUSSION**

To the best of our knowledge, this is one of the largest cohort studies comparing the safety and efficacy of CBZ and VPA as adjuncts in the treatment of inpatients suffering from the more severe forms of AWS. There is some evidence, both in the whole study sample and in some subgroups, that CBZ may be less effective in preventing WS and was associated with a higher incidence of predominantly adverse CNS effects. The significant trend of VPA being more effective in preventing WS than CBZ in the univariate analysis was not, however, established in the multivariate analysis. WS as the cause of admittance significantly predicted for WS in the further course of AWS. The risk for DT was increased in older people. While the first finding seems reasonably established (Rathlev et al., 2006), older age as an independent risk factor of developing DT during AWS is not commonly reported (Wetterling et al., 2001).

Despite our fairly large cohort, our results should be interpreted cautiously, as there are several limitations.

First, it was a retrospective single-center cohort study comparing non-randomly selected subjects of two different treatment episodes. Even though treatment was protocol driven, we cannot exclude some differences in the quality of treatment between the two episodes (e.g. more skilled doctors and nurses in the later period using VPA as the AED). Although treatment of our patients followed a standardized protocol, dosing and timing of each drug differed slightly and was dependent on the final discretion of the attending physician. Despite the validated AWS score used here, there can be ambiguity in the interpretation and scoring, especially of the non-objective mental items. Finally, it is unknown whether co-therapy with clonidine or haloperidol (owing to their potency to precipitate WS) may have increased the occurrence of complications although there was a higher need for both of these medications in the VPA group, which was the group with the lower rate of WS.

Second, our treatment samples were not balanced equally in every respect and we cannot be sure that there were other unknown cofounders. Nevertheless, subgroup analysis accounting for these imbalances (more seizures in previous withdrawal episodes and more patients admitted with WS in the CBZ group) still suggests that VPA is the preferable agent to prevent WS. Even though there was a longer duration of addiction and a higher approximated daily ethanol intake in the CBZ group, our data do not provide sufficient evidence that these differences caused a higher complication rate (WS, DT) in the CBZ group—despite some authors suggesting such a correlation (Schuckit et al., 1995; Wojnar et al., 1999). Tolerance toward alcohol, prolonged duration and increased amount of alcohol intake are factors known to be important, at least in animal models. However, unlike animal models, only one-third of the variance in the development of complications of AWS in humans can be attributed to the quantity, duration and frequency of alcohol ingestion, making these variables relatively weak predictors (Gorelick and Wilkins, 1986).

Third, despite dependence on BZD being an initial exclusion criterion, ~20% of patients tested positive in urine at admission—in most cases due to preclinical treatment of WS or agitation with a single dose of BZD that was beyond our influence. The severity and complications of AWS may therefore have been adulterated. However, our subgroup analysis still suggests that VPA is more effective than CBZ in preventing both WS and DT, as these complications were more frequent in the CBZ group as well as in those patients who were explicitly tested negative for BZD in urine.

Our cohort study fails (and was not intended) to answer the question whether AEDs have a general place as adjuncts in the treatment of the more severe forms of AWS. According to some guidelines and recommendations (Brathen et al., 2005; Mayo-Smith, 1997; Minozzi et al., 2010), AEDs are not generally recommended in the treatment of AWS, at least in patients known to have a low risk of developing WS or DT. It is yet to be answered whether AEDs would be indicated for reasons beyond their anticonvulsant property (e.g. anti-kindling activity), but promising results of small and well-conducted trials suggest that they may have a role (Ait-Daoud et al., 2006; Johnson et al., 2007; Longo et al., 2002; Malcolm et al., 2002; Mueller et al., 1997). The GABAergic and anti-glutamatergic properties of both CBZ and VPA might save doses of BZD or

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**Fig. 1. Concentration-time profile of sustained-release CBZ (200 mg, three times daily) and VPA (300 mg, four times daily) in six randomly selected AWS patients. A one-phase association function was fitted to concentration vs. time data of VPA and CBZ using GraphPad Prism® Version 5. The thin lines indicate the interpolated times till the lower ends of the therapeutic ranges of CBZ (10 h; solid line) and VPA (37 h; dotted line) have been reached. Serum CBZ and VPA were determined by a standardized fluorescence polarization immunoassay (TDx assay; Abbott Laboratories). Generally accepted therapeutic levels of CBZ are (4–11 mg/l) and VPA (50–100 mg/l), respectively.**
CMZ (Reoux et al., 2001). Despite lacking a placebo-control group, we can say that our VPA group needed significantly less additional CMZ to control AWS than the CBZ group. However, even if AEDs may be beneficial in ameliorating the severity of AWS, one must recall that both CBZ and VPA may interact with other therapeutic agents and so should be used with care (Patsalos and Perucca, 2003; Perucca, 2006).

At present, there are numerous studies demonstrating the efficacy and safety of VPA in ameliorating AWS, either as monotherapy, or as an adjunct to BZD or other agents (Bocci and Beretta, 1976; Hammer and Brady, 1996; Longo et al., 2002; Malcolm et al., 2001; Minuk et al., 1995; Myrick and Anton, 1998; Reoux et al., 2001; Rosenthal et al., 1998). Open trials have consistently shown that patients receiving VPA required less of standard medications for AWS, their symptoms resolved sooner and they experienced fewer seizures ( Bastie, 1970; Lambie et al., 1980). However, authors of a recent review concluded that VPA should not replace conventional therapy nor be used as adjunct therapy for management of mild-to-moderate AWS (Lum et al., 2006).

Despite frequent gastrointestinal and central nervous side effects of CBZ in the treatment of AWS (Hillbom et al., 1989), additional studies support its beneficial use. Some of these studies have demonstrated that CBZ has equal or superior efficacy to lorazepam, oxazepam, CMZ, tiapride as well as placebo in reducing withdrawal severity (Malcolm et al., 2001, 2002). However, in a study using CBZ (1200 mg/day) as monotherapy for AWS, treatment with CBZ had to be prematurely discontinued due to intolerable CNS side effects in ~55% of the patients (Hillbom et al., 1989). In other studies comparing CBZ with CMZ, no relevant difference in their efficacy could be seen (Ritola and Malinen, 1981; Seifert et al., 2004). A recent review of the Cochrane Collaboration found insufficient evidence to favor any AED for the treatment of AWS, although the occurrence of seizures tended to be more common among participants who were treated with other drugs (e.g. BZD) than those treated with AEDs. Comparing CBZ with BZD, results favor CBZ for AWS and this result suggests that AEDs and specifically CBZ may actually be more effective in treating some aspects of AWS when compared with BZD, the current first-line regimen for AWS. Differences between specific AEDs, especially comparing VPA against CBZ, could not be seen because of the limited number of studies comparing one anticonvulsant with another. Also, the large variety of outcomes and rating scales limited the significance of this review (Minozzi et al., 2010).

Therapeutic drug levels of the AED therapy as administered in our study were presumably achieved more rapidly in the CBZ group. This is at least confirmed by our kinetic analysis performed prospectively in 2010, where we could demonstrate that VPA administered in the same dose was insufficient to achieve therapeutic drug concentrations within the early and critical stage of AWS (Fig. 1). It may be conceivable that VPA offers some therapeutic properties (during therapy for AWS) even in doses that are below the generally accepted therapeutic threshold to act as an anticonvulsant.

Achieving rapidly the targeted CBZ plasma concentration may be one reason for more frequent side effects being observed in the CBZ group. The ability of VPA to be administered by an initial oral (or intravenous) loading dose without causing significant side effects makes VPA an especially appealing option, given that the rapid onset of AWS requires pharmacotherapy to be rapidly acting (Hirschfeld et al., 1999). Additionally, early and aggressive treatment of AWS is warranted to block kindling (Gonzalez et al., 2001). This is believed to be achieved more favorably using VPA compared with CBZ with its known risk of producing side effects when not started gradually (Powell et al., 2010).

In conclusion, our study suggests that VPA may offer some benefits compared with CBZ in the adjunct treatment of moderate-to-severe AWS. VPA was associated with a shorter need for pharmacological treatment, fewer ICU transfers and a more favorable side-effect profile compared with CBZ. There was a trend (not significant after adjusting for potential confounders) that VPA may be more effective than CBZ in reducing complications during AWS, especially WS. However, the results of this retrospective cohort study do not justify yet any implementation into clinical routine until these results are confirmed in a larger prospective study.

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