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# Treatment of alcohol withdrawal: tiapride and carbamazepine versus clomethiazole.

## A pilot study

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**Abstract** In Germany, clomethiazole (CLO) and benzodiazepines are predominantly used as therapeutic agents in the treatment of the alcohol withdrawal syndrome (AWS). These agents have disadvantages such as sedation, risk of respiratory insufficiency, and cardiovascular complications as well as addictive potential. Alternatively, it could be demonstrated that both tiapride (TIA) and carbamazepine (CBZ) are efficient in the treatment of AWS with less toxicity. However, they seem to be less effective in AWS than CLO as single agents. But no systematic comparison of the combination of TIA and CBZ against an established therapeutic standard can be found in the literature. Therefore, we compared the combination of TIA and CBZ with CLO in two open exploratory studies with matched samples. Outcome parameters were heart rate, blood pressure, complications, withdrawal symptoms (CIWA-Ar scale), and general clinical state (CGI scale). A retrospective evaluation of medical records (30 TIA+CBZ, 30 CLO) was followed by an open prospective study (40 TIA+CBZ, 40 CLO). Both studies revealed similar efficacy in terms of psychopathologic and vegetative symptoms. Vegetative recovery seems to be faster with TIA+CBZ. Results of this exploratory study have to be confirmed by a controlled double-blind study with severity of AWS as an experimental factor.

**Key words** Tiapride • Carbamazepine • Clomethiazol • Alcohol with drawal syndrome • Delirium tremens

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## Introduction

Alcohol dependence has a high prevalence in the Federal Republic of Germany and other developed Western nations (Soyka 1998). The majority of people with alcohol dependence will experience an alcohol withdrawal syndrome (AWS) when intake of alcohol stops. Delirium tremens is a severe manifestation of AWS and can be observed in 5 %–15 % of cases (Feuerlein 1992). Untreated it may lead to a lethal outcome in 15–30 % (Feuerlein 1992; Turner et al. 1989). With current state of the art treatment, mortality can be reduced to 1–8 % of cases (Feuerlein 1992). However, the pharmacological treatment of AWS has been a controversial issue so far: about 150 treatment strategies have been identified in the literature (Williams and McBride 1998; Erstad and Cotugno 1995; Saitz et al. 1995; Tiecks and Einhäupl 1994; Rommelspacher et al. 1991). Up to now no therapeutical standard has been established despite agreement on the general and specific objectives of the treatment of AWS (Table 1). The substances predominantly used for AWS treatment are summarized in Table 2 (modified from Schied and Mann 1988; Feuerlein 1992). They differ in their therapeutic effectiveness and their adverse side effects. None of today's treatment regimen of AWS can be seen as optimal (Tiecks and Einhäupl 1994) regarding efficacy and side effects as quoted in Table 2.

**Table 1** Criteria for optimal treatment of AWS

| General | Specific |
|---|---|
| • High efficacy against all withdrawal symptoms | • Dampening of psychomotor disturbance |
| • Prevention from delirium tremens | • Reduction of vegetative hyperarousal |
| • Low risk of secondary complications | • Increase of convulsive threshold |
| • Easy adjustment to course of withdrawal | • Antipsychotic efficacy |
| • High safety range | |

Williams & McBride (1998); Tieks & Einhäupl (1994); Feuerlein (1992); Guthrie (1989); Turner, et al. (1989)

In Central Europe treating the AWS with clomethiazole[1] is virtually regarded as a standard procedure (Morgan 1995; Tiecks and Einhäupl 1994; Majumdar 1990). However, it has not been approved for use in the United States as it may cause respiratory insufficiency. In North America benzodiazepines are used as a first choice in AWS (Holbrook et al. 1999). Both clomethiazole and benzodiazepines reduce psychomotor disturbances and hyperarousal, they increase seizure threshold, but they lack direct antipsychotic action (Table 2). The main therapeutical risks are central respiratory depression (with increased nasopharyngeal secretion in clomethiazole), cardiovascular depression at high doses, strong addictive potential and sedation which interferes with psychotherapeutic contacts during the early phase of withdrawal (Erstad and Cotugno 1995; Tiecks and Einhäupl 1994; Rommelspacher et al. 1991; Turner et al. 1989). However, there is increasing agreement that pharmacotherapy of AWS should in fact promote these patients' motivation for participation in psychotherapy and rehabilitation programs as early as possible (Gallhofer 1998; Rommelspacher et al. 1991).

Alternative pharmacotherapeutic schedules should be comparable to clomethiazole or benzodiazepines in their effectiveness, but their side effects should be more acceptable (cf. Table 2).

[1] Distraneurin® (ASTRA GmbH); for pharmacological properties see Benkert and Hippius (1996); Morgan (1995)

Antipsychotic drugs decrease the already lowered seizure threshold in AWS and may cause extrapyramidal symptoms and tardive dyskinesia. Some have anticholinergic properties with inherent delirious potential and may induce vegetative symptomatology themselves (Busch and Frings 1987). Clonidine is used for treatment of adrenergic hyperactivity, but may cause hypotension (Tiecks and Einhäupl 1994).

Carbamazepine[2], a tricyclic anticonvulsant, has been used in the treatment of AWS since the late 1960 s (Thome et al. 1994; Gottesleben et al. 1995; Stuppaeck et al. 1990; Agricola et al. 1982; Ritola and Malinen 1981; Brune 1966). It has no addictive potential and has a positive effect on motoric and psychopathologic symptoms of the AWS. Apart from its anticonvulsive effect carbamazepine also decreases vegetative symptomatology and psychomotor restlessness (Thome et al. 1994; Busch and Frings 1987). Carbamazepine is mainly preferred for its acceptable side-effect profile and lack of addictive potential (Albani et al. 1995; Busch and Frings 1987). In long-term treatment the side effects of carbamazepine are particularly low, if the initial dose does not exceed 800 mg and is distributed in single doses of 200 mg throughout the day (Thome et al. 1994; Busch and Frings 1987). Results from open and double blind studies sug-

[2] Tegretal® (Novartis Pharma); also marketed by a number of other companies using different trade names; for pharmacological properties see Albani et al. (1995), Schmutz (1985)

**Table 2** Substances predominantly used in AWS treatment

| | Therapeutical efficacy | | | |
|---|---|---|---|---|
| | Decrease of psychomotor disturbance | Antipsychotic efficacy | Increase of seizure threshold | Decrease of vegetative hyperarousal |
| Neuroleptics | + | ++ | ⇓ | (+) |
| Benzodiazepines | ++ | 0 | ++ | ++ |
| Clomethiazole | ++ | (+) | ++ | ++ |
| Carbamazepine | (+) | 0–+ | ++ | + |
| Clonidine | 0 | 0 | 0 | ++ |
| Tiapride | + | 0 | 0 | + |
| Ethanol | ++ | 0 | + | ++ |

| | Side effects | | | | | | |
|---|---|---|---|---|---|---|---|
| | Respiratory depression | Seizure threshold ⇓ | Hypotonia | Extra-pyramidal | Liver | Addictive potential | Sedation |
| Neuroleptics | 0 | ++ | + | ++ | + | 0 | 0 |
| Benzodiazepines | + | 0 | + | 0 | 0 | ++ | ++ |
| Clomethiazole | ++ | 0 | ++ | 0 | 0 | +++ | ++ |
| Carbamazepine | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Clonidine | 0 | 0 | +++ | 0 | 0 | 0 | 0 |
| Tiapride | 0 | 0 | 0 | (+)[1] | 0 | 0 | 0[2] |
| Ethanol | (+) | 0 | (+) | 0 | ++ | +++ | + |

Schied & Mann (1988), Feuerlein (1992) (modified)
[1] low incidence of EPS (Peters & Faulds, 1994)
[2] decrease of psychomotor agitation, no direct sedation (Peters & Faulds, 1994)

gest carbamazepine to be an alternative to clomethiazole and benzodiazepines in treating the AWS (review by Thome et al. 1994). However, adding another drug with some sedating or psychomotor relaxant properties seems desirable (Busch and Frings 1987; Thome et al. 1994). Preferably this drug should support the benefits of carbamazepine; therefore it should neither have severe sedating or cataleptic effects, nor impair communication or cognition, nor have cross-dependence properties.

Tiapride[3], a substituted benzamide, has been used for AWS treatment since the late 1970 s, especially in France (Franz et al. 1995; Peters and Faulds 1994; Murphy et al. 1983; Agricola et al. 1982; Clemens et al. 1982; Cance et al. 1975). Main indications of tiapride are extrapyramidal symptoms or other dyskinesias, hyperkinesias, Huntington's Chorea and also geriatric agitation and restlessness (Franz et al. 1995; Steele et al. 1993; Aschoff 1982). Although there are some case reports on the improvement of hallucinations after treatment with tiapride (Lopéz Zanón et al. 1993), tiapride has mainly anxiolytic properties and reduces agitation (Peters and Faulds 1994; Steele et al. 1993). It has, in general, a low incidence of side effects, even in long-term treatment. The most frequent, however rare, side effects according to studies cited by Peters and Faulds (1994) are drowsiness, extrapyramidal symptoms, dizziness, and orthostatic hypotension. Tiapride has no antihistaminic action and is known to control psychomotor restlessness without causing considerable benzodiazepine-like sedation (Franz et al. 1995). Side effects of both carbamazepine and tiapride can be regarded as negligible compared to other agents used in the pharmacotherapy of AWS.

Considering profiles of wanted and unwanted effects from a pharmacological point of view the combination of tiapride and carbamazepine as a treatment of AWS appears to be promising (Table 2). All of the four main symptoms of withdrawal can possibly be influenced accompanied by only minor side effects. Efficacy against paranoid symptoms and hallucinations cannot clearly be deduced from the drugs' pharmacological profiles. However, this is true for all other substances except antipsychotics. Carbamazepine also seems to lack a direct effect on paranoid symptoms, hallucinations or thought disorders (Albani et al. 1995).

The authors know through personal communication that the combination of tiapride and carbamazepine has been already used in clinical settings with success. However, this combination is almost ignored in the scientific literature. A published case report (Gallhofer 1998) as well as results from an open study comparing the combination of tiapride and carbamazepine against carbamazepine alone (Baltes et al. 1998) indicate that it may be useful to compare this combination with a well-established therapeutical approach as already suggested by Busch and Frings (1987). To fill this gap we conducted two open exploratory bicentric studies as a first step investigation. It is the first study comparing the treatment of acute AWS using a combination of tiapride and carbamazepine with a single drug therapy using clomethiazole.[4]

## Methods

A first exploratory study was performed using a *retrospective evaluation* of case records in patients with AWS. In a second study we used a *prospective study design*. After a general description of patients, instruments and treatment, both studies are presented separately.

### Patients

We included consecutively admitted patients with a diagnosis of AWS (ICD 10: F10.3, F10.4) in two neighbouring psychiatric hospitals with a similar structure of catchment areas. One hospital used clomethiazole (CLO) as a single agent, the other hospital treated patients with a combination of tiapride (TIA) and carbamazepine (CBZ). Polysubstance abusers were excluded. In order to minimize sampling effects, groups were strictly paralleled in terms of sociodemographic as well as illness-related variables by a scientist (H. G.) blind to the treatment effects on the patients. During the course of the study none of the patients suffered severe withdrawal symptoms with cardiovascular decompensation requiring intensive care treatment.

### Assessment

The authors developed a questionnaire to record comprehensive sociodemographic and anamnestic data including other alcohol-related disorders as well as specific withdrawal symptoms during alcohol withdrawal treatment in the patient's history[5]. These data as well as values of efficacy variables at baseline were used to identify parallel groups prior to onset of treatment. Severity and course of withdrawal symptoms were assessed using the Ciwa-Ar scale (Addiction Research Foundation Clinical Institute Withdrawal Assessment for Alcohol; Sullivan et al. 1989; Erstad and Cotugno 1995; Rommelspacher et al. 1991). General clinical state of the patients was assessed using the CGI scale (Clinical Global Impression; CIPS 1996). Additionally, the frequency of alcohol withdrawal complications was recorded[6]. Heart rate and blood pressure served as objective parameters of the progress of withdrawal.

### Treatment

The dosage of orally administered CLO was adjusted to individual severity of symptoms by the responsible physician according to published guidelines (Benkert and Hippius 1996; Tiecks and Einhäupl 1994; Rommelspacher et al. 1991). In general, 2–4 capsules (384–768 mg) were given initially. During the first two hours a maxi-

[3] Tiapridex® (Sanofi-Synthelabo); for pharmacological properties see Dose and Lange (2000), Steele et al. (1993)

[4] It should be noted that clomethiazole as well as carbamazepine are approved for treatment of AWS in Europe. Tiapride is approved for this indication in European countries except Germany and Finland.

[5] The following characteristics were recorded: amount of alcohol consumption, hours of alcohol abstinence before inclusion into the study, abuse of other drugs, alcoholic type according to Jellinek; psychopathologic and neurologic symptoms during preceding withdrawal; somatic, psychologic, social consequences of alcohol abuse. The questionnaire is available from the first author.

[6] Complications recorded during treatment: epileptic seizures, Wernicke syndrome, Korsakow syndrome, circulatory disturbances, sudden falls, esophageal/gastrointestinal hemorrhage or disturbances, exsiccosis, hypokalemia

mum of 8 capsules (1536 mg) could be dispensed depending on the severity of the symptoms. Subsequently 2 capsules (384 mg) could be given every 1 to 2 hours up to a maximum of 24 capsules (4608 mg) per day, also depending on symptom severity (Table 3 shows the actually given doses). Following an initial plateau phase lasting 3–5 days the daily dosage was gradually reduced to zero. Male patients on TIA+CBZ received 300 mg TIA and 200 mg CBZ every 4 hours up to the maximum daily dosage (1200 mg TIA, 800 mg CBZ). Females received no more than 600 mg CBZ per day. Following a plateau level of dosage lasting for 3 (males) or 4 (females) days, the daily dosage of both substances was gradually reduced to zero.

### Retrospective study

Only patients with medical records containing a case history and a complete and comprehensive documentation of the withdrawal treatment were selected. A total of 71 patients were assessed, 35 patients being treated with TIA+CBZ, and 36 patients treated with CLO. Five TIA+CBZ patients and six CLO patients were excluded to obtain parallel groups with regard to means or frequencies of sociodemographic and illness related variables. In the final sample we included 30 patients in each treatment group (for mean daily dose see Table 3, 16-day scheme; treatment period, TIA+CBZ: mean = 12 days, minimum = 5 d, maximum = 16 d; CLO: mean = 9 d, minimum = 6 d, maximum = 12 d). All patients were assessed at baseline and on days 3, 5, and 10 after onset of treatment. All ratings were based on medical and psychopathological information as documented in the medical records. For the assessment of treatment effects data from the CGI scale, complications, and vegetative data were considered.

### Prospective study

Eighty six patients (TIA+CBZ=44, CLO=42) were included. The procedure to obtain parallel groups was the same as in the retrospective study (Table 4) and required the exclusion of six patients (final sample n=40 in each group; for mean daily dose see Table 3; 10-day scheme; treatment period, TIA+CBZ: mean = 10 days, minimum = 6 d, maximum= 16 d; CLO: mean = 8 d, minimum = 4 d, maximum = 11 d). All patients were assessed 1 hour before onset of withdrawal treatment (baseline), 6 hours after starting treatment ($t_1$), on days 2 to 5 ($t_2$–$t_5$) as well as on day 7 and day 10 ($t_6$ and $t_7$), always at 4:00 p. m. The recorded variables corresponded to the respective variables in the retrospective study. In addition the Ciwa-Ar score was rated on every time-point of the schedule.

**Table 3** Mean dose of medication

| | Retrospective study | | | Prospective study | | |
|---|---|---|---|---|---|---|
| Day | CBZ | TIA | CLO | CBZ | TIA | CLO |
| 1 | | | | 540±215 | 915±358 | 715±520 |
| 2 | | | | 770±72 | 1283±267 | 1453±511 |
| 3 | 810±145 | 1183±139 | 1747±766 | 763±100 | 1215±114 | 1328±611 |
| 4 | | | | 705±126 | 1100±204 | 1115±558 |
| 5 | 773±182 | 1150±161 | 1178±523 | 640±134 | 948±266 | 885±544 |
| 7 | | | | 510±201 | 688±386 | 459±374 |
| 10 | 603±318 | 813±434 | 121±205 | 230±342 | 340±526 | 72±149 |

*CBZ* carbamazepine [mg]; *TIA* tiapride [mg]; *CLO* clomethiazole [mg]. mean ± standard deviation

**Table 4** Sample characteristics

| | Retrospective study | | | Prospective study | | |
|---|---|---|---|---|---|---|
| | TIA+CBZ | CLO | p | TIA+CBZ | CLO | p |
| *Sociodemographics* | | | | | | |
| N | 30 | 30 | | 40 | 40 | |
| Sex [f/m] | 6/24 | 6/24 | n. s. | 4/36 | 3/37 | n. s. |
| Age | 42 (14) | 45 (11) | n. s. | 43 (11) | 44 (14) | n. s. |
| Weight | 75 (11) | 70 (19) | n. s. | 80 (15) | 72 (18) | n. s. |
| Height | 172 (12) | 173 (12) | n. s. | 179 (8) | 174 (10) | n. s. |
| Marital status* | 14/7/4/5/0 | 13/6/3/8/0 | n. s. | 15/11/13/1/0 | 17/15/3/4/1 | $p < 0.05$ |
| School graduation* | 1/12/11/6 | 1/17/5/7 | n. s. | 1/22/10/7 | 0/24/9/6 | n. s. |
| Professional qualifications* | 4/21/5 | 3/21/6 | n. s. | 8/29/3 | 4/32/4 | n. s. |
| *Alcohol related history* | | | | | | |
| Duration of alcohol abuse | 15 (10) | 15 (10) | n. s. | 14 (15) | 15 (25) | n. s. |
| Quantity of alcohol consumption | 280 (134) | 246 (101) | n. s. | 290 (188) | 320 (191) | n. s. |
| Blood alcohol concentration | 1.0 (1.6) | 1.2 (1.5) | n. s. | 0.52 (2.1) | 0.76 (1.2) | n. s. |
| Number of AWS treatments | 2.5 (7) | 3.5 (8) | n. s. | 1 (4) | 2 (6) | n. s. |
| *Values at baseline* | | | | | | |
| CIWA-Ar | 31 (26) | 32 (14) | n. s. | 21 (14) | 20 (12) | n. s. |
| CGI–1 (severity of illness) | 6 (2) | 6 (2) | n. s. | 6 (1) | 6 (2) | n. s. |
| Heart rate | 110 (24) | 104 (33) | n. s. | 108 (24) | 112 (24) | n. s. |
| Systolic blood pressure | 145 (40) | 150 (40) | n. s. | 140 (34) | 150 (30) | n. s. |
| Diastolic blood pressure | 95 (20) | 93 (20) | n. s. | 90 (20) | 90 (20) | n. s. |

*TIA+CBZ* tiapride/carbamazepine group; *CLO* clomethiazole group; *p* error rate (Mann Whitney U Test; Chi-Square Test);
values are frequencies or medians (interquartile ranges in parentheses), dependent on type of variable;
* marital status: married/single/separated/divorced/widowed; school graduation: special school/secondary school/junior high school/high school; professional qualifications: no/apprenticeship or vocational training/university

### Statistical analyses

Frequency data were analysed using the chi-square test or Fisher's exact test dependent on expected cell frequencies. During treatment, group differences regarding level or course of target variables were tested by means of an analysis of variance with repeated measures (between groups factor 'group', 'G', representing differences due to the type of medication; repeated measure factor 'course', 'C'; degrees of freedom corrected according to Huyn-Feldt). If overall effects were significant specific effects were analyzed by follow-up tests. In case requirements for parametric testing were questionable, results of parametric tests were confirmed by appropriate non-parametric tests.

## Results

### Retrospective study

There was no significant difference between groups at baseline (see Table 4). Both types of treatment resulted in a reduction of heart rate and blood pressure (Fig. 1; highly significant main effects 'course'). Overall, the diastolic blood pressure decreased faster in the TIA+CBZ group (significant interaction between 'group' and linear trend component of 'course'). The mean diastolic pressure during treatment was lower within TIA+CBZ (significant main effect 'group'). Decrease in systolic pressure and heart rate did not differ significantly between groups. Three patients suffered generalized epileptic seizures during treatment with CLO, whereas no seizures occurred in the TIA+CBZ group. However, this difference was not statistically significant. The only significant difference in adverse side effects turned out to be a higher rate of gastrointestinal disturbances in the group treated with TIA+CBZ (day 3: TIA+CBZ, n=12; CLO, n=1; $p < 0.001$; day 5: TIA+CBZ, n=5; CLO, n=0; $p < 0.06$)[7].

Ratings of severity of illness (CGI 1; Fig. 2) showed improvement during both treatments (significant main effect 'course'). During the first three days severity ratings improved faster in the TIA+CBZ than in the CLO group (significant interaction 'group' x 'course'). A moderate difference of the respective CGI ratings remained throughout the entire course of treatment (trend in main effect 'group'). Changes of patients' state (CGI 2; Fig. 2) as well as therapeutical efficacy (CGI 3) were considered better in the TIA+CBZ group (significant main effect 'group'). Differences between groups were obvious on day 3 and declined during further course of treatment (significant interaction 'group' x 'course'). No therapeutical risks were found (CGI 4) within any group.

### Prospective study

At baseline only the marital status differed between the groups (see Table 4). No differences were found regarding adverse symptoms at baseline, except gastrointestinal disturbances which were more frequent within the CLO group (TIA+CBZ=0, CLO=7; $p < 0.02$). At baseline differences in the number of patients with generalized epileptic seizures (TIA+CBZ=5, CLO=2) as well as disturbances of circulation (TIA+CBZ=12, CLO=7) were not statistically significant.

Vegetative parameters (Fig. 3) decreased during treatment in both groups (highly significant main effects 'course'). Mean heart rate was lower in the TIA+CBZ group (significant main effect 'group'; simple comparisons significant on days 2, 7, 10). Simple com-

[7] We assume that this effect is due to known side effects of rapid CBZ dosing

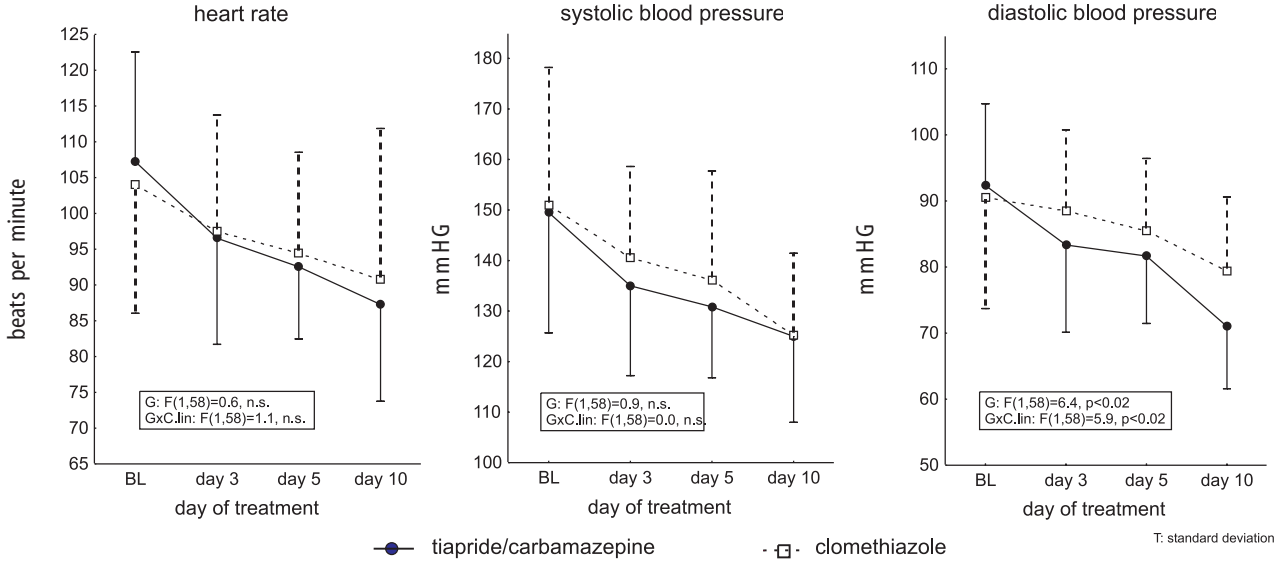


**Fig. 1** Retrospective study. Vegetative arousal. *BL* Baseline. Results of analyses of variance inserted: *G* factor 'medication group'; *GxC.lin* interaction between factor 'medication group' and linear trend component of factor 'course'; *n. s.* not significant.

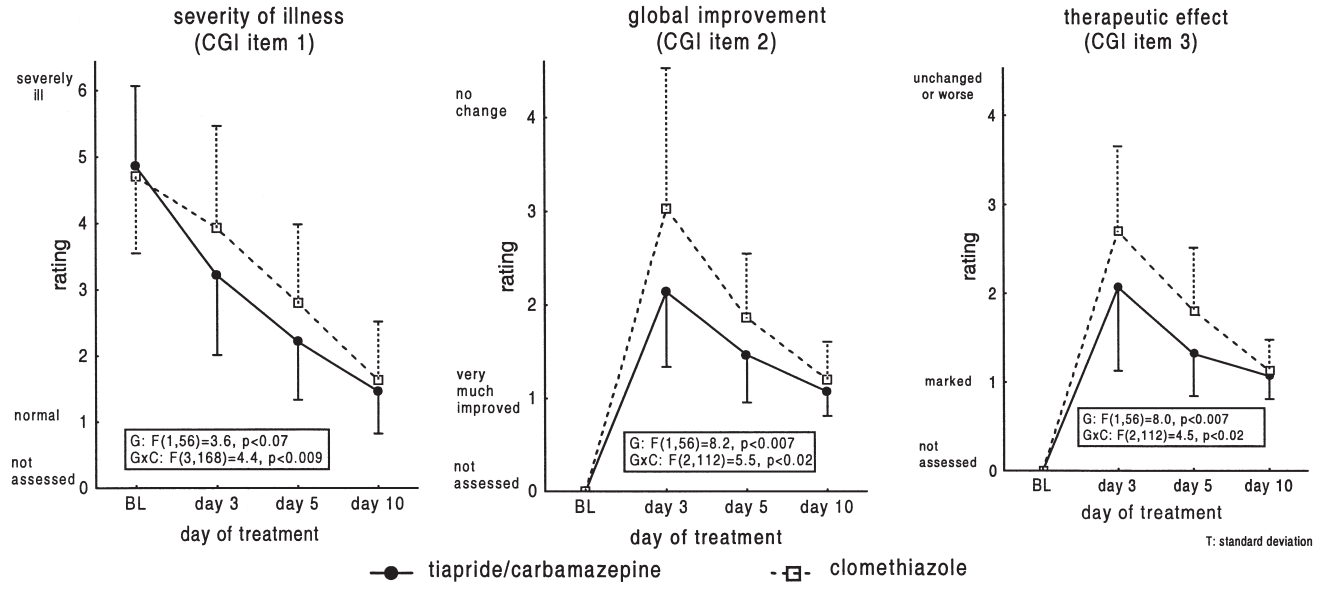


**Fig. 2** Retrospective study. Clinical Global Impression (CGI; items 1–3). *BL* Baseline. Results of analyses of variance inserted: *G* factor 'medication group'; *GxC* interaction between factor 'medication group' and factor 'course'.

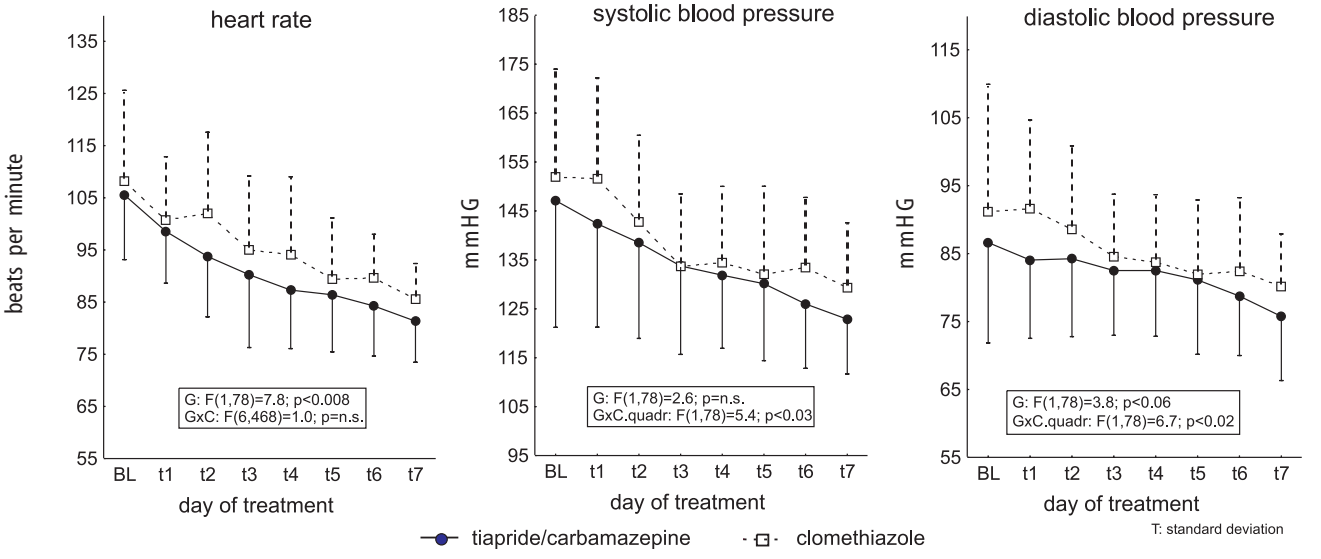


**Fig. 3** Prospective study. Vegetative arousal. *BL* Baseline; *t1 … t7* time during treatment. Results of analyses of variance inserted: *G* factor 'medication group'; *GxC* interaction between factor 'medication group' and factor 'course'; *GxC.quadr* interaction between factor 'medication group' and quadratic trend component of factor 'course'.

parisons also showed a lower systolic blood pressure in the TIA+CBZ group (significant at 6 hours after treatment onset, and on days 7 and 10), however, the main effect 'group' was not significant. Detailed analyses revealed an almost linear decrease of systolic blood pressure in TIA+CBZ throughout the course of treatment. In CLO, on the other hand, no decrease of blood pressure could be observed after 6 hours of treatment but was detected for the first time on day 2 (Fig. 3). Correspondingly, trend analysis showed significant interactions between 'group' and the quadratic trend component of 'course'. Similar differences between both groups were seen in diastolic blood pressure levels.

Regarding CGI items 1–3, the analyses of variance revealed no differences between groups in terms of improvement on clinical state. On day 10 a small but significant difference with regard to illness severity (CGI 1) was rated in favour of the CLO group (TIA+CBZ=2.3, CLO=2.1, $t(78)=3.3$, $p < 0.003$). Clinical withdrawal symptoms (Ciwa-Ar; Fig. 4) significantly decreased during treatment within both groups (main effect 'course', $F(7,546)=240$, $p < 0.001$). The reduction of withdrawal symptoms was more pronounced in the TIA+CBZ treatment group (significant main effect 'group', simple comparisons significant on days 4, 5, 7; there was no significant difference at the end of the trial period). The

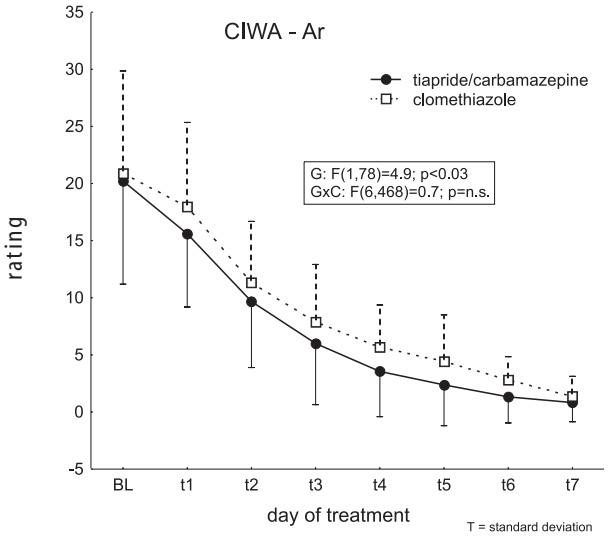


**Fig. 4** Prospective study. Severity of withdrawal symptoms (CIWA-Ar-scale). *BL* Baseline; *t1*… *t7* time during treatment.
Results of analyses of variance inserted: *G* factor medication group; *GxC* interaction between factor group and factor course; *n. s.* not significant.

frequency of complications did not differ significantly between groups. Using TIA+CBZ no withdrawal seizures were observed after onset of treatment, whereas 2 CLO-treated patients exhibited generalized seizures up to the 4$^{th}$ day of treatment. Differences in complications observed at baseline leveled off during treatment.

## Discussion

These pilot studies examined the clinical value of the combination of tiapride and carbamazepine compared with clomethiazole in the treatment of the AWS. On one hand, the combination of tiapride and carbamazepine tended to be beneficial in reducing vegetative symptoms such as mean heart rate and blood pressure both in the prospective and in the retrospective study. The CGI scores in the retrospective study indicated significant superiority of tiapride/carbamazepine over clomethiazole. Withdrawal symptoms, as assessed by the Ciwa-Ar scale in the prospective study, improved faster during tiapride/carbamazepine treatment compared to clomethiazole. On the other hand, the first CGI item ("severity of illness") was rated in favor of the clomethiazole group on the last study day. Although most differences were found to be statistically significant, differences in mean values were small suggesting little clinical significance. Due to the pilot character of the study, conclusions should be drawn carefully. The combination of tiapride and carbamazepine seemed at least equivalent to clomethiazole regarding vegetative parameters, general clinical state and withdrawal symptoms. Complications occurred only rarely and therapeutic risks were not identified in either type of treatment. Remarkably, no seizures were observed in the tiapride/carbamazepine groups, whereas generalized withdrawal seizures were reported in the clomethiazole groups in both studies.

Although there is widespread clinical evidence that carbamazepine (Thome et al. 1994) and tiapride (Peters and Faulds 1994) are useful in the treatment of AWS, the exact mechanism of action is not fully understood. We assume that combined tiapride and carbamazepine mutually reinforce the alleviation of psychotic and vegetative symptoms of the AWS, whereas they complete each other regarding psychomotor disturbance and seizure threshold (cf. Table 2). The mechanism of action of carbamazepine could be associated with a modulation of increased activity of excitatory structures (NMDA receptors, catecholamines) and decreased function of inhibitory receptors such as GABA-A receptors in the AWS (Thome et al. 1994). In such systems carbamazepine has been suggested to have various sites of action. Inhibition of dopamine synthesis, modulation of glutaminergic, GABAergic, adrenergic and cholinergic systems as well as anti-kindling effects have been discussed (Thome et al. 1994).

Tiapride, a selective dopamine $D_2$-receptor antagonist, has been categorised as an atypical neuroleptic drug and is particularly active at receptors which have been sensitised to dopamine (Peters and Faulds 1994, Dose and Lange 2000). With its high affinity to dopamine receptors and no affinity to other neurotransmitters of the brain, tiapride is especially well suited for treatment of disorders related to functional dopamine hyperactivity (Dose and Lange 2000). PET analyses show that even at higher doses tiapride does not exceed a $D_2$-receptor occupancy of 80 %, which is in accordance with the finding that tiapride rarely causes acute extrapyramidal symptoms and has so far never induced tardive dyskinesias (Dose and Lange 2000). Animal and clinical studies have shown that tiapride has anxiolytic properties but the mechanism of action is uncertain. Results from a small number of studies indicate that the clinical efficacy of tiapride in the treatment of agitation, aggressiveness, anxiety and sleep disorders in the elderly appears to be superior to that of placebo, chlorpromazine, lorazepam and meprobamate (Steele et al. 1993, Dose and Lange 2000) and equivalent to haloperidol (Allain et al. 2000). It seems to exert a beneficial effect on vigilance and alertness in elderly patients and mentally healthy controls and causes less sedation than chlorpromazine (Cathala and Autret 1978, Steele et al. 1993). In elderly subjects memory performance decreased after treatment with benzodiazepines and increased after tiapride (Leger et al. 1984). Franz et al. (1995) found negative effects on memory function of elderly subjects after treatment with lormetazepam but not tiapride in a randomized double-blind cross-over study.

The limitations of open studies are sample effects, rating biases or systematic effects that are not controlled by random design. Differences in the quality of medical records might also have affected the results. Therefore, a randomised study tiapride/carbamazepine vs. clomethi-

azole is already in preparation. Additionally, a controlled, double blind study is necessary. To determine whether the potential superiority of tiapride/carbamazepine can be shown in all degrees of severity of AWS, the severity of alcohol withdrawal should be introduced as an explicit experimental factor.

Central respiratory depression or dependence are not expected when using a combination of tiapride and carbamazepine. A lack of sedative action allows patients more alertness than on clomethiazole, benzodiazepines or antipsychotics. Therefore the ability to communicate and to follow cognitive oriented psychotherapy is not restricted. Provided the findings of this study can be confirmed in future investigations, the increased benefit and lower risk using this combination might be a promising treatment strategy for the alcohol withdrawal syndrome.

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