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Pregabalin, tiapride and lorazepam in alcohol withdrawal syndrome: a multi-centre, randomized, single-blind comparison trial

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ABSTRACT

Introduction The aim of this trial was to compare lorazepam with non-benzodiazepine medications such as pregabalin and tiapride in the treatment of alcohol withdrawal syndrome (AWS). These drugs were chosen for their inhibitorial effects on the hypersecretion of neurotransmitters usually observed in AWS. Craving reduction and improvement of psychiatric symptoms were the secondary end-points. **Methods** One hundred and ninety subjects affected by current alcohol dependence were considered consecutively: 111 were enrolled and divided into three groups of 37 subjects each. Within a treatment duration of 14 days, medication was given up to the following maximum doses (pregabalin 450 mg/day; tiapride 800 mg/day; lorazepam 10 mg/day). Withdrawal (CIWA-Ar), craving [visual analogue scale (VAS); Obsessive and Compulsive Drinking Scale (OCDS)], psychiatric symptoms [Symptom Check List 90 Revised (SCL-90-R)] and quality of life (QL-index) rating scales were applied. **Results** On the CIWA-Ar score, all the groups showed a significant reduction between times ($P < 0.001$) with a higher reduction for the pregabalin group ($P < 0.01$) on items regarding headache and orientation. Retention in treatment was lower in the tiapride group ($P < 0.05$), while the number of subjects remaining alcohol free was higher in the pregabalin group ($P < 0.05$). Significant reduction between baseline and the end of the treatment was found in all the groups at the OCDS and the VAS for craving, at the SCL-90-R and QL-index ($P < 0.001$). **Discussion** All the medications in the trial showed evidence of safety and efficacy in the treatment of uncomplicated forms of AWS, with some particular differences. The efficacy of pregabalin was superior to that of tiapride, used largely in research trials and, for some measures, to that of the 'gold standard', lorazepam. Accordingly, pregabalin may be considered as a potentially useful new drug for treatment of AWS, deserving further investigation.

Keywords Alcohol withdrawal, benzodiazepines, CIWA-Ar, craving, pregabalin, tiapride.

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INTRODUCTION

Alcohol withdrawal syndrome (AWS) can be a life-threatening condition affecting alcohol-dependent patients who discontinue or decrease their alcohol consumption too suddenly [1,2]. Discontinuation of alcohol ingestion results in the nervous system hyperactivity and dysfunction that characterizes alcohol withdrawal [3]. Chronic alcohol exposure induces brain neuroadaptative changes in order to compensate for the alcohol-induced destabilization to restore a neurochemical equilibrium [4]. Long-term exposure to alcohol causes adaptive changes in several neurotransmitter systems, including gamma-aminobutyric acid (GABA) receptors, glutamate receptors and central noradrenaline and dopamine activity [5]. Glutamate represents the most common excitatory neurotransmitter in the human brain, acting on several types of receptors in the central nervous system (CNS). The one most affected by alcohol is the N-methyl-D-aspartate (NMDA) receptor [6]. GABA is the major inhibitory neurotransmitter, and binds to a fast-acting receptor complex denoted as GABA-A, which hyperpolarizes the cell membrane and thereby inhibits neural activity [6]. GABA plays a key role in the neurochemical

mechanisms on the basis of intoxication, tolerance and withdrawal [7]. In addition, alcohol withdrawal symptomatology has also been found to be correlated positively with dopamine hyperactivity [8]. However, the neurobiology of AWS represents a complex system involving not only glutamate and GABA but many other neurotransmitters and neuromodulators, such as dopamine, noradrenaline, serotonin (5-HT), corticotropin-releasing factor (CRF) and adenosine acetylcholine (ACHe) [9].

Ethanol withdrawal in humans and animals is characterized by CNS hyperexcitability that results in both physical and 'affective' signs of dependence. GABA agonists decrease CNS hyperexcitability during ethanol withdrawal and decrease ethanol withdrawal-induced convulsions [7].

Withdrawal symptoms usually develop within 6–24 hours after the last drink. In withdrawal syndromes ranging from light to moderate forms, symptoms include increase in blood pressure and pulse rate, tremors, hyperreflexia, irritability, anxiety and depression [1,2]. Mild manifestations of AWS can contribute to the so-called 'hangover', although AWS and hangover represent two different, even if partially overlapping, phenomena (for review: [10]). The symptoms of severe AWS may progress to more complicated forms characterized by delirium tremens [11], seizures [12] and coma [13]. In these forms, cardiac arrest and death may occur in 5–10% of patients [14,15]. In alcohol-dependent patients, the possible development of AWS should also be considered after an acute alcohol intoxication episode [16]. Repeated withdrawal episodes may contribute to the development of alcohol dependence and to negative consequences associated with excessive alcohol consumption [17]. In addition, a protracted withdrawal syndrome has been described recently [18] as a combination of physical and psychopathological symptoms that lasts for a long period of time beyond the acute syndrome.

Assessment of AWS is critical to facilitate adequate treatment measures. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) has emerged as the 'gold standard' observer-rated measure of AWS severity [19], particularly in the 10-item revised form (CIWA-Ar; [20,21]).

The main objectives of the clinical management of AWS are to decrease the severity of symptoms, prevent more severe withdrawal clinical manifestations such as seizures and delirium tremens and facilitate entry of the patient into a treatment programme in order to attempt to achieve and maintain long-term abstinence from alcohol [22,23]. The ideal drug for AWS should have a rapid onset and a long duration of action, few significant side effects, a wide margin of safety, a metabolism not dependent on liver function and absence of abuse potential [23,24].

At present, benzodiazepines (BZs) are the drugs of choice in the treatment of AWS [25,26] as they have proved their efficacy in ameliorating symptoms and decreasing the risk of seizures and delirium tremens [27].

While BZs are widely accepted agents in the pharmacological management of AWS [28–30], side effects associated with these drugs are common. For example, the use of BZs are associated with increased risk of excess sedation, memory deficits and respiratory depression in patients with liver impairment [26,31]. The sedative and psychomotor deficits caused by BZs have an additive effect with alcohol that is particularly problematic in the outpatient treatment of alcohol withdrawal [32]. Benzodiazepines have abuse and dependence liability [32–37] which constitutes a limitation to their use in subjects affected by substance use disorder [26,31].

In our study we compare lorazepam with non-benzodiazepine medications such as pregabalin and tiapride. These drugs were chosen for their inhibitorial effects on the hypersecretion of neurotransmitters usually observed in AWS.

Pregabalin acts as a presynaptic modulator of the excessive release, in hyperexcited neurones, of excitatory neurotransmitters, including glutamate [38] and monoaminergic neurotransmitters [39,40]. Pregabalin binds selectively to the α^2–δ subunit protein of voltage-gated calcium channels, and rapidly reduces the influx of calcium, subsequently reducing the exocytosis of synaptic vescicles in the synaptic cleft. Pregabalin has relatively little effect on neuronal function under conditions of normal activity [41] and its effect appears to be correlated strongly with the degree of hyperexcitation of the presynaptic neurone. It is not protein-bound, has an eliminatory half-life of 6 hours and is primarily (92%) excreted renally. It exhibits few drug–drug interactions, does not inhibit cytocrome P450 enzymes, nor do these enzymes alter its pharmacokinetics. Evidence derived from different double-blind placebo-controlled studies suggests that pregabalin may be efficacious in the treatment of general anxiety disorder [42–46] and in the relapse prevention of alcohol-dependent subjects [47,48]. The therapeutic rationale of pregabalin is the putative effect on both seizure risk and anxiety in alcohol withdrawal, without significant risk for an abuse potential or risk of overdose.

Tiapride, a benzamide, has a D2 and a D3 receptor antagonist activity with no affinity for D1 and D4 receptors in limbic brain areas [49], and is used frequently for treatment of hyperkinetic disorders, agitation and aggressiveness [50]. Tiapride does not cause dependence or respiratory depression and does not reduce vigilance during treatment. Recently, it has been suggested for treatment of alcohol withdrawal syndrome [51] for its effect in reducing dopamine hyperactivity. When evidenced in alcohol withdrawal, previous research suggests

tiapride to be effective in psychovegetative symptoms, such as hyperhidrosis and tremor, but not in seizures and hallucinations [52–55]. Different studies have proposed the association of tiapride and carbamazepine, with positive results [56–59]. The therapeutic rationale of tiapride is the effect on psychovegetative symptoms in alcohol withdrawal, without a significant risk for an abuse potential or risk of overdose. This may be of relevance for patients with less severe forms of AWS, including outpatients.

The aim of our study was to compare lorazepam, a benzodiazepine of choice in the treatment of AWS, with non-benzodiazepines medications such as pregabalin and tiapride. Primary outcome measures were the reduction of withdrawal symptoms, the number of days remaining in treatment and the maintenance of abstinence. Secondary outcomes measures were the reduction of alcohol craving, psychiatric comorbid symptoms and safety parameters.

METHODS

Patients and treatment

Between December 2006 and September 2008, 190 subjects affected by current alcohol dependence referring to the alcohol treatment unit of the day hospital, department of psychiatry and drug dependence of the University General Hospital 'A. Gemelli' in Rome and to the out-patient alcohol unit 'Villa Silvia' at Senigallia (AN) were considered consecutively for the study. All the patients were evaluated by attending psychiatrists using the Structured Clinical Interviews for DSM-IV (SCID I, SCID II) [60,61]. Inclusion criteria were: age between 18 and 75 years; a daily alcohol consumption of more than 80 g of alcohol during the previous 24 hours; and diagnosis of alcohol dependence according to DSM-IV-TR [62] criteria. Exclusion criteria were the current presence of: delirium tremens or hallucinosis; evidence of mental disorders severely interfering with cognitive capacity; epilepsy; severe cardiac failure; diabetes mellitus; severe liver impairment; liver encephalopathy; kidney failure; neoplastic diseases; lack of cooperating relatives; regular intake of anticonvulsants, antidepressants or antipsychotics; pregnancy or lactation; or a history of severe adverse reaction or well-known hypersensitivity to pregabalin, tiapride and benzodiazepines. Patients with blood alcohol concentration lower than 0.1 g/l were assessed using the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) [20,21] scale, a scoring system for quantitative evaluation of physical symptoms of AWS. Only subjects with a CIWA-Ar score equal to or higher than 10 (defined as moderate AWS requiring pharmacological treatment) were enrolled ultimately in the study. Consequently, severe AWS was included in the study.

The diagram showing subject flow by treatment group is described in Fig. 1.

Random assignment was achieved in a non-centre-specific manner and was stratified according to age and sex to ensure a relative balance in the total number of patients among groups.

Study procedures

Within a treatment duration of 14 days, medication was given up to the following maximum doses (pregabalin 450 mg/day; tiapride 800 mg/day; lorazepam 10 mg/day). Within this range, medication was score-guided to achieve a minimum of withdrawal symptomatology as measured with the CIWA-Ar. In a previous study the administration of score-guided or symptom-triggered medication as part of an individualized treatment decreased both treatment duration and amount of medication used, and was as efficacious as standard fixed-schedule therapy for alcohol withdrawal [25]. All packaging of treatments was identical in appearance.

A placebo group was not included because we are comparing novel treatments to well-established therapy such as lorazepam, which was compared to placebo in different trials [26].

The drug therapy was administered by the principal investigator from 8 a.m. to 4 p.m. and by a referred family member from 4 p.m. to 8 a.m.

CIWA-Ar [20,21] and the Visual Analogue Scale for Craving (VASc) [63] were administered once a day (immediately before the first daily administration of the drug) on days 1, 2, 3, 4, 5, 6, 7 and 14. We decided to assess craving and withdrawal at 8 a.m. because at that time patients had to stay inside the out-patient unit, not influenced by external stressors. The same time of assessment was reported in other studies concerning alcohol detoxification [5,64]. The Italian version of the Obsessive and Compulsive Drinking Scale (OCDS) [65] was administered on days 1 and 14. Psychiatric symptomatology, assessed by the Symptom Check-List 90 Revised (SCL-90-R) [66] and quality of life [67] were evaluated on days 1 and 14. Baseline values were those collected on day 1 before the first drug administration. The whole study was performed on a single-blind design. However, investigators who performed CIWA-Ar and other scales at different times of treatment were always the same, and they were always unaware as to which drug being administered to patients.

Abstinence from alcohol was evaluated on the basis of the participant's self-evaluation and a family member interview. Abstinence was confirmed by determining blood alcohol concentration randomly at each out-

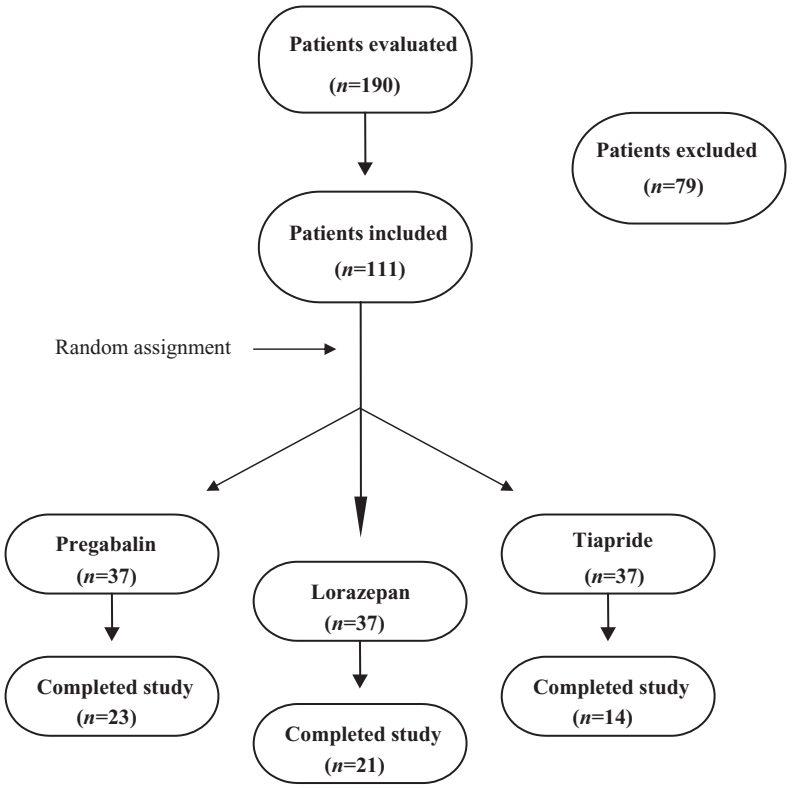

Figure 1 Diagram of subject flow by treatment group

patient control, and by measuring alcohol abuse hepatic indices [aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and mean cellular volume (MCV)]. Toxicological urinalysis was performed at each out-patient control in order to identify polydrug abuse.

A rescue protocol was available if the patient did not respond to the treatment similarly to the randomization. Specifically, if the CIWA-Ar remained higher than 10 or increased during the first 2 hours, an oral dose of 0.75 mg/kg diazepam [22] and/or an intramuscular dose of 10 mg haloperidol [68] would be administered.

Safety parameters were monitored through electrocardiogram (ECG), urinalysis, haematological and clinical chemical analyses of blood samples at the start and end of the study (day 14).

The study protocol complied fully with the guidelines of the Ethics Committee of the Catholic University of Rome, and was approved by the Institutional Review Boards in accordance with local requirements. It was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1964) and subsequent revisions. After receiving information about the drug, any possible side effects and the dose rate, as well as information about the possibility of dropping out of the study at any time, all patients (or their legal representatives) provided their written informed consent prior to randomization. Each patient was informed that an alcohol relapse, non-compliance or the onset of any side effects would lead to their exclusion from the trial. However, patients were free to leave the study at any time.

Data analysis

The three treatment groups were compared. Given a non-normal distribution of the data, only non-parametric tests were used. Baseline demographic and clinical features were compared across groups using a χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Spearman's correlation coefficient was used to verify the correlations between OCDS and VASc. Primary outcome measures were: time to dropout (number of days remaining in treatment), reduction of withdrawal symptoms as to CIWA-Ar and the maintenance of abstinence (a return to drinking any alcohol marked the end of the abstinence). Secondary outcomes measures were: reduction of alcohol craving (VASc; OCDS), psychiatric symptoms (SCL-90-R) and safety parameters.

Primary and secondary efficacy analyses were performed on the intent-to-treat population, which included all randomly assigned patients who took at least one dose of study medication.

Time to dropout was compared across groups using Kaplan–Meier survival curves and the log-rank test.

Differences in psychiatric and withdrawal symptoms and craving scores before and after the treatment were

calculated for each group: comparisons within each treatment group were carried out by Wilcoxon's paired test, while possible differences across treatment groups were again investigated by Kruskal–Wallis test.

Next, we dichotomized the outcome of treatment considering patients remaining abstinent by the end of the study or relapsed/dropped. We compared these two groups according to baseline demographic and clinical variables by means of χ^2 test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Finally, to determine what factors, if any, were associated with remaining abstinent, we entered variables that were significant at $P < 0.10$ in the bivariate analyses into a multivariable model using logistic regression. We examined all variables for multi-collinearity. We used the Hosmer–Lemeshow goodness-of-fit statistic to check the model fit. We defined *P*-values of 0.05 or below as statistically significant. We report the findings as odds ratios (ORs) and *P*-values.

RESULTS

Patients and disposition

A total of 190 patients were screened, of whom 79 were excluded from the study. There were no significant differences between the baseline characteristics of patients who did not pass the screening compared with those who were included in the study. The three groups of randomized patients did not vary in terms of socio-demographic and clinical (SCID-I, SCID II) characteristics, craving (OCDS, VASc), withdrawal (CIWA-Ar) scores and psychiatric symptomatology (SCL-90-R) at baseline (Table 1). Patients affected by multiple substance abuse and with a dual diagnosis were distributed equally in the three samples. The additional Axis I diagnoses were in the areas of mood disorders (pregabalin: 11; tiapride: 9; lorazepam: 10), anxiety disorders (pregabalin: 2; tiapride: 3; lorazepam: 2), impulse control disorders (pregabalin: 3; tiapride: 2; lorazepam: 1), and eating disorders (tiapride: 2; lorazepam: 1). The additional Axis II diagnosis were borderline (pregabalin: 3; tiapride: 2; lorazepam: 1), antisocial (pregabalin: 1), avoidant (pregabalin: 2; lorazepam: 1), histrionic (pregabalin: 2; tiapride: 3; lorazepam: 1), passive–aggressive (pregabalin: 2; tiapride: 3; lorazepam: 3), non-otherwise specified (pregabalin: 2; tiapride: 1; lorazepam: 3) and schizoid (pregabali: 1; tiapride: 1) personality disorders.

Multiple substance abuse, other than alcohol abuse, was represented by cannabis abuse (pregabalin: 8; tiapride: 5; lorazepam: 6), cocaine abuse (pregabalin: 4; tiapride: 3; lorazepam: 7), benzodiazepine abuse (pregabalin: 1; tiapride: 2) and tobacco smoking (pregabali: 20; tiapride: 18; lorazepam: 23).

Efficacy

The number of subjects remaining alcohol free for the entire study period [pregabalin: 23 (62.2%); tiapride: 14 (37.8%); lorazepam: 21 (56.8%)] was significantly different in the three treatment groups, with a higher number in the pregabalin group ($\chi^2 = 4.19$, $P = 0.04$). The rescue protocol was applied in just one patient of the tiapride group for the presence of the typical symptoms of delirium tremens.

The survival curve of time to dropout (retention in treatment) is shown in Fig. 2. The survival function showed that patients treated with pregabalin remained in treatment for a longer time compared to both those groups treated with tiapride and lorazepam, but differences are statistically significant only in comparison with tiapride (log-rank test = 3.87, $P = 0.04$), while there were no statistically significant differences between patients treated with pregabalin and lorazepam (log-rank test = 0.82, $P = 0.36$) or lorazepam and tiapride (log-rank test = 0.88, $P = 0.34$). The survival curve of time to relapse (first alcohol use), resemble closely the survival curve of time to dropout (data not shown). However, levels of significance were not reached, given the low number of patients included in this analysis and the resulting low statistical power.

At baseline, mean total CIWA-Ar score was not different between groups. When analysed separately, all the groups showed a significant reduction between times (Friedman test = 191.5, $P < 0.001$ for pregabalin, 136.7, $P < 0.001$ for lorazepam, 167.65, $P < 0.001$ for tiapride). The decrease in the CIWA-Ar score was significant between all times except between days 6 and 7 in the pregabalin group, days 5 and 6 in the lorazepam group and days 6 and 7 in the tiapride group (Fig. 3).

Significant differences between groups of treatment were found with regard to items 9 (headache, fullness in head) and 10 (orientation and clouding of sensorium) of CIWA with an higher reduction for pregabalin group (Kruskal–Wallis test = 7.5, $P = 0.02$; 8.8, $P = 0.01$).

In relation to craving, a significant reduction between baseline and the end of the treatment was found in all groups at both the OCDS (Table 2) and the VASc (Fig. 4). Significant differences were not evidenced between groups. In the entire sample, VASc scores were correlated significantly with those of obsessive symptoms of OCDS at baseline (day 1) (Spearman's rho = 0.31; $P < 0.001$) and at the end of the study (day 14) (Spearman's rho = 0.32; $P = 0.002$).

All the treated patients showed a statistically significant improvement in scores on the quality of life scale (Table 2). Between groups, differences were not found.

In relation to the comorbid psychiatric symptoms (SCL-9-R), the global score (GSI: General Symptom Index)

Table 1 Socio-demographic characteristics, alcohol history and clinical data of the sample.

	Lorazepam *n = 37*	*Tiapride* *n = 37*	*Pregabalin* *n = 37*
Parameter	*n (%)*	*n (%)*	*n (%)*
Socio-demography			
Age (mean, SD)			
Males	24 (65)	23 (62)	22 (59)
Females	13 (35)	14 (38)	15 (41)
Marital status			
Single	11 (29.7)	10 (27.1)	13 (35.1)
Married	17 (45.9)	18 (48.6)	12 (32.4)
Separated/divorced	9 (24.4)	7 (18.9)	9 (24.4)
Widowed	0	2 (5.4)	3 (8.1)
Level of education			
Elementary school	3 (8.1)	4 (10.8)	2 (5.4)
Lower secondary school	13 (35.1)	14 (37.8)	14 (37.8)
High school education	12 (32.4)	14 (37.8)	16 (43.2)
Degree	9 (24.4)	5 (13.6)	5 (13.6)
Employment condition			
Retired	4 (10.8)	5 (13.6)	5 (13.6)
Employed	22 (59.5)	20 (54)	25 (67.5)
Unemployed	11 (29.7)	12 (32.4)	7 (18.9)
Alcohol-related history			
Duration of alcohol dependence (years: mean, SD)	9.9, 4.5	9.3, 5.2	8.9, 4.8
Daily drinks[a] (mean, SD)	8.9, 4.5	7.9, 3.5	8.2, 2.5
Values at the baseline			
CIWA-Ar score (mean, SD)	12.89, 9.06	16.97, 8.81	17.17, 8.32
VASc score (mean, SD)	3.28, 3.49	5.26, 3.31	3.45, 3.11
Dual diagnosis (Axis I)			
Affective disorders	10 (27)	9 (24.4)	11 (29.7)
Impulse-control disorder	1 (2.7)	2 (5.4)	3 (8.1)
Anxiety disorders	2 (5.4)	3 (8.1)	2 (5.4)
Eating disorders	1 (1.7)	2 (5.4)	0
Dual diagnosis (Axis II)	0	1 (2.7)	1 (2.7)
Cluster A	2 (5.4)	5 (13.6)	6 (16.2)
Cluster B	1 (2.7)	0	2 (5.4)
Cluster C	6 (16.2)	4 (10.8)	4 (10.8)
NOS			

[a]One drink = 12 g or 0.5 oz. CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol-revised; VASc: Visual Analogue Scale for Craving; SD: standard deviation; NOS: not otherwise stated.

reduced significantly in all the groups (Table 3). With regard to the single items, the differences between baseline and the end of the treatment are also shown in Table 3. Significant differences between the three groups of treatment were found in single symptoms of interpersonal sensitivity (Kruskal–Wallis test = 10.7, $P = 0.005$), depression (Kruskal–Wallis test = 8.5, $P = 0.01$), hostility (Kruskal–Wallis test = 12.6, $P = 0.002$) and GSI (Kruskal–Wallis test = 7.9, $P = 0.02$), with a higher reduction in the pregabalin group.

Considering the entire sample of patients, logistic regression analysis showed that a higher OCDS subscore for compulsive craving at baseline was associated with a higher risk (OR = 1.17, $P = 0.03$) of relapse in alcohol consumption before the end of the treatment.

Safety and tolerability

Common adverse events (whether or not considered treatment-related) occurred in one (2.7%) patient in the pregabalin group (confusion) and in one (2.7%) patient in the lorazepam group (sedation). In the tiapride group no adverse event was observed during the entire study period. The overall rate of study discontinuation due to adverse event was 2.7 % ($n = 1$) in the pregabalin group, due to confusion.

No clinically relevant differences between groups were seen in the mean change from baseline for any vital signs, ECGs, haematology or clinical chemistry parameters.

Comparing hepatic alcohol abuse indices before and after treatment administration, we found a significant

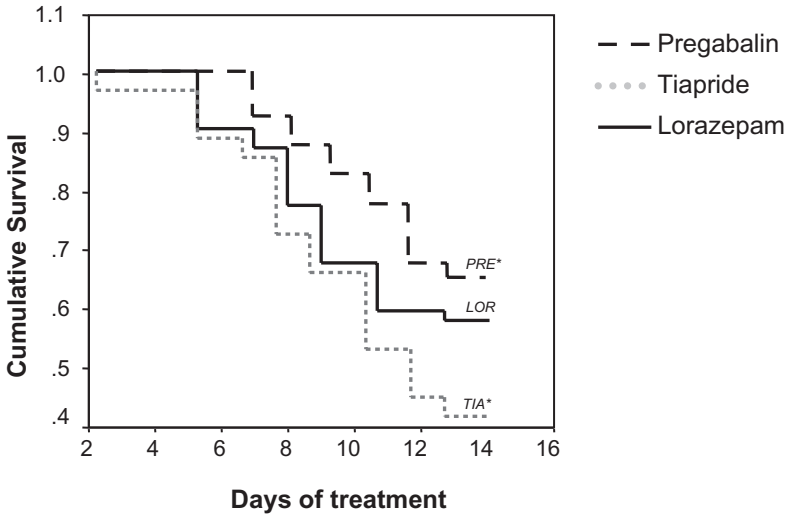

Figure 2 Survival remaining in treatment. *$P < 0.05$ between pregabalin and tiapride

Table 2 Mean change from baseline (pre) at last assessment (post) for the Obsessive and Compulsive Drinking Scale (OCDS) total, obsessive and compulsive components and quality of life (QL index) in the three groups. Differences within and between groups are reported.

			Differences within groups			*Differences between groups*
			Pre (T1)	*Post (T2)*		
Parameter	*Medication*	*n*	*Mean ± SD*	*Mean ± SD*	*Z[a](p)*	*X[2b](P)*
OCDS						
Total	Lorazepam	37	20.03 ± 8.71	10.94 ± 9.4	−3.982 (<0.001)	4.129 (0.127 NS)
	Tiapride	37	18.1 ± 7.44	11.16 ± 9.34	−2.814 (0.005)	
	Pregabalin	37	19.25 ± 7.09	8.47 ± 7.71	−4.991 (<0.001)	
Obsessive	Lorazepam	37	8.53 ± 5.25	4.97 ± 4.51	−3.331 (<0.001)	0.672 (0.715 NS)
	Tiapride	37	9.06 ± 4.61	5.72 ± 4.67	−2.619 (0.009)	
	Pregabalin	37	8.2 ± 4.29	4.16 ± 3.84	−4.095 (<0.001)	
Compulsive	Lorazepam	37	12.32 ± 4.35	5.97 ± 5.29	−4.208 (<0.001)	0.925 (0.630 NS)
	Tiapride	37	15.03 ± 12.42	6.32 ± 5.33	−3.918 (<0.001)	
	Pregabalin	37	12.4 ± 3.69	5.16 ± 4.66	−5.19 (<0.001)	
QL index	Lorazepam	37	5.78 ± 1.06	7.19 ± 1.22	−3.25 (<0.001)	3.570 (0.168 NS)
	Tiapride	37	6.35 ± 1.46	7.15 ± 1.22	−3.307 (<0.001)	
	Pregabalin	37	6 ± 0.816	7.47 ± 0.87	−3.482 (<0.001)	

[a]Wilcoxon signed-ranks test; [b]Kruskall–Wallis test. NS: not significant; SD: standard deviation.

decrease in the values of GGT ($P < 0.01$), AST ($P < 0.01$) and ALT ($P < 0.01$) in all the treatment groups with no significant difference between groups. Apart from a significant decrease in cholesterol levels ($P < 0.05$), biochemical analysis of glucose, low-density lipoprotein, high-density lipoprotein, non-esterified fatty acids and triglycerides, there were no significant differences in biochemical markers between baseline and the end of treatment. Mean change in weight from baseline to the end of treatment was +0.3 kg in the pregabalin group, −0.3 in the lorazepam group and +0.4 in the tiapride group.

At drug discontinuation, we observed no side effects due to drug suspension in either group.

DISCUSSION

At present, benzodiazepines represent the 'gold standard' in the management of patients with AWS [26,29]. However, the use of benzodiazepines is associated with several side effects, such as risk of excess sedation, memory deficits and respiratory depression in patients with liver impairment, as is often the case in alcoholics.

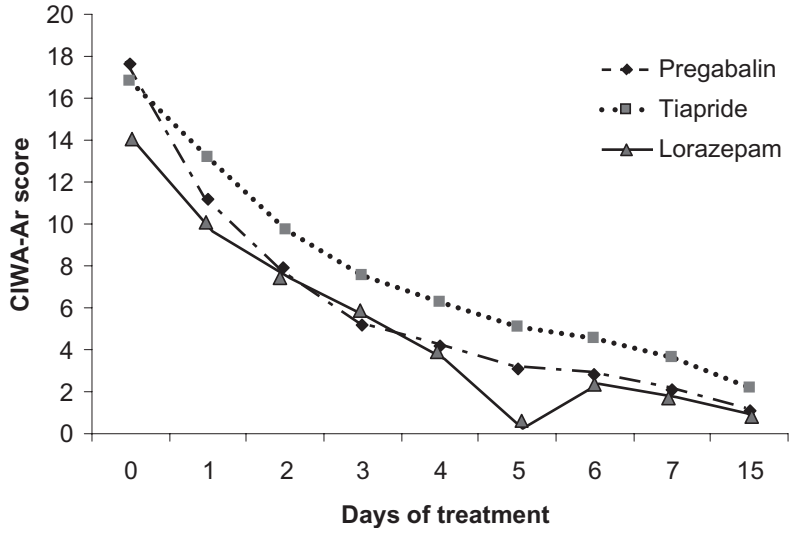

Figure 3 Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) has emerged as the 'gold standard' observer-rated measure of alcohol withdrawal syndrome (AWS) severity-revised [19], (CIWA-Ar) scores over days of detoxification

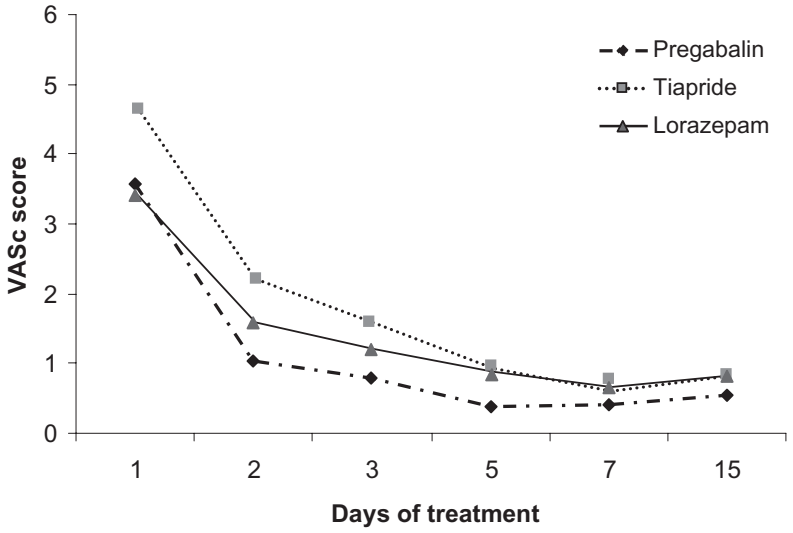

Figure 4 Visual Analogue Scale for Craving (VASc) scores over days of detoxification

Moreover, benzodiazepines could have addictive properties, which constitutes a limitation to their use in subjects affected by substance use disorders [31,33]. Consequently, the discover of new potentially useful drugs for the treatment of AWS is of considerable practical importance, as confirmed by the growing research interest in non-benzodiazepines medications in the treatment of AWS [69].

To our knowledge, this multi-centre, randomized, single-blind clinical trial is the first parallel group study to compare the efficacy of lorazepam, tiapride and pregabalin for alcohol dependence. Additionally, our sample was composed of heavy drinking alcoholics, with moderate to severe AWS, an average intake of eight drinks per day and a history of abuse/dependence for more than 3 years.

All the medications in the study showed evidence of safety and efficacy, with some particular differences. Overall, our results indicate that pregabalin and lorazepam are comparable for the treatment of AWS and craving for alcohol. However, pregabalin at flexible dosages (mean: 275.8 ± 95.6 mg/day), lower than those prescribed for treatment of partial seizures [70], was shown to be more effective than lorazepam and tiapride in the management of some symptoms of the AWS (headache and clouding of sensorium), at least in its uncomplicated form. Moreover, pregabalin showed a better outcome in terms of relapse rate and the number of patients retained in treatment.

The observed suppressant effect of pregabalin on AWS, as in the present study, together with its efficacy in reducing alcohol craving and intake [47,48], feature pregabalin as a promising, and perhaps unique, pharmacotherapy for alcohol dependence. This drug is of particular interest in view of its efficacy in two major aspects of the disorder, namely AWS and maintaining abstinence from alcohol intake. This specific ability of pregabalin should,

Table 3 Mean change from baseline (pre) at last assessment (post) for the Symptom Check List 90 Revised (SCL-90-R) scores in the three groups. Differences within and between groups are reported.

			Differences within groups			*Differences between groups*
			Pre (T1)	*Post (T2)*		
Parameter	*Medication*	*n*	*Mean ± SD*	*Mean ± SD*	*Z[a](p)*	*X[2b](P)*
Somatization	Lorazepam	37	0.90 ± 0.51	0.47 ± 0.39	−4.160 (<0.001)	1.171 (0.557 NS)
	Tiapride	37	1.21 ± 0.65	0.75 ± 0.64	−3.213 (<0.001)	
	Pregabalin	37	0.93 ± .60	0.41 ± 0.36	−4.586 (<0.001)	
Obsessive–compulsive	Lorazepam	37	1.17 ± 0.72	0.67 ± 0.65	−4.380 (<0.001)	4.703 (0.095 NS)
	Tiapride	37	1.09 ± .73	0.60 ± 0.45	−3.276 (<0.001)	
	Pregabalin	37	1.3 ± .82	0.67 ± 0.61	−4.317 (<0.001)	
Interpersonal sensitivity	Lorazepam	37	0.90 ± 0.65	0.53 ± 0.54	−3.573 (<0.001)	10.75 (0.005)
	Tiapride	37	0.69 ± 0.49	0.47 ± 0.51	−2.566 (0.01)	
	Pregabalin	37	1.01 ± 0.77	0.47 ± 0.50	−4.641 (<0.001)	
Depression	Lorazepam	37	1.11 ± 0.74	0.66 ± 0.62	−3.937 (<0.001)	8.514 (0.014)
	Tiapride	37	1.27 ± 0.76	0.77 ± 0.69	−2.724 (0.006)	
	Pregabalin	37	1.48 ± 0.87	0.76 ± 0.60	−4.736 (<0.001)	
Anxiety	Lorazepam	37	1.07 ± 0.73	0.59 ± 0.64	−3.862 (<0.001)	3.67 (0.160 NS)
	Tiapride	37	1.1 ± 0.69	0.63 ± 0.65	−3.466 (<0.001)	
	Pregabalin	37	1.21 ± 0.79	0.53 ± 0.43	−4.796 (<0.001)	
Anger–hostility	Lorazepam	37	0.61 ± 0.45	0.47 ± 0.47	−2.465 (0.014)	12.601 (0.02)
	Tiapride	37	0.72 ± 0.53	0.49 ± 0.66	−2.685 (0.007)	
	Pregabalin	37	0.89 ± 0.81	0.39 ± 0.48	−4.668 (<0.001)	
Phobic anxiety	Lorazepam	37	0.49 ± 0.47	0.25 ± 0.33	−3.627 (<0.001)	2.126 (0.345 NS)
	Tiapride	37	0.75 ± 0.79	0.45 ± 0.62	−2.555 (0.011)	
	Pregabalin	37	0.66 ± 0.71	0.31 ± 0.40	−4.122 (<0.001)	
Paranoid ideation	Lorazepam	37	0.99 ± 0.67	0.69 ± 0.62	−2.367 (0.018)	3.519 (0.172 NS)
	Tiapride	37	0.84 ± 0.64	0.62 ± 0.70	−1.766 (0.077)	
	Pregabalin	37	1.05 ± 0.72	0.70 ± 0.67	−3.657 (<0.001)	
Psychoticism	Lorazepam	37	0.61 ± 0.55	0.35 ± 0.41	−3.175 (<0.001)	1.864 (0.394 NS)
	Tiapride	37	0.65 ± 0.55	0.42 ± 0.55	−2.492 (0.013)	
	Pregabalin	37	0.57 ± 0.53	0.32 ± 0.38	−4.562 (<0.001)	
Global severity index	Lorazepam	37	0.94 ± 0.52	0.56 ± 0.48	−4.639 (0.000)	7.932 (0.019)
	Tiapride	37	1 ± 0.53	0.62 ± 0.53	−3.771 (0.000)	
	Pregabalin	37	1.08 ± 0.62	0.54 ± 0.41	−4.923 (0.000)	

[a]Wilcoxon Signed Ranks Test; [b]Kruskall Wallis Test. NS: not significant; SD: standard deviation.

theoretically, results in a vastly simplified pharmacotherapy and higher compliance of treatment.

Other points in favour of the employment of pregabalin were represented by the reduction of specific symptoms in the areas of anxiety, hostility and psychoticism.

The results presented are in agreement with those observed in our previous studies on alcohol relapse prevention, where pregabalin was comparable to naltrexone to reduce craving and alcohol consumption, but with a significantly higher reduction of withdrawal scores [47,48].

Despite the use of pregabalin in the treatment of anxiety symptoms, no rebound anxiety was noted during drug discontinuation. This profile is in contrast to the occurrence of discontinuation symptoms and rebound anxiety when therapeutic doses of benzodiazepines are discontinued abruptly after some weeks of therapy [71,72].

With regard to tiapride, it is interesting to note its favourable effect on the compulsive aspect of alcohol craving during the first days of withdrawal. This may be determined by the reduction of the hypersecretion of dopamine induced by alcohol withdrawal. Apart from these aspects, the results of the present study show that the administration of low doses of tiapride are as effective as lorazepam in the treatment of AWS. The application of the rescue protocol for a patient of the tiapride group for delirium tremens suggests that the use of tiapride should

be limited to non-severe and non-complicated types of alcohol withdrawal.

Finally, liver function tests in all the treated subjects showed significantly improved results, with no difference between groups. This is due clearly to the suspension of alcohol intake, as indicated by the decrease in GGT, but the parallel reduction in indices of hepatocellular damage point to the safety of the drug. These data, together with haematological and ECG responses, corroborate what has been described previously with lorazepam, tiapride and pregabalin in other psychopathological and neurological conditions [73–85], confirming their favourable safety profile in alcoholics.

The results of this study need to be interpreted with caution due to its limitations. First, the absence of a placebo group is a weakness that tempers the interpretation of the results. Secondly, the single-blind design possibly caused a bias in evaluating efficacy, although investigators who gave the scales were always unaware as to which drug being administered to patients. Thirdly, the findings for AWS must be treated with caution due to the high number of statistical comparisons, and also because there was a tendency (non-significant) for CIWA-Ar baseline scores to be higher in the lorazepam and pregabalin groups compared with the tiapride group.

In conclusion, the results of the present study indicate that the efficacy of pregabalin in the treatment of uncomplicated forms of AWS is superior to that of tiapride, used largely in research trials and clinical practice and, for some measures, to that of the 'gold standard', lorazepam. Accordingly, pregabalin may be considered as a new potentially useful drug for treatment of AWS, deserving further investigation. Despite this, we wish to emphasize that at present benzodiazepines still represent the drug of choice in treating AWS, also considering their proven efficacy in preventing complicated forms such as delirium tremens and epileptic seizures.

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