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ORIGINAL INVESTIGATION

Etifoxine is non-inferior than clonazepam for reduction of anxiety symptoms in the treatment of anxiety disorders: a randomized, double blind, non-inferiority trial

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Abstract

Objective To determine whether etifoxine, a non-benzodiazepine drug of the benzoxazine family, is non-inferior compared with clonazepam in the treatment of anxiety disorders.

Method A randomized controlled double blind trial with parallel groups was conducted. A total of 179 volunteer patients with a diagnosis of anxiety disorder (DSM-IV), between 18 and 64 years of age, participated in this study. The experimental group received 150 mg/day of etifoxine and the control 1 mg/day of clonazepam, both in three daily doses for 12 weeks. This treatment was completed by 87 participants, and 70 were available for follow-up at 24 weeks from start of treatment. The primary objective was a non-inferiority comparison between etifoxine and clonazepam in the decrease of anxiety symptoms (HAM-A) at 12 weeks of treatment. Secondary outcomes included the evaluation of medication side effects (UKU), anxiety symptoms at 24 weeks of treatment, and clinical improvement (CGI). Data analysis included multiple imputation of missing data. The effect of etifoxine on the HAM-A, UKU, and CGI was evaluated with the intention of treatment, and a sensitivity analysis of the results was conducted. Non-inferiority would be declared by a standardized mean difference (SMD) between clonazepam and etifoxine not superior to 0.31 in favour of clonazepam.

Results Using imputed data, etifoxine shows non-inferiority to clonazepam on the reduction of anxiety symptoms at the 12-week (SMD = 0.407; 95% CI, 0.069, 0.746) and 24-week follow-ups (SMD = 0.484; 95% CI, 0.163, 0.806) and presented fewer side effects (SMD = 0.58; 95% CI, 0.287, 0.889). LOCF analysis shows that etifoxine is non-inferior to clonazepam on reduction of anxiety symptoms and adverse symptoms even when no change was assigned as result to participant whom withdrew. Non-inferiority could be declared for clinical improvement (SMD = 0.326; 95% CI, − 0.20, 0.858).

Conclusion Etifoxine was non-inferior to clonazepam on reduction of anxiety symptoms, adverse effects, and clinical improvement.

Keywords Anxiety · Etifoxine · Clonazepam · Benzodiazepines · Non-inferiority trial

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Introduction

Anxiety disorders have, as the main symptom, the presence of excessive fear and anxiety, associated with behavioural alterations that can generate malaise and disability (Sherbourne et al. 2010; Vallejo and Bulbena 2015); these include a set of diagnoses whose aetiology includes neuroendocrine (Martin et al. 2009; Milton and Holmes 2019), genetic (Kendrler et al. 2008), evolutionary (Ojeda 2007), and psychological factors (Otte 2011).

Recent guidelines (Baldwin et al. 2014; Andrews et al. 2018) recommends SSRI (e.g., fluoxetine and paroxetine) and SRNI (e.g., duloxetine and venlafaxine) as first-line treatments, because they are effective at short and long term and

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are well tolerated. Nevertheless, it is important to evaluate other classes of medication, because there are patients that do not respond to SSRI or are intolerant to them. Among other antidepressants, like TCA and MAOI, are available anxiolytics like hydroxyzine (Ferreri and Hantouche 1998) or buspirone (Chessick et al. 2006) and benzodiazepines (Ashton 1994). These drugs are not without problems: on the one hand, the latency of several weeks for the effect of antidepressants to begin and, on the other hand, the significant adverse effects of benzodiazepines, which include sedation, cognitive alterations, risk of abuse, and dependency (Curran 1991; Woods et al. 1992; Ashton 1994; Zandonai et al. 2018). In many countries, it has been stipulated that benzodiazepines should be used for short periods (2 to 4 weeks), but these recommendations are not considered by patients or even doctors (Lader 2011).

In Chile, benzodiazepines have had a high prescription rate, becoming a public health problem in the 1980s, principally due to self-medication and abuse (Danhier et al. 1988; Fritsch et al. 2005), leading to the establishment of controlled prescription in 1995. In primary care, its consumption among patients reached 40%, with 30% self-medication, 4 to 10% dependency, and a mean time of use of 6.9 years (Busto 1991; Galleguillos et al. 2003; Olivera 2009). Therefore, it is necessary to consider others drugs with similar or better therapeutic responses on anxiety symptoms and general clinical improvement with less adverse effects. Clonazepam is the most commonly used benzodiazepine among the Chilean population (42%) (Yates and Catril 2009; Bozzo 2010), with an SMD = 0.58 over placebo according to meta-analysis of Bandelow et al. (2015).

Etifoxine (6-chloro-2-ethylamino-4methyl-4-phenyl-4*H*-3,1-benzoxazine hydrochloride) is a non-benzodiazepine drug of the benzoxazine family with anxiolytic effects that act via an agonist mechanism in the $GABA_A$ receptor. It has an affinity with chloride channel coupled to the $GABA_A$ receptor complex and binds to these receptors via an allosteric site distinct from benzodiazepines. Indeed, it has been shown that etifoxine preferentially acts on $GABA_A$ receptors containing the β_2 or β_3 subunit, in addition to a modulating action on the effect of neuro-steroids in the same receptor (Choi and Kim 2015). Recent studies show that anxiety states can be modulated by the effect of physiological processes such as inflammation, immunity, oxidative stress, and gut microbiota; the anxiolytic effect of etifoxine could be linked to its considerable anti-inflammatory activity in the central nervous system and its effects on the immune system and neuroendocrine system (Nuss et al. 2019). Etifoxine is extremely bioavailable (approximately 90%) and does not bind to blood cells. It does, however, strongly bind to plasma proteins (88–95%). After oral administration, etifoxine is rapidly absorbed by the gastrointestinal tract. The time to maximum blood concentration is 2–3 h. It is rapidly metabolized in the liver to form several metabolites. Its half-life is about 6 h, and half-life of its active metabolite, diethyl-etifoxine, is almost 20 h. It can also cross the placental barrier. It is mainly excreted in the urine and bile as metabolites, and small amounts are excreted in unchanged form (Choi and Kim 2015).

Previous randomized studies have shown that etifoxine, compared with benzodiazepines, have fewer side effects and have similar or better effects on anxiety symptoms and clinical improvement. Also, it has the important advantage of not being related to withdrawal symptoms and dependence (Stein 2018). Compared with lorazepam, etifoxine presents fewer adverse effects on attention, memory, and psychomotor development in people without anxious symptomatology in the first 6 h of application (Micallef et al. 2001). Also, it is shown to be equivalent in its effect on clinical improvement and decrease in anxiety symptoms in people diagnosed with anxiety disorder at 28 days (Nguyen et al. 2006). Compared with alprazolam, etifoxine presents a greater decrease in anxiety symptoms after discontinuing treatment, a similar degree of clinical improvement and fewer side effects due to anxious symptomatology at 35 days of treatment (Stein 2015). Finally, in relation to phenazepam, etifoxine presents a decrease in anxiety symptoms and clinical improvement at 6 and 7 weeks of treatment (Aleksandrovsky et al. 2010).

Certain adverse effects of etifoxine, though infrequent, have been described including skin reactions, colitis, and metrorrhagia (Nguyen et al. 2006). Some series of cases of cytolytic hepatitis have also been published (Mennecier et al. 2003; Moch et al. 2012; Cottin et al. 2016).

Regarding regulation of the drug in Chile, etifoxine was approved for use for psychosomatic manifestations of anxiety under Act 3/10 of 2010 by the Chilean Public Health Institute. It is relevant to consider that as reasons for denying approval in the first instance, the need for comparative studies in longer periods with greater number of patients was noted, in order to guarantee the efficacy and safety of the drug (Instituto de Salud Pública de Chile 2010). Its last registration is from the year 2016, with code F-22632/16, which is valid until the year 2021 (Instituto de Salud Pública de Chile 2020).

Although the literature shows clear evidence of the effectiveness of etifoxine in controlling anxiety symptoms, previous studies have not included an aspect as important as drug tolerance. Additionally, in other studies the maximum treatment time has been only 6 weeks, with a maximum follow-up of 1 week. Therefore, it is necessary to evaluate its effectiveness in longer-term treatments as well as its effects in a longer-term follow-up. It is worthwhile to note that there is no specific information about the effectiveness of etifoxine in Latin America or about its efficacy compared to clonazepam. Hence, the objective was to study the non-inferiority of etifoxine vs clonazepam in the treatment of anxiety disorders in patients from primary medical centres in the provinces of Concepción and Ñuble in Chile. As a secondary objective, we

studied the differences of side effects between etifoxine and clonazepam.

Materials and methods

Study design and participants

Our study design was a controlled randomized double blind study with parallel groups of patients with anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, agoraphobia with panic attacks, and agoraphobia without panic attacks, according to the DSM-IV criteria) who attended in 10 primary medical centres in the provinces of Concepción and Ñuble, Chile. In previous studies on etifoxine, as Stein (2018) points out, sampling in patients already diagnosed has been used to determine the effect of the drug on certain disorders. Instead, in our study, the focus was to obtain a representative sample of anxious disorders in the population considering primary-level patients. The prevalence of specific disorders was very low, and as such, anxious disorders were considered a broad category, and attention was focused on the level of symptoms.

The medical centres were randomly selected among the total institutions dependent on the health services of Concepción (21) and Ñuble (26). Having selected these, subjects were contacted in the waiting room of each centre in October 2013 and March 2015. The planned sample size, 129 subjects in each group, was calculated to test the hypothesis of non-inferiority, using as reference SMD = 0.31, with a power of 0.8 and significance level of 0.05. This value was selected, because it is the lowest confidence interval for the effect of clonazepam vs placebo according to the meta-analysis of Bandelow et al. (2015). Considering these possible losses, the projected sample size was increased to 140 patients in each group.

Procedure and instruments

Sociodemographic information, including age, was collected from patients who consented to participate, and subjects between 18 and 64 years were considered. The following exclusion criteria were established: risky alcohol or drug consumption, using the version of AUDIT validated in Chile, which considers a cut-off point of 6 or more points (Alvarado et al. 2009), using a questionnaire from the National Service for the Prevention and Rehabilitation of the Consumption of Drugs and Alcohol (Servicio Nacional para la Prevención y Rehabilitación del Consumo de Drogas y Alcohol, SENDA); the use of antidepressants in therapeutic doses and/or benzodiazepines in any dose in the preceding 2 weeks, through direct questioning; a history of having been in psychotherapeutic treatment in the preceding 6 months, information taken from the clinical history of the patient; and finally, severe medical illness and/or physical and/or neurological condition (mental retardation, cognitive decline, sensory deficiencies, and others) that would impede participation in the evaluations, information also taken from the clinical history. Patients who fulfilled the inclusion profile were screened for anxiety disorder using Goldberg's General Health Questionnaire (GHQ-12) in the version validated for Chile by Araya, Wynn, and Lewis (Araya et al. 1992). Patients who scored as a "probable case" (seven or more points) were re-evaluated to confirm the presence of anxiety disorder using the Composite International Diagnostic Interview, version 2.0 (CIDI 2.0) (Robins et al. 1981, 1988). In addition, the depression module of the CIDI was applied to exclude possible cases of comorbidity, due to the repercussions that it could have on the results that were referred for treatment in the same health centre; specifically, all patients diagnosed with mild, moderate, or severe depression according to DSM-IV criteria were excluded.

Until this phase, all instruments were applied by non-clinicians, who were previously trained and supervised during the period of application.

All patients in whom the presence of one of the anxiety disorders considered in this study was confirmed were given an appointment for an interview with general physicians. These physicians were previously trained, and patients were jointly evaluated by two physicians to establish adequate reliability between evaluators. These physicians applied the following: the HAM-A evaluation (Hamilton 1959; Lobo et al. 2003), specifically the version validated in Spanish by Lobo et al. (Lobo et al. 2003) and broadly used in Chile (Krebs et al. 2012; Nogales-Gaete et al. 2012; De La Maza et al. 2015), to evaluate the severity of symptoms. Also used were the UKU Side Effect Rating Scale (Lingjærde et al. 1987), to identify the presence of possible symptomatology at the beginning of treatment, and the Clinical Global Impression Scale (CGI) (Guy 1976), which evaluates the severity of symptoms (CGI-S) and their improvement (CGI-I), associated with therapeutic interventions.

The HAM-A is given through questions from an interviewer who records the patients' answers and consists of 14 items that evaluate the psychological, physical, and behavioural aspects of anxiety. The scores vary between 0 and 56 points. HAM-A is the most frequently used instrument to evaluate effectiveness of anxiety disorders (Hamilton 1959).

The UKU scale applied by a clinician, designed by the Scandinavian Society of the Psychopharmacology Committee of Clinical Investigations (Lingjærde et al. 1987), evaluates a minimum of 48 psychological and somatic symptoms arising from the consumption of psychotropic drugs as well as their causal relationship with medication and their degree of interference in everyday life. This study used the version translated into Spanish by the Faculty of

Medicine of Valencia, previously used in Chile (Cavieres 2008).

The Clinical Global Impression Scale, previously used in Chile (Boehme and Durán 2012), was also applied by an interviewer. This scale gives qualitative information about the severity of symptoms and about the change experienced by the patient with respect to the baseline. The concept of improvement refers to the existing distance between the current state of the patient and the state registered at the beginning of treatment; it can only be completed during or after the treatment.

Intervention

Two types of interventions were performed. The experimental group was given 150 mg/day of etifoxine, one dose in the morning, one in the afternoon, and one at night, over 12 weeks. The dosage was fixed and corresponded to a medium dose, since it is recommended in the medication brochure (Alfa Beta 2019). The control group was given 1 mg/day of clonazepam, 0.25 mg in the morning, 0.25 mg in the afternoon, and 0.50 mg at night. Although the clonazepam dose is lower compared with the other studies that use a maximum of 2.0 mg/day (Martins Valenca et al. 2000; Knijnik et al. 2008), we preferred to use this dose to minimize side effects and to represent the dosage most frequently used in primary care in Chile (Yates and Catril 2009; Bozzo 2010).

Detailed information was given to doctors about prescription and possible side effects prior to the study. Doctors were informed to keep the doses of the medications without modification, except in cases in which the absence of improvement or the presence of side effects caused discontinuation of the trial.

Randomization and masking

Random assignment to one group or the other was performed when receiving the patient, prior to the first interview with the general physician, using the procedure of flipping a coin. This was performed by an administrator who, after the medical consult, gave the drugs to the patients, which safeguarded the blindness of the evaluating physician. The result of the assignation was registered and sent to the researchers in a closed envelope, to be disclosed at the end of the trial.

To safeguard the blindness of the treatment for the patients, both drugs were re-encapsulated, adjusting the size and colour of the capsule and the containers to be used to make them similar.

Upon finishing the treatment, at the end of the 12 weeks, the participants were newly evaluated by a general physician, who again applied the clinical evaluation scales (HAM-A, UKU, and CGI-I). In parallel, participants were re-evaluated with the CIDI interview. As the application of the evaluations was carried out during the last day of treatment, medication was active at the time of this evaluation. Twelve weeks later, at the 24-week follow-up, a clinician applied the HAM-A to the participants.

Outcomes

The measurement for primary results was the evaluation of anxiety symptoms, measured by the HAM-A, 12 weeks from the beginning of treatment. The measures of the secondary results included evaluation of the side effects of each medication, measured by the UKU. Also measured was the degree of improvement in the CGI-I at the end of treatment (12 weeks) and anxiety symptoms, measured by the HAM-A, at 24 weeks after beginning treatment.

Bias control

Assignment to the groups was performed at random by a person distinct from the researchers, evaluators, and clinicians. Researchers did not participate in the sample selection procedures and were blind to the group to which each participant belonged. Patients were blind to their treatment, which was safeguarded by a procedure of encapsulating the drugs, such that the pharmaceutical form was similar for both. Data analysis was blind to the group to which each case belonged.

Data analysis

Data analysis was conducted using R, version 3.2 (R Core Team 2019). A descriptive analysis for the sociodemographic and clinical variables for the control and experimental groups was conducted. Using the Mann-Whitney *U* test, the possible presence of differences between the groups by age, years of study, GHQ, and AUDIT was studied, in addition to the differences in the baseline of the HAM-A, UKU, and CGI-S. Using the Chi-square test, the presence of differences by sex, having a stable partner, and having stable work was investigated, in addition to the prevalence of the disorders studied. Because an important number of people invited to participate did not consent to be part of the study, the probability of participating was evaluated by applying logistical regression, using as predictors the variables of sex, age, years of study, civil status, occupation, GHQ points, and AUDIT points. Similarly, considering the high rate of attrition, adherence to treatment at 12 weeks was evaluated, including as predictors the same variables used to predict the probability of participating, in addition to the baseline HAM-A and UKU. In the latter tests, the differentiation was made between the psychological and physical symptoms evaluated in the first stage as well as the type of drug administered. Thus, the points on the HAM-A, for baseline, after 12 and 24 weeks, and those in the UKU, differentiating physical and mental symptoms, for

baseline and at 12 weeks were described for each phase of the study.

Given the presence of missing data possible to be predicted by observed variables, multiple imputations were performed using chained equations, with 10 imputed bases and 15 iterations. Results of the observed data and those of the imputed data were compared. The effect of etifoxine on the HAM-A and UKU was evaluated by intention to treat using a mixed-effects regression model, subjected analysis of covariance (ANCOVA), controlling the effect of the sociodemographic variable that best predicted adherence to treatment, age, added to the GHQ as an indicator of general psychological symptomatology. Differences between participants and centres were modelled using a random intercept model. The estimated means for weeks 12 and 24 in the HAM-A and for week 12 in the UKU were compared. Non-inferiority of HAM-A and UKU on week 12 was declared if the lower limit of the 95% CI for the difference in estimated means between experimental and control group was greater than SMD = 0.31; pooled standard deviation was used for this analysis. If the 95% CI lies above 0, there is evidence for superiority, and this result was assessed using a conventional null hypothesis of no difference (Committee for Proprietary Medicinal Products 2001). For HAM-A and UKU, a version of the likelihood ratio test adapted for multiple imputations called $_{m}$ was used; for CGI-I, a *t*-test was used. Furthermore, on each outcome, the hypothesis of moderation of the type of anxiety disorder in the difference between control and experimental group was studied using a likelihood radio test with a model that includes an interaction between each type of anxiety disorder, time, and group vs a model that only includes the interaction between time and type of anxiety disorder.

To study the influence of missing data on the results, the relative increase in variance (RIV) was studied in trial to evaluate the extent to which its power is affected by the lost datum. In addition, a sensitivity analysis was conducted, using the assumption that in patients without data (lost cases), the treatment is ineffective, which is equivalent to using as imputation the method of last observation carried forward (LOCF). This assumption is, with high probability, false, but it gives a useful reference point, in the sense that it gives missing data the least effect estimable. For the significance level for all trials of the statistical hypothesis, $\alpha = 0.05$ was used.

Ethical safeguards

The study was authorized by the Bioethics Committee of the School of Medicine of the University of Concepción and by the Ethics Committees of the corresponding health centres. The protocol was pre-registered at the Faculty of Medicine (N° UR 262326401), to avoid selective reporting of results and maximum transparency of the process.

The participants were contacted in the waiting room of each health centre and invited to participate. Those who accepted expressed their choice by signing an informed consent form, a request form repeated the moment when the CIDI interview was given and at the beginning of treatment. Some cases such as alcohol and/or drug dependence and/or depression identified during the recruitment process were referred for attention. The data were treated as a set, safeguarding the identity of each patient.

Results

A total of 3834 subjects were contacted in the waiting room of one of the centres. Considering those who declined to participate, the presence of the exclusion criteria, and the results of the screening, 537 possible cases were identified; in 330 cases, it was possible to apply the CIDI interview. In total, 294 cases that were positive for one of the anxiety disorders were included in the study, and in which the subjects were invited in the end to participate in the clinical trial, of these, 179 consented to participate. Once the enrolled participants were interviewed by the physician, they were randomized, and treatments were indicated; 96 entered the experimental group (etifoxine) and 83 the control group (clonazepam). A total of 87 participants finished the 12-week treatment, 47 in the experimental group and 40 in the control group. The 24-week follow-up was completed by 70 participants, 37 in the experimental group and 33 in the control group (Fig. 1). The majority of the participants were women (94.9%); 60.6% had some type of partnered relationship, and only 11.6% signalled that they had stable work. The mean of the clinical impression measured using the CGI-S was 3.92, which is close to the category of "moderately ill". The remaining results of the descriptive analysis of the sample are presented in Table 1. No significant differences were observed between the experimental and the control groups by age, years of study, partnered relationship, presence of stable work, and points on the GHQ, AUDIT, HAM-A, CGI-S, and UKU.

With respect to the DSM-IV diagnoses, no significant difference was observed between the phases of the experiment. Distinct specific phobias stood out for their frequency (49.7%), which presented a high comorbidity with social phobias (96.4%).

Analysis of the probability of participating and remaining in the study

The loss of cases among the 294 subjects invited to the study and the 179 who finally entered demanded a probability analysis of entering the study to understand whether this lack of participation met some pattern or was random. This is a procedure that allows the model of multiple imputations to be adjusted and simultaneously offers antecedents to evaluate

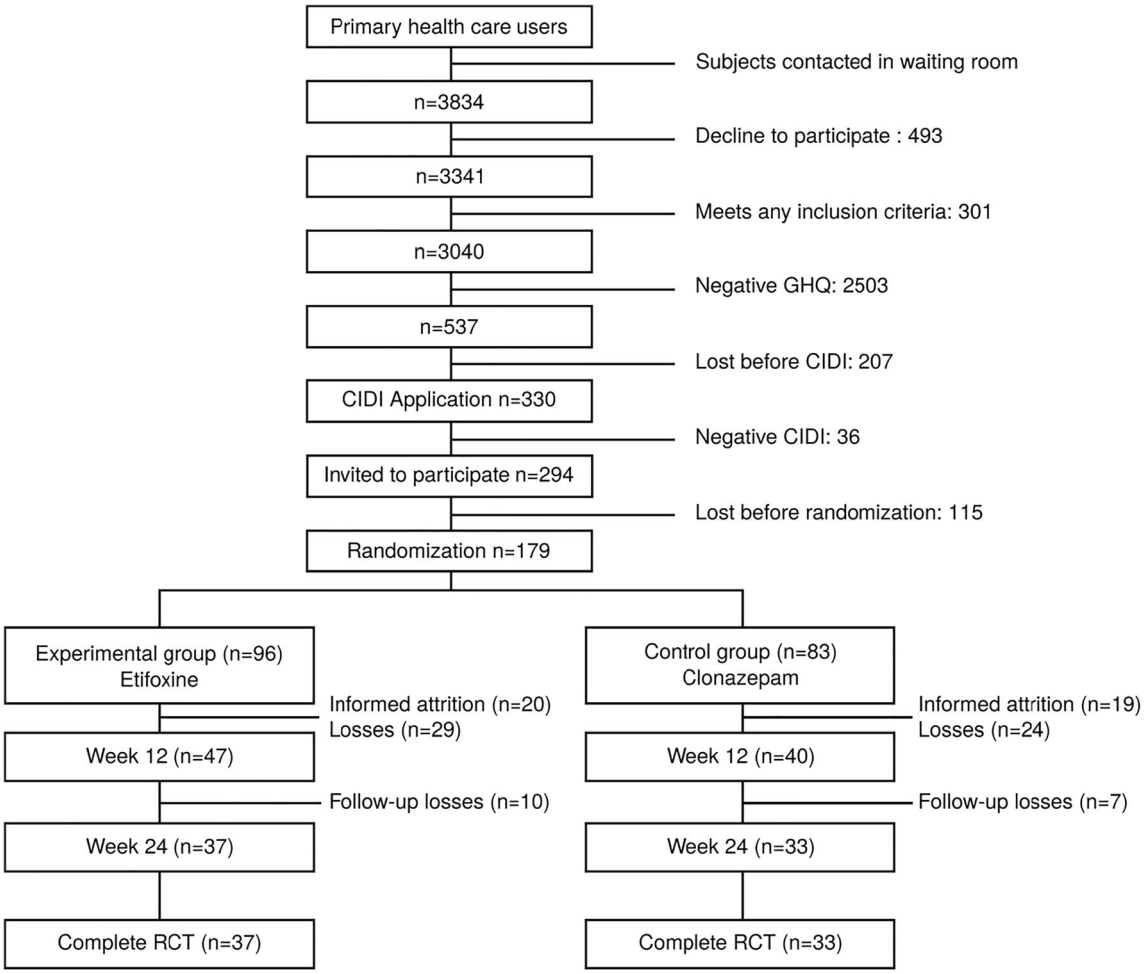

Fig. 1 CONSORT flow diagram

the internal validity of the results. A method of analysis that considers missing data was used to avoid affecting the results of each of the estimations of the study.

The results of the regression model of the probability of entering the study showed that the principal predictor of non-participation, in terms of the change in deviance, was the points on the AUDIT ($p = 0.003$). Specifically, it was observed that the greater the alcohol problem, the lower the probability that the people invited would participate in the study.

The next step was to investigate the probability of remaining in the study at the 12-week follow-up. A first result showed that the type of drug used did not affect participation ($p = 0.403$). What did predict was a greater level of symptomatology, evaluated with the UKU at baseline, which decreased participation in the follow-up ($p < 0.001$), whereas higher points on the HAM-A increased participation ($p = 0.004$).

Results of variable imputation

When analysing the results of the variable imputation process, a mild increase in points on the HAM-A at 12 and 24 weeks, in the imputed bases, was observed in the control group, indicating that the loss was produced in cases presenting less improvement. The result of imputing data in the UKU scale showed that these remained practically identical.

Regarding the group that received etifoxine, lower values in the HAM-A questionnaire were observed in the imputed base at the 12-week evaluation, and somewhat greater values were observed at the 24-week follow-up, indicating that the loss of data was observed in those cases with a greater decrease in symptoms.

Analysis of the causes of attrition

From the 92 patients who did not complete the 12-week treatment, 49 from the etifoxine group and 43 from the clonazepam group, it was possible to obtain information about the causes of attrition in 39, 20 from the etifoxine group and 19 from the clonazepam, leaving 53 cases for which there was a loss of follow-up. Considering the reported causes, it is notable that the majority of cases (27) corresponded to actual or potential problems with the medication. It is interesting to note

Table 1 Sociodemographic description and description of clinical variables of the sample ($n = 179$)

	Etifoxine	Clonazepam	Total	p Value[c]
N	96	83	179	
Mean age:(SD)	40.75 (12.2)	41.82 (13.53)	41.25 (12.81)	0.57
[min-max]	18–65	19–66	18–66	
With stable partner %	57.4%	64.1%	60.6%	0.45
Women %	95.7%	93.9%	94.9%	0.83
Stable work %	10.8%	12.5%	11.6%	0.90
Years of study: mean (SD)	9.15 (3.29)	9.11 (3.79)	9.13 (3.52)	0.69
GHQ: mean (SD)	8.36 (1.4)	8.2 (1.42)	8.29 (1.41)	0.42
AUDIT: mean (SD)	0.62 (1.01)	0.66 (1.06)	0.64 (1.03)	0.97
HAM-A total: mean (SD)	26.85 (6.76)	26.53 (8.06)	26.7 (7.37)	0.78
CGI: mean (SD)	3.96 (0.77)	3.89 (0.77)	3.92 (0.77)	0.35
UKU: mean (SD)	48.11 (7.58)	47.02 (7.6)	47.61 (7.59)	0.60
Generalized anxiety disorder %	33.3%	28.9%	31.28%	0.64
Panic without agoraphobia % [a]	21.9%	34.9%	27.73%	0.08
Agoraphobia with panic % [a]	11.5%	7.2%	9.50%	0.48
Agoraphobia without panic %[a]	20.8%	19.3%	20.11%	0.94
Social phobia	31.2%	31.3%	31.28%	0.99
Specific phobias[b]	53.1%	47.0%	50.3%	0.50

[a] Mutually exclusive. [b] Includes phobias of animals, blood, and nature as well as situational phobias. [c] Difference between clonazepam and etifoxine groups calculated by Chi-square test for categorical variables and Mann-Whitney U test for numerical variables

that all of the medical indications to suspend treatment for possible pharmacological interactions affected etifoxine and not clonazepam (Table 2).

To explore the possible relationship between the causes of attrition and the conditions of entry, a regression analysis with the HAM-A and UKU values in the twelfth week was conducted, using the same probability analysis regressors as remaining at week 12, and the predicted curves for those who abandoned the study were graphically analysed. Regarding the HAM-A, it was observed that in the clonazepam group, subjects who abandoned due to experiencing discomfort all had high baseline HAM-A values. Second, the patients with etifoxine who abandoned due to lack of improvement were those who had low baseline HAM-A values; it could be interpreted that in these patients, there was no room for improvement. Third, regarding the UKU, similarly to the findings observed regarding the HAM-A, it was observed that the patients who abandoned due to experiencing discomfort were those with high UKU baseline values. Therefore, it could be concluded that the indicators of improvement could have been overestimated, although in a similar manner for both arms.

Analysis of anxiety symptoms

To analyse the changes in anxiety symptoms measured by HAM-A scale, a mixed effects model was used, analogous to repeated measure analysis of variance (ANOVA), in which the variables that most strongly affected remaining in treatment, i.e., AUDIT and age, were controlled. An omnibus test was performed to detect any differences in HAM-A means

Table 2 Causes of attrition, second stage

Cause of attrition	Etifoxine	Clonazepam	Total
Felt well and thought it was unnecessary to keep taking it	5	3	8
Could not go get it	2	2	4
Had some discomfort with the medication	4	4	8
Had no improvement	2	3	5
Medical indication to avoid problems with another medication or illness	4	0	4
Someone recommended that they not use it	3	7	10
No information	29	24	53
Total	49	43	92

between the experimental and control group in baseline, 12-week, and 24-week follow-up. Comparing the model that only considers the mean points on the HAM-A at all moments, the points on the AUDIT, age, and time with a model that includes the interaction of the type of drug with time, the difference was significant for etifoxine ($_m$ (2; 99.390) = 3.770; p = 0.026) (Fig. 2). No significant moderation effect of the type of anxiety disorder on the differences between the control and experimental groups was found ($_m$ (20; 1917.884) = 1.039; p = 0.411).

The estimated difference in means between etifoxine and clonazepam at 12 weeks was 3.6 points in favour of etifoxine (SMD = 0.404; 95% CI, 0.077, 0.731). Because the confidence interval does not include zero, superiority could be asserted (t(56.04) = 2.31, p = 0.025). The effect of missing data on the variance of SMD indicator was 1.16, which would indicate that the confidence interval of this difference could have decreased approximately half if there had been complete information.

The estimated difference in the follow-up, at 24 weeks, was 3.55 points in favour of etifoxine (SMD = 0.398; 95% CI, 0.148, 0.648). Like the difference at 12 weeks, etifoxine shows to be superior to clonazepam at 24 weeks (t(537.582) = 2.745, p = 0.006). The relative increase in variance was 0.26, which would indicate that despite the important level of attrition, there was less variability on confidence interval due to missing data.

Analysis of adverse side effects

To analyse the changes in the UKU scale, which evaluates adverse side effects, a mixed effects model, analogous to repeated measures ANOVA, was used, in which the variables that most strongly affected remaining in treatment were also controlled: points on the baseline AUDIT and age. When comparing the model that only considers the mean difference between the groups, the AUDIT, age, and time, with a model that includes the interaction between the moment of evaluation and the type of drug, the difference was significant ($_m$ (1, 32.014) = 22.289; p < 0.01), with lower points for etifoxine. There is no moderation effect of type of anxiety disorder on the differences between the control and experimental group ($_m$ (12; 4167.355) = 0.810; p = 0.641).

The difference in the estimated means at 12 weeks was 5.83 points in favour of etifoxine (SMD = 0.59; 95% CI, 0.304, 0.881). The confidence interval shows superiority of etifoxine vs clonazepam on adverse effects (t(68.44) = 4.72, p < 0.001). The relative increase in variance of this coefficient is 0.57, which would indicate that the confidence interval of this difference could have a width of 75% of the current one if the information had been complete. It should be noted that UKU had lower scores at 12 weeks compared with baseline for both clonazepam and etifoxine that seems counterintuitive; however, some of the potential side effects measured by UKU

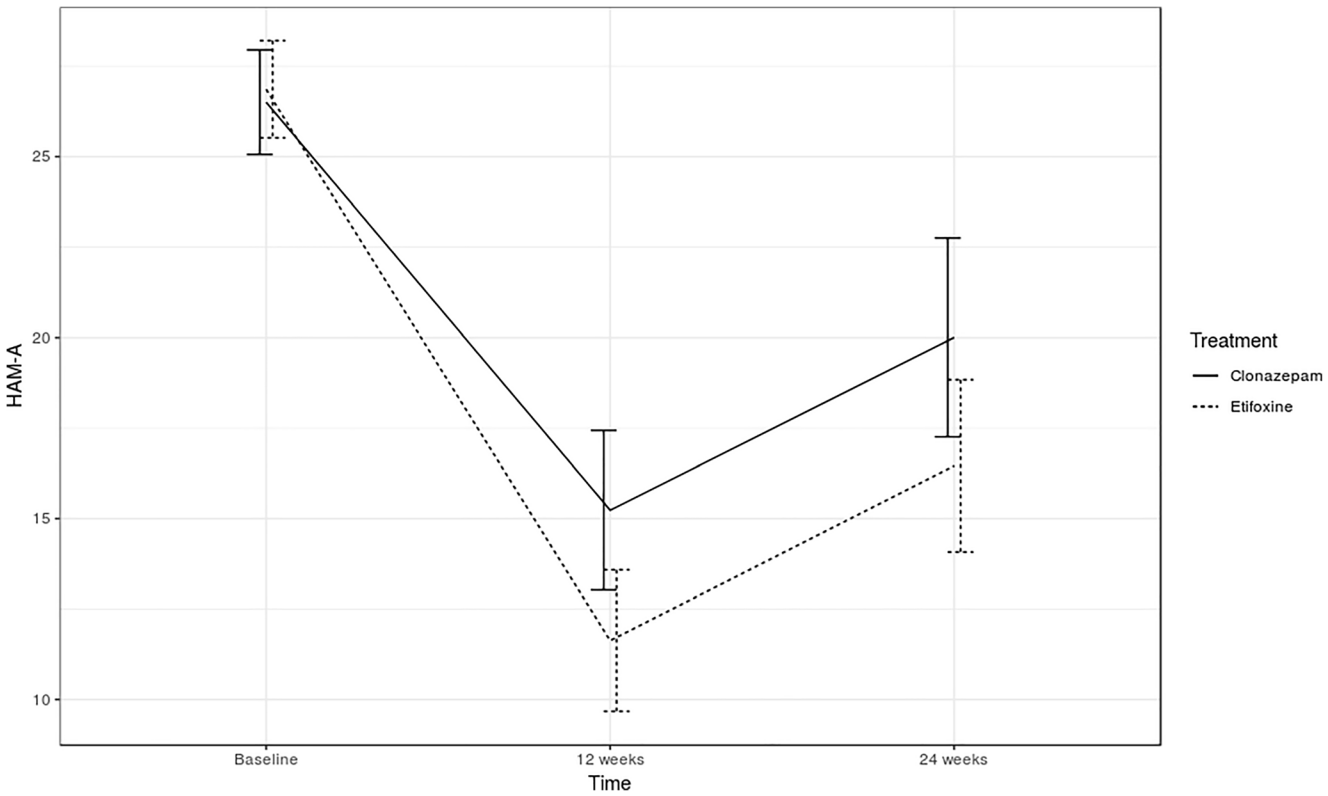

Fig. 2 HAM-A estimated means, by type of drug and time

are symptoms of anxiety disorders, so a decrease in anxiety symptoms is expected in this scale.

Analysis of clinical improvement

The mean for both groups in the CGI-I at 12 weeks was 1.50 (SD = 0.70; 95% CI, 1.32–1.67), which represents an improvement between the categories of "much better" and "moderately better". For etifoxine, the mean at 12 weeks was 1.39 (SD = 0.60; 95% CI, 1.16–1.64), whereas for clonazepam, it was 1.62 (SD = 0.78; 95% CI, 1.34–1.90), which indicates a perception of greater improvement among patients treated with etifoxine. However, this difference of 0.23 (SMD = 0.306) implies a 95% CI of − 0.21 and 0.83 that includes the 0 but does not cross the margin of − 0.31 SMD, so non-inferiority can be declared for clinical improvement. No moderation effect of type of anxiety disorder was found ($_m$ (6; 193) = 0.127; p = 0.993). The increase in relative variance was 1.99, indicating that the significance test was severely affected by missing data.

Sensitivity study

In the case of the HAM-A, the use of LOCF yielded better results for etifoxine than clonazepam at stage two (12 weeks; SMD = 0.07; 95% CI, − 0.192, 0.333) and at stage three (24 weeks; SMD = 0.149; 95% CI, − 0.113, 0.412). In the case of the UKU, the use of LOCF resulted in a model with better results for etifoxine than clonazepam (SMD = 0.214; 95% CI, − 0.032, 0.459). This result shows the non-inferiority for etifoxine compared with clonazepam using LOCF.

Discussion

The main findings of this study were as follows: (1) HAM-A scores favoured etifoxine compared with clonazepam at the 12- and 24-week follow-ups, with significant differences on both evaluations; (2) there were less adverse side effects in etifoxine group, measured by UKU; and (3) etifoxine is non-inferior to clonazepam in clinical improvement at the 12-week evaluation, measured by CGI-I. It should be considered that both medications have the typical curve presented in clinical trials of anxiolytics, with a decrease in symptoms at the end of treatment (12 weeks) and a subsequent increase, but below the original value, in the follow-up (24 weeks). Furthermore, no differences were found in the treatment effect attributable to the specific anxiety disorders.

The findings are promising, because analyses for HAM-A and UKU not only show that etifoxine is not inferior to clonazepam but could even show superiority after using standard null hypothesis tests. These results are consistent with prior findings that indicate that etifoxine has fewer side effects compared with alprazolam (Stein 2015) and lorazepam (Micallef et al. 2001) and has a better or similar decrease of anxiety symptoms and clinical improvements compared with alprazolam (Stein 2015), lorazepam (Micallef et al. 2001), and phenazepam (Aleksandrovsky et al. 2010). The high attrition ratio, however, is something to be taken into consideration when analysing this superiority. Sensitivity analysis of the results, assuming the imputation of lost cases, shows that in the worst-case scenario (if we suppose that all of the lost cases did not demonstrate any effect), maintains the conclusion of non-inferiority of etifoxine, measured by the HAM-A and UKU scales.

Undoubtedly, an important limitation in our study is the high attrition rate, which implies a lower number of subjects enrolled in the study than the number considered in the original design of the sample and an important loss in the follow-up. With respect to this issue, the analysis of the probability of participating shows that the higher scores on AUDIT are associated with lower probability of enrolment, which accounts for a symptomatology that—if present—could be being managed artificially by alcohol consumption, without this being ego-dystonic for the subject. It is necessary to considerer that people with risky alcohol consumption (6 or more points on AUDIT) were excluded in the previous step. Age is a relevant variable, in the sense that older people have a lower probability of entering into the study, particularly whenever they are offered an intervention not spontaneously requested that was added to that of their other morbidities and that also referred them to a place and setting different from their usual health centre.

Of the patients who did enrol in the study, that is, those who were randomized and, consequently, consented to participate in the clinical trial, the loss at the end of treatment (12 weeks) reached 46.8% and 46.9% for the experimental and control groups, respectively, and it was lower, 8% for both groups, at follow-up (24 weeks). The analyses of the probability of remaining in the study show that the type of drug used did not affect adherence. Rather, it was the score on the HAM-A and the adverse effects scale, both at baseline. With respect to HAM-A scores, the relationship was not direct but rather quadratic, and the greatest probability of remaining in the study occurred in the cases with moderate to severe symptomatology, although it decreased as the severity increased excessively. In the case of the adverse effects scale, which collects diverse symptomatology, both physical and psychological, those who had fewer symptoms at the beginning of the study had a greater probability of remaining in it. Here, it is important to note that the scale was applied at baseline—prior to initiating treatment—to identify possible confusion between already present symptoms and the possible adverse effects of the therapy. Both results show a lower interest in continuing in a study to which they had been invited in those who had fewer symptoms, who most likely did not have, or appear to have, an

explicit need for the treatment. On the other hand, the abandonment of the trial by those who had more symptoms raises the question of whether those who abandon do so because they do not perceive an improvement, or because they feel better.

Conclusions

This study gives the first results that analyse non-inferiority on effectiveness and adverse effects of etifoxine versus clonazepam. It is also the study with the longest duration that compares etifoxine with another benzodiazepine, with a follow-up at 24 weeks; the previous study of longer duration only contemplated a follow-up at 7 weeks (Aleksandrovsky et al. 2010). Finally, this is the first study in Latin America that evaluates etifoxine for treating anxiety disorders.

The high attrition rate forces us to be cautious in the results, so these should be considered preliminary and must be corroborated in a subsequent study. Further research should include a pragmatic design, under real-life practice conditions, to produce results that allow to assert the superiority of etifoxine on routine settings. Also, it is necessary to study a broader sample to analyse possible differential gender and diagnostic effects of etifoxine in these groups.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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