

Efficacy of etifoxine compared to lorazepam monotherapy in the treatment of patients with adjustment disorders with anxiety: a double-blind controlled study in general practice

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Adjustment Disorders With Anxiety (ADWA) account for almost 10% of psychologically motivated consultations in primary care. The aim of this double-blind randomised parallel group study was to compare (non-inferiority test) the efficacies of etifoxine, a non-benzodiazepine anxiolytic drug, and lorazepam, a benzodiazepine, for ADWA outpatients followed by general practitioners. 191 outpatients (mean age: 43, female: 66%) were assigned to receive etifoxine (50 mg *tid*) or lorazepam (0.5–0.5–1 mg /day) for 28 days. Efficacy was evaluated on days 7 and 28 of the treatment. The main efficacy assessment criterion was the Hamilton Rating Scale for Anxiety score (HAM-A) on Day 28 adjusted to Day 0. The anxiolytic effect of etifoxine was found not inferior to that of lorazepam (HAM-A score decrease: 54.6% vs 52.3%, respectively, $p = 0.0006$). The two drugs were equivalent on Day 28. However, more etifoxine recipients responded to the treatment (HAM-A score decreased by $\geq 50\%$, $p = 0.03$). Clinical improvement (based on Clinical Global Impression scale CGI, Social Adjustment Scale Self-Report SAS-SR, and Sheehan scores) was observed in both treatment arms, but more etifoxine patients improved markedly ($p = 0.03$) and had a marked therapeutic effect without side effects as assessed by CGI, $p = 0.04$. Moreover, 1 week after stopping treatment, fewer patients taking etifoxine experienced a rebound of anxiety, compared to lorazepam (1 and 8, respectively, $p = 0.034$). Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS—etifoxine; lorazepam; adjustment disorders with anxiety; general practice setting

INTRODUCTION

Adjustment Disorder With Anxiety (ADWA) is defined as a clinically significant anxiety occurring within 3 months after the onset of an identifiable psychological stressor, and lasting no longer than 6 months after the stressor or its consequences have ceased (DSM IV) (American Psychiatric Association,

1994). It is associated with significant impairment in social role functioning, frequently manifested as decreased performance at work or school and temporary changes in social relationships. It is a common pathology in primary care, accounting for almost 10% of outpatients with psychological complaints consulting General Practitioners in France (Semaan *et al.*, 2001). This disorder is usually treated with anxiolytic drugs, in first-line benzodiazepines (BZD). However, because of the frequent and well-known BZD-related side effects including anterograde amnesia, sedation, tolerance, dependence, it is an interest to dispose of alternative treatments (Ashton, 1994; Curran, 1991; Laurijssens and Greenblatt, 1996; Schweizer, 1998; Woods *et al.*, 1992).

Etifoxine (6-chloro-2-ethylamino-4-methyl-4-phenyl-4H-3,1-benzoxazine hydrochloride) is a non-

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benzodiazepine compound, prescribed in France since 1979 for psychosomatic manifestations of anxiety. Its anxiolytic properties have been shown in rodents: etifoxine reduces stress-induced physiological and endocrine modifications, like hyperthermia, activation of colonic activity (Boissier *et al.*, 1972; Verleye and Gillardin, 2004). Binding and electrophysiological experiments have demonstrated that etifoxine enhances the inhibitory GABAergic system notably implied in the regulation of anxiety, as do benzodiazepines, barbiturates and neurosteroids, by different ways (Hamon *et al.*, 2003; Schlichter *et al.*, 2000; Verleye *et al.*, 1999, 2001, 2002). 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 (Hamon *et al.*, 2003). The second way might involve the stimulation of mitochondrial-type benzodiazepine receptors known to control neurosteroid synthesis like allopregnanolone, also positive modulator of GABA_A receptors with anxiolytic-like properties (Akwa and Baulieu, 1999, Akwa *et al.*, 1999; Brot *et al.*, 1997; Schlichter *et al.*, 2000). As sedative properties of benzodiazepines are mediated by the GABA_A receptor α_1 subtype (McKernan *et al.*, 2000), etifoxine, with regard to its pharmacological profile, might be distinguished from benzodiazepines in general in terms of its clinical effects and safety.

In humans, its efficacy in the treatment of ADWA has previously been shown in a double-blind controlled study (Servant *et al.*, 1998). Compared to lorazepam, a short-acting BZD (elimination half-life of 12 h), no impairment in vigilance, mnemonic or psychomotor performance was revealed in healthy young subjects receiving single oral doses of etifoxine (50 and 100 mg) (Micallef *et al.*, 2001).

Considering that general practitioners are often the first physicians consulted for clinical manifestations of anxiety (sleep disorders, dysautonomic dysfunctions as tachycardia, gastro-intestinal disturbances, sweating...) and that ADWA has been shown to be frequent in their practice, this study was conducted in outpatients followed by general practitioners (GP). The objective was to compare, using a non-inferiority test, the efficacies of etifoxine and lorazepam monotherapies in the treatment of ADWA, over a period of 1 month. Lorazepam was chosen as control drug because of the numerous studies documenting its effects (Blin *et al.*, 2001; Cohn and Wilcox, 1986; Fontaine *et al.*, 1986; Garcia *et al.*, 2000; Hindmarch and Gudgeon, 1980; Laakmann *et al.*, 1998; Lemoine

et al., 1996), its recognized efficacy on anxiety disorders, and its wide use in these indications in general practice.

MATERIALS AND METHODS

Study design

A prospective study was conducted according to a randomized double-blind parallel group design, by 36 general practitioners (GP), throughout four regions in France (Arras, Marseille, Dijon and Rennes), from February 2002 through March 2004. Before starting the trial, the GP were trained to diagnose ADWA among their outpatients by intensive course performed by the coordinator, including training for tests and scales, video presentation of clinical cases, to diagnose ADWA and make differential diagnosis with generalized anxiety disorder, depression or other disorders. Moreover, DSM IV criteria for ADWA diagnosis were recalled in the patient Case Report Form and had to be checked on the inclusion criteria list.

ADWA patients included in the study were randomly assigned to receive per os one of the treatments, etifoxine (150 mg/day) or lorazepam (2 mg/day). They were asked to take the study drug daily during 28 days, at usual dosages (50 mg 3 times a day for etifoxine, and 0.5–1 mg by day for lorazepam), dosages in conformity with the French Summary of Product Characteristics (SPC) for each drug. Study medications (provided to the investigators by Biocodex laboratory) were presented as identical-appearing capsules to maintain the double-blind fashion. Randomization was realized by the coordinator centre, by a centralized procedure.

After the visit of selection, the patients attended three visits: at 1 week of treatment (Day 7), at the end of the treatment (Day 28) and 1 week after stopping treatment (Day 35).

In accordance with the current version of the declaration of Helsinki and French law, this study was approved by the local Ethic committee (CCPPRB Marseille), and all patients provided written informed consent before study participation.

Patients

One-hundred and ninety one outpatients were randomized by general practitioners. Two patients were excluded from analysis because of lack of data under treatment. Overall, 189 patients received one of the study treatment: etifoxine (E) for 93 patients and

lorazepam (L) for 96 patients. To be eligible for inclusion, the patients, male or female, aged from 18–65 years had to meet the criteria for ADWA as defined in the Diagnostic and Statistical Manual of mental disorders (DSM-IV): marked anxiety, with impairment of social functioning, occurring within 3 months after the onset of an identifiable psychological stressor. They were required to have a baseline HAM-A total score ≥ 20 . Other inclusion criteria were a score ≥ 5 in at least one of the sub-scales of the Sheehan disability scale, rating a significant impairment, and a score < 20 in the Montgomery-Asberg Depression Rating scale (MADRS) (Montgomery *et al.*, 1985), excluding significant depressive symptomatology. Patients who met clinical criteria for major depressive disorder were also excluded, as well as patients presenting with any other evolutive psychiatric disorder (e.g. generalized anxiety disorder, anxiety related to mourning, panic disorder and psychosis). Other non-inclusion criteria were contra-indications to the study drugs, i.e. a history of myasthenia, decompensated respiratory insufficiency, alcohol or drugs abuse, hypersensitivity to the study drugs and pregnant or lactating women. Patients were not allowed to have a regular treatment with BZD or other psychotropic drug, beta blocker therapy nor any drug that could have effects on the nervous system, or medication that could interfere with the study treatments metabolism (carbamazepine, phenytoine, primidone, rifampicine, griseofulvine, phenobarbital and probenecide), within the month preceding inclusion or during the study.

Efficacy assessments

Efficacy was evaluated on days 7 and 28, using the Hamilton rating scale for anxiety (HAM-A) (Hamilton, 1959), the Clinical Global Impression scale (CGI) (Rickels *et al.*, 1976), the Social Adjustment Scale Self-Report (SAS-SR) (Weissman and Bothwell, 1976), and disability assessment with the Sheehan scale (Andrew *et al.*, 1997). The main efficacy assessment criterion was HAM-A score on Day 28, adjusted to Day 0.

CGI scale is assessing severity of illness, clinical global improvement and the efficacy index, i.e. the ratio therapeutic effect/ side effects.

Sheehan disability scale includes three sub-scales: work, family and social life. It realizes a sensitive and simple measure of disability of the patient in each area. A significant impairment in an area is rated by a score ≥ 5 in the corresponding sub-scale.

Social Adjustment Scale Self-Report (SAS-SR), was evaluated at baseline and on Day 28. This self-questionnaire of 54 items measures overall social adjustment performance within six key areas of social functioning: work, social and leisure activities, relationships with extended family, role as marital partner, parental role and role within family unit. Each question is rated from 1 (normal) to 5 (most impaired). The overall mean score ranges from 1 to 5. In a general community sample, the mean score reported was of 1.59 (Weissman *et al.*, 1978).

Safety assessments

All adverse events were recorded throughout the study. Beside that, evaluations of memory (immediate and delayed free recall of images) were performed on Days 7 and 28 of treatment, and compared to Day 0. Two hours after the intake of treatment, the patients were presented 20 pictures. They had to recall in 3 min the maximum of pictures immediately (immediate free recall). The same test was repeated more than 10 min later (delayed free recall).

On Day 35, patients were questioned about occurrence of symptoms evocating a rebound of anxiety within the week after the end of the treatment (open questionnaire about the presence of somatic or psychic troubles since stopping the treatment). On the same day, HAM-A, Sheehan and CGI scales were also performed.

Statistical analysis

Sample size was determined to achieve 80% power to detect a difference inferior to 2.5 points in HAM-A total score on Day 28 between the two groups of treatment.

Populations were defined as follows:

- Patients who received at least one intake of the treatment constituted the safety population. There were 189 patients, 93 in etifoxine group (E), and 96 in lorazepam group (L).
- The intent-to-treat population (ITT) was composed of 185 patients (E: 91; L: 94) who received at least one dose of treatment and had at least one on-treatment HAM-A data (primary assessment parameter). Two patients from etifoxine group and two from lorazepam group were excluded from ITT because of premature withdrawal before the first on-treatment evaluation (on Day 7), one patient for withdrew consent and one for adverse events in each group of treatment.

- Efficacy analysis was conducted in ITT population. Safety analysis concerned the whole-analyzed population (safety population).

The groups of treatment were compared on HAM-A total score using a non-inferiority test (Schuirmann) by Days 7 and 28. Etifoxine efficacy was judged non-inferior to that of lorazepam if the difference in HAM-A total score between the groups (CI 90%) was inferior to 2.5.

Efficacy equivalence between the groups was assumed if the difference in HAM-A total score between the groups (CI 90%) was included in the equivalence margins [−2.5; 2.5].

Responders to the treatment were defined as patients showing a 50% or greater decrease from baseline in HAM-A total score on Day 28. They were compared by chi-square test.

To compare the other parameters (CGI, Sheehan and SAS-SR scales), Student test or Wilcoxon non-parametric test were used for quantitative data, and chi-square test or Fisher exact test for qualitative data.

Safety parameters (adverse events, memory tests during the study, CGI and HAM-A scores on Day 35) were compared using Student test or non-parametric Wilcoxon test.

Data were analyzed with SAS (Statistical Analysis System version 8.2), and the significance level for all statistical tests was 0.05.

RESULTS

Demographic data and clinical characteristics

From the 191 ADWA patients enrolled in the study, 189 patients were analysed, 93 in etifoxine group, and 96 in lorazepam group.

At inclusion, the two groups of treatment were found comparable with regard to all variables measured: age, sex, history, depression scale MADRS, anxiety assessment (HAM-A scores), severity of the disease (CGI), social impairment (Sheehan and SAS-SR scores) and memory test scores. Baseline characteristics of the 189 analysed patients are described in Table 1. Their mean age was 43 (range 18 to 68) and 66% were female. A history of depression or anxiety disorders was reported for 29% of the patients. They were free from major depression, as clinically determined, and according to the MADRS scale (mean score was 14.7 ± 3.6). The main psychological events identified as responsible for the disorders were related to family (40.7% of patients), work (29.6%), health (8.5%) and relationships (6.9%).

The baseline HAM-A mean total score was 25.5 ± 4.0 (25.3 ± 3.5 in etifoxine group vs 25.7 ± 4.4 in lorazepam group, range 20–38).

Clinical Global Impression mean severity score was 4.5 ± 0.7 , corresponding to a moderate to marked illness (moderate illness is rated by a score of 4).

Table 1. Baseline characteristics of patients ($n = 189$)

	Etifoxine	Lorazepam	Total
N	93	96	189
Age-mean (SD)	44.0 (13.4)	42.0 (13.1)	43.0 (13.3)
[min-max]	[18–66]	[20–68]	[18–68]
Women %	62.4	69.8	66.1
History of depression or anxiety %	25.8	32.3	29.1
MADRS mean score: mean (SD)	14.5 (3.5)	14.8 (3.8)	14.7 (3.6)
stress factor (% of patients):			
• family	38.7	42.7	40.7
• work	30.1	29.2	29.6
• health	10.8	6.3	8.5
• relationships	4.3	9.4	6.9
HAM-A total score: mean (SD)	25.3 (3.5)	25.7 (4.4)	25.5 (4.0)
[min-max]	[20–36]	[20–38]	[20–38]
CGI severity score mean (SD)	4.5 (0.7)	4.5 (0.8)	4.5 (0.7)
Sheehan score—work mean (SD)	5.2 (2.2)	5.3 (2.3)	5.2 (2.2)
Sheehan score—social mean (SD)	5.7 (1.5)	6.0 (1.9)	5.8 (1.7)
Sheehan score—family mean (SD)	5.3 (1.7)	5.4 (2.1)	5.3 (1.9)
SAS-SR total score mean (SD)	2.4 (0.6)	2.4 (0.6)	2.4 (0.6)
Memory test: immediate free recall of images number of correct responses/20 (SD)	9.7 (2.7)	9.8 (2.5)	9.8 (2.6)
Memory test: delayed free recall of images number of correct responses/20 (SD)	8.7 (3.1)	8.7 (2.7)	8.7 (2.9)

Table 2. Mean HAM-A scores (\pm SD) and percentage of responders on Day 28 in ITT population

	ITT (N = 185)		p
	Etifoxine (n = 91)	Lorazepam (n = 94)	
HAM-A score on Day 0	25.2 \pm 3.5	25.6 \pm 4.2	NS
HAM-A score on Day 28	11.4 \pm 5.9	12.2 \pm 6.4	0.0002*
HAM-A score Variation (Day 28-Day 0) (%)	-54.6 \pm 23.5	-52.3 \pm 24.2	0.0006*
Responders on Day 28 (%)	72	56	0.0288**

*Schuirmann's non-inferiority test.

** χ^2 test.

The non-inferiority margin was 2.5 for the difference between groups in mean HAM-A score.

Based on the mean HAM-A total score, etifoxine efficacy was not inferior to that of lorazepam on Day 28.

Moreover, more patients in etifoxine group were responders to treatment, defined as patients with a 50% or greater decrease from baseline in HAM-A total score.

As measured with the Sheehan scale, disability was clinically significant (mean score ≥ 5) in all areas. Impairment in social area was significant in 82% of patients, in 67% of them in work area and in 67% of them in family area.

In the questionnaire SAS-SR, 53% of patients declared to have a paid professional activity. Social life, leisure and work were also the most impaired areas in this scale (mean score for social life/ leisure: 2.9; for work area: 2.6). The baseline mean total score was 2.4 \pm 0.6.

Six patients from etifoxine group (6.5%) and seven from lorazepam group (7.3%) discontinued the study, mainly for adverse events (E: 2, L: 5), the others due to withdrew consent, protocol violation or failure to return.

Overall, 176 patients completed the study, 87 in etifoxine group (93.5%) and 89 in lorazepam group (92.7%). Compliance (as assessed by therapeutic units return) to treatment was respectively of 95.2% and 95.5%.

Efficacy analysis. Efficacy analysis was conducted in ITT (n = 185) population.

HAM-A total score

Improvement of anxiety, assessed by HAM-A score, was shown in the two groups of treatment (Table 2, Figure 1).

The mean HAM-A total score at Day 28 was of 11.4 in etifoxine group versus 12.2 in lorazepam group, corresponding to a decrease from baseline by 54.6 \pm 23.5 % versus 52.3 \pm 24.2 %, respectively. The mean difference (etifoxine-lorazepam HAM-A scores) was -0.56 (CI 90%: [-2.1, +0.98]). Analysis of HAM-A scores concluded to the non-inferiority of etifoxine compared to lorazepam (p = 0.0002).

The two drugs had equivalent activities. Moreover, the percentage of responders to the treatment, defined as patients having shown a 50% or greater HAM-A total score decrease from baseline, was significantly

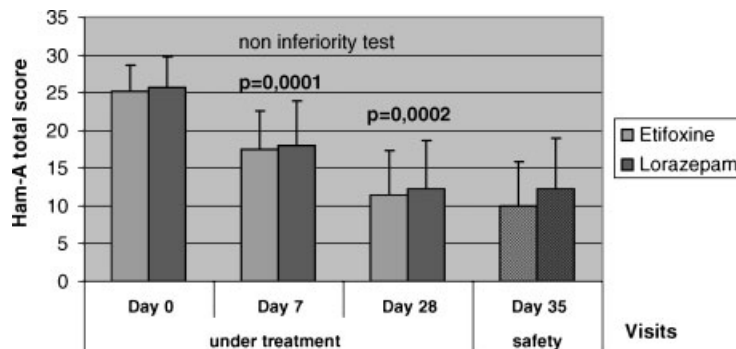


Figure 1. Evolution of mean HAM-A total score by visit, in ITT population

Table 3. Mean HAM-A scores (\pm SD) and percentages of responders on Day 7 in ITT population

HAM-A	ITT ($N = 185$)		<i>p</i>
	Etifoxine ($n = 91$)	Lorazepam ($n = 94$)	
HAM-A score on day 0	25.2 \pm 3.5	25.6 \pm 4.2	NS
HAM-A score on day 7	17.5 \pm 5.3	18.0 \pm 5.6	0.0001*
HAM-A score variation (Day 7–Day 0) (%)	–30.9 \pm 17.5	–30.1 \pm 19.8	<0.0001*
Responders on day 7 (%)	16	18	NS**

*Schuirmann's non-inferiority test.

** χ^2 test.

The non-inferiority margin was 2.5 for the difference between groups in mean HAM-A score.

Based on the mean HAM-A total score, etifoxine efficacy was not inferior to that of lorazepam on Day 7.

No significant difference between the groups was observed in the percentage of responders to treatment on Day 7, defined as patients with a 50% or greater decrease from baseline in HAM-A total score.

higher with etifoxine than with lorazepam (72 % vs 56 %, $p = 0.0288$).

The benefits of treatment appeared from the first week in both groups of treatment (Table 3). On Day 7, etifoxine and lorazepam were found to be equivalent with regard to HAM-A scores, and decrease in mean HAM-A total score was 30.9% and 30.1%, respectively ($p < 0.0001$).

Clinical global impression

Clinical Global Impression improved in both groups on Day 28. Severity of disease was decreased with etifoxine as with lorazepam (CGI-severity scores were 2.7 and 2.8, respectively, $p > 0.05$).

Patients were divided into two categories for analysis. Patients 'with little or no improvement' were the patients scored by their physician '3', '4' and '5' in CGI-global improvement scale, while 'markedly improved' patients included those scored '1' and '2' ('very much improved' and 'much improved').

Categorical analysis of CGI-global improvement showed results in favour of etifoxine (Figure 2).

Clinical improvement was significantly higher in etifoxine group with regard to the number of patients markedly improved (73.3% vs 57.1%; $p = 0.0222$) and the efficacy index: the percentage of patients having a marked therapeutic effect (notably diminished anxiety) without side effects was superior in etifoxine group (78.9% vs 62.6%; $p = 0.0383$).

Sheehan disability scale

At one month of treatment, disability assessed by Sheehan scale decreased in the two groups, for each subscale, without significant difference between the treatments. Mean Sheehan scores decreases from

baseline in work, social and family areas were by 38.8%, 49.0% and 42.0%, respectively in etifoxine group and by 35.1%, 37.4% and 30.4%, respectively in lorazepam group.

SAS-SR scale

The mean total score on Day 28 was found similar in etifoxine and in lorazepam groups (2.0 ± 0.6), corresponding to a decrease from baseline by 17.1% and 17.4%, respectively. This improvement concerned particularly the most impaired factors at inclusion, that were 'work' and 'social life-leisure' areas.

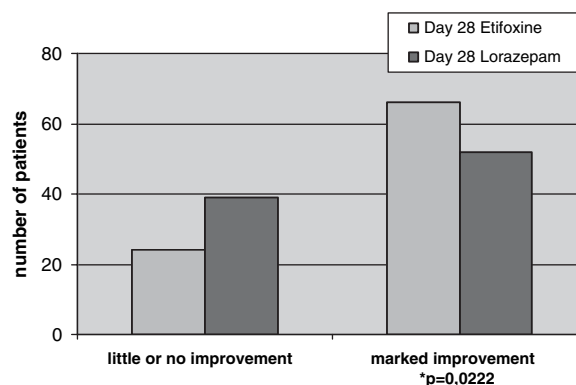


Figure 2. Clinical Global Impression: global improvement on Day 28 in ITT population Compared to lorazepam, clinical improvement was significantly higher in etifoxine group with regard to the number of patients markedly improved (73.3% vs 57.1%; $p = 0.0222$). Patients with 'little or no improvement': score 3, 4 or 5 Patients with 'marked improvement': score 1 or 2

Table 4. Main safety results by treatment group

Safety	Etifoxine <i>n</i> = 93	Lorazepam <i>n</i> = 96	Total <i>N</i> = 189	<i>p</i>
Number of adverse events (AE)	30	39	69	NS
Number of patients with AE (%)	19 (20.4)	28 (29.2)	47 (24.9)	NS
Most frequent AE: drowsiness. Number of patients (%)	10 (10.7)	18 (18.7)	28 (14.8)	NS
Number of withdrawal related to AE	2 (2.1)	5 (5.2)	7 (3.7)	NS
Number of patients with a HAM-A total score increase on Day 35	1	8	9	0.034
Number of patients with psychological or somatic disorders on Day 35	2	5	7	NS

Safety analysis. Analysis was conducted in the exposed population (*n* = 189). The main safety results are reported in Table 4.

Adverse events

No significant difference was observed between the two groups for the adverse events incidence, severity, and imputability to the study treatments. No serious adverse event linked to treatment occurred.

Sixty-nine adverse events (AE) were reported during the study, in 20% of patients with etifoxine (*n* = 19) and 29% of patients with lorazepam (*n* = 28). Of them, 19 were imputed to etifoxine and 29 to lorazepam treatment.

Drowsiness was the only AE that occurred in more than 5% of the patients. It concerned 10 patients receiving etifoxine and 18 receiving lorazepam (10.7% and 18.7%, respectively, *p* = 0.12).

From the 13 patients who discontinued the study (E: 6, L: 7), seven withdrew because of adverse event reliable to treatment (E: 2, L: 5). One patient from etifoxine group stopped the treatment because of an urticaria. But the primary reason for premature withdrawal was the occurrence of neuropsychic adverse events, in the 6 other cases. One patient in etifoxine group experienced anxiety with nausea, and 5 patients in lorazepam group presented neuropsychic AE (3 cases of excessive sedation, one increased anxiety and one case of visual hallucinations).

Memory tests

Results in memory tests on Day 28 were comparable in the two groups of treatment: on average, the number of recalled images, on a total of 20, increased two from baseline, in immediate and delayed tests. The mean number of recalled images was of 12.1 ± 2.3 in etifoxine group versus 12.3 ± 2.6 in lorazepam group in the immediate tests, and respectively 11.1 ± 2.7 versus 11.0 ± 3.0 in the delayed tests.

Detection of rebound symptoms

On Day 35, one week after stopping treatment, the results in HAM-A (Figure 1), Sheehan and CGI scales remained comparable to those on Day 28.

The anxiolytic effect persisted one week after the end of treatment: mean HAM-A total scores in etifoxine and lorazepam groups were 10.0 and 12.2, respectively (*p* = 0.0241), and the percentage of markedly improved patients was higher in etifoxine recipients (73.6% vs 58.4%, *p* = 0.0272).

Comparison of mean HAM-A and CGI scores did not detect an increase in anxiety from Day 28 to Day 35. When questioned, seven patients (E: 2, L: 5, non-significant difference) complained of psychological or somatic disorders since stopping the treatment.

However, individual data showed that nine patients had a HAM-A total score increase from Day 28 to Day 35, considered as clinically relevant to assess a rebound of anxiety (HAM-A total score increasing from Day 28 to a value ≥ 20 on Day 35). One patient in etifoxine group (1.1%) had a clinically significant increased score (from 7 to 24: +242.8%) versus 8 patients in lorazepam group (9.1%), with an increase in HAM-A total score ranged by 23.5% (score 17–21) to 1050.0% (score 2–23).

According to this criteria, fewer patients presented a rebound of anxiety in etifoxine group compared to lorazepam group (1 vs 8, *p* = 0.0343).

DISCUSSION

Few studies concerned management of ADWA in general practice settings. Semaan *et al.*, in an estimation of the prevalence of ADWA in outpatients, showed that it was a common pathology in primary care. Its prevalence in patients with psychological complaints was 9.2% when eventually associated to other psychiatric disorders, and 4.5% without any other psychiatric disorder. ADWA had a notable impact on work (50% of patients) and conjugal life (32%). In 91% of the cases, GPs estimated that the

patients required a specific treatment (74% of the patients were prescribed a pharmacological therapy, mostly associated to psychotherapy). Anxiolytic drugs were usually prescribed (65%), more than antidepressants and hypnotic drugs. Only 2.6% of cases were sent to a psychiatrist (Semaan *et al.*, 2001).

Efficacy of etifoxine on ADWA has previously been assessed in a double blind controlled study carried out in primary care setting (Servant *et al.*, 1998). This study compared the efficacies and tolerance of etifoxine and buspirone in patients treated for four weeks. Using HAM-A total score and CGI as endpoints, this trial showed that both treatments were efficient and safe, but the global improvement score and the efficacy index were significantly better in the etifoxine group.

The 189 ADWA outpatients enrolled in our trial presented the same baseline characteristics than those described in Semaan's study: they were mostly female (2/3), aged about 40 years, had a professional activity (more than 50%) and identified work and family-associated problems as main causes of their anxious disorder. Impairment in social functions, assessed by Sheehan scale and SAS-SR was significant at inclusion.

The primary result of this study was that the anxiolytic effect of etifoxine, assessed by HAM-A total scores, was found not inferior to that of lorazepam. This result was demonstrated by one month of treatment, but also from the first week of treatment.

The two drugs were found equivalent in efficacy on Day 28 (respective HAM-A score decrease: 54.6% vs 52.3%). However, more etifoxine recipients were responders to the treatment (HAM-A score decreased by $\geq 50\%$). Clinical improvement (based on CGI, SAS-SR, and Sheehan scores) was observed in both treatment arms, but was better in etifoxine group with regard to percentage of patients improved markedly and of patients with markedly diminished anxiety without side effects. One week after stopping treatment, these benefits on anxiety, assessed by HAM-A and CGI mean scores, were globally maintained in the two groups and were comparable to those on Day 28. But significantly more patients presented a rebound of anxiety (relevant HAM-A increase) in lorazepam group.

Multiple approaches, including pharmacologic treatment, psychotherapy, or combined therapies, are proposed to manage ADWA patients, notably to prevent the adjustment disorder from developing into a chronic condition, such as generalized anxiety disorder (Schatzberg, 1990).

This study confirms the interest of etifoxine in treatment of ADWA, compared to lorazepam. Like most non-placebo-controlled clinical trials on therapeutic in the domain of anxiety disorders, the difficulty in our studied population is to evaluate in the therapeutic response the part of placebo-type improvement (Schweizer and Rickels, 1997), even if the control drug lorazepam is considered a high-potency benzodiazepine in anxiety disorders (Chouinard, 2004). In a previous report, a one-month treatment with lorazepam in anxious patients have shown the same level of anxiety improvement than in our study control group (Cohn and Wilcox, 1986). The dose of lorazepam chosen for our patients, i.e. 2 mg/day, was conform with the French SPC recommendations. The results on HAM-A scores were similar to that previously found in patients treated during 8 weeks with 3 or 4 mg/day lorazepam for generalized anxiety disorder (Bourin and Malinge, 1995).

In patients enrolled in our trial, efficacy of etifoxine was found non-inferior to that of lorazepam by one month of treatment. These treatments were shown equivalent, the difference in mean HAM-A total score between the two groups (CI 90%) being included in the equivalence margins [2.5; +2.5]. These margins have been chosen on the base of previous clinical trial using HAM-A comparison (Rickels, 1997, Cohn and Wilcox, 1986). However, there is no consensus concerning the difference between groups required to be clinically relevant. In a placebo-controlled study on venlafaxine efficacy in anxious disorders, this limit was a difference of 4 points in HAM-A score between the groups (Gelenberg *et al.*, 2000).

But most of the studies on psychotropic drugs admit as definition of clinical response to therapy an improvement of 50% from baseline. According to guidelines for establishing remission in patients with depression and anxiety, clinical response to treatment can be defined on this base, while remission is corresponding to a score of ≤ 7 on HAM-A scale, a score of 1 on the Clinical Global Impression, and a score of ≤ 5 on the Sheehan Disability scale (Ballenger, 1999).

In our study, compared to lorazepam group, more patients were responders to treatment in etifoxine group, and more patients were markedly improved (scores 1 and 2 in CGI-global improvement). Our study was designed to compare by a non-inferiority test two psychotropic drugs on the bases of HAM-A differences, and led to the conclusion of non-inferiority of etifoxine compared to lorazepam. Clinical response rates, classically used in trials on anxiolytic drugs, were found in favour of etifoxine

group. Even if it was a secondary assessment criteria, these results worth to be considered.

Beyond the response on clinical symptoms of anxiety (HAM-A scores and Clinical Global Improvement), it was important to assess adjustment disorders and social functional impairment, with their repercussions on quality of life (Sheehan and SAS-SR scales). By 1 month of treatment, these parameters were improved in both groups. The level of social adjustment assessed by SAS-SR scale did not reach at one month of treatment the values previously found in a community sample (Weissman *et al.*, 1978), but was better than on inclusion. It might require a longer delay to normalize than other scales, as suggested in a recent study on venlafaxine in generalized anxiety disorder (beginning from 8 weeks of treatment in this trial) (Boyer *et al.*, 2004).

Another point to underline is the rapid onset of therapeutic effect in etifoxine recipients, from the first week of treatment, as in lorazepam group. This is important to consider, notably because ADWA is concerning mainly working people. Among alternative therapies to benzodiazepines, buspirone, an anxiolytic drug of 5-HT_{1A} partial agonist class, has proven its efficacy on anxious disorders with less induced sedation than lorazepam (Cohn and Wilcox, 1986), but its action was found delayed compared to that of benzodiazepines clobazam and lorazepam (1 week for BZD vs 3 weeks for buspirone) (Lemoine *et al.*, 1996).

Concerning the safety analysis, side effects as drowsiness occurred in this study were observed with the two treatments, without significant difference between the groups.

On average, the memory free-recall tests were not impaired in etifoxine nor in lorazepam group. These results seem discordant with those reported in previous studies in healthy volunteers, where a deficit in delayed free-recall was observed after single doses of lorazepam, compared to etifoxine (Micallef *et al.*, 2001) or to placebo (Matthews *et al.*, 2002). These differences could be mainly explained by the difference of schedule in the realization of the memory tests. First of all, the delay between the drug intake and the immediate free recall tests was rarely respected. It has been the only assessment criterion that represented a difficulty for general practitioners. Otherwise, in our study, the delayed free recall tests had to be performed in real conditions of consults, in a delay of 10 min or more after the first test, while this delay was of 50 min in previous studies performed in center experimental conditions. Second, lorazepam-induced memory impairment in studies in healthy volunteers (Micallef

et al., 2001; Matthews *et al.*, 2002) was observed with higher doses of lorazepam (2 mg and 2.5 mg, respectively). The tests in our study were realized after a dose of 0.5 mg of lorazepam (the daily dosage was of 0.5, 0.5, 1 mg). The results could be in line with those of studies performed in healthy young volunteers receiving low doses of lorazepam, showing an improvement in explicit episodic memory test (File *et al.*, 1999), or on the psychomotor performance without sedation and memory impairment (Bourin *et al.*, 1994). Lastly, effects in patients of the anxiety reduction on mnemonic performances or a tolerance phenomenon after repeated intakes are to be considered (Curran, 1992).

One of the limiting factors to benzodiazepine use, besides the sedative and cognitive side effects, is the risk of dependence and withdrawal syndrome. In this study, identification of withdrawal symptoms was based on comparison of mean HAM-A and CGI scores between Day 28 and Day 35, and on an open questionnaire about troubles within the week following the end of the treatment. Rebound of anxiety was not expected, according to the design of this trial, as lorazepam was administered at usual dosage for a period of one month. Indeed, factors contributing to BZD physical dependence are a high daily drug dose, a long duration of treatment (more than 3 months), and association with other psychological disorders (Isacson, 1992, 1997; Schweizer and Rickels, 1998; Rickels *et al.*, 1990). However, the number of patients with an increase in HAM-A score one week after stopping one month of treatment was significantly higher in lorazepam group, compared to etifoxine group (8 vs 1, $p = 0.0343$). Confirmation of low propensity of etifoxine for withdrawal syndrome in patients might require the use of specific standardized rating scales, to point out not only differences in anxiety scores, but also occurrence of new symptoms (Bourin, 1988; Petursson and Lader, 1984).

In conclusion, in this study performed in ADWA outpatients followed by general practitioners, etifoxine was at least as effective on anxiety as lorazepam, at usual doses for 1 month. Moreover, after one month of treatment, a significantly higher percentage of etifoxine recipients experienced a marked decrease in anxiety without side effects. With regards to the efficacy results and the lower incidence of anxiety rebound after the end of the treatment compared to lorazepam, these results suggest that etifoxine could be an interesting alternative therapy to benzodiazepines for ADWA. Further studies should be carried out to confirm these benefits both on clinical signs of anxiety and social adjustment, and on safety, at longer term.

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