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Etifoxine impairs neither alertness nor cognitive functions of the elderly: A randomized, double-blind, placebo-controlled crossover study☆

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Abstract
Etifoxine hydrochloride (Stresam®), a treatment indicated for psychosomatic manifestations of anxiety, could be an alternative to benzodiazepines. While no impact on alertness and cognitive functions has been proven among youth, data on elderly are lacking. The primary objective of this study was to measure the impact of etifoxine, lorazepam or placebo on alertness in the elderly. The secondary objectives were to evaluate cognitive performances and adverse effects. In this randomized, placebo-controlled, double-blind, 3-way crossover design, 30 healthy volunteers aged 65 to 75 years underwent three one-day sessions. After treatment intake, standardized cognitive tests were conducted using the Cambridge Neuropsychological Test Automated Batteries and other psychological tests (Stroop, Rey Auditory Verbal Learning Test, Digit

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Span). The reaction time (RTI) as primary endpoint was analysed using a 3 × 3 latin square variance analysis. A 100-mg dose of etifoxine has no deleterious impact on alertness and causes no cognitive disorders as compared to placebo (RTI: 744 ± 146 ms *versus* 770 ± 153 ms; p = 1.00). As expected, a 2-mg dose of lorazepam impairs alertness (RTI: 957 ± 251 ms *versus* placebo; p < 0.0001) and cognitive functions. A similar frequency of adverse events was observed with etifoxine and placebo while their incidence was 3-fold higher with lorazepam, drowsiness being the most frequent adverse event. No serious adverse events were observed. This study demonstrates in the elderly that a single dose of etifoxine does neither impair alertness nor any of the cognitive parameters evaluated. Etifoxine may be a good option when anxiolytic treatment is required, especially in elderly people.
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1. Introduction

Elderly people of at least 65 years of age represent 8.5% (617 million) of the world's population and this proportion is expected to increase to 17% by 2050 (He et al., 2016). The elderly population is highly prone to develop psychiatric morbidities due to ageing of the brain, problems with physical health, cerebral pathologies, and factors such as a decrease in economic independence and the breakdown of family support systems (Varma et al., 2010). Anxiety is an important clinical concern in older adults, although little is known about its prevalence in this population. Adjustment disorder appears to be a significant cause of anxiety symptoms in community-dwelling elderly persons, especially those presenting personal health-related problems (Arbus et al., 2014).

Benzodiazepines (BZDs) are among the most widely prescribed psychotropic drugs for anxiety (Lagnaoui et al., 2004; Pringle et al., 2005). In France, 80–92.3% of BZDs are prescribed to people of at least 65 years of age (Lasserre et al., 2010), even though concerns have been raised about the adverse event profile of these agents, including cognitive dysfunction and the potential risk for dependence (Stewart, 2005; Tan et al., 2011; Picton et al., 2018).

Etifoxine (Stresam®) is an anxiolytic drug, which is currently prescribed for the treatment of psychosomatic symptoms of anxiety. Etifoxine is a benzoxazin that does not belong to the benzodiazepine family, but that has anxiolytic properties (Verleye and Gillardin, 2004). In previous randomized controlled trials, etifoxine demonstrated a similar anxiolytic effect to lorazepam and alprazolam in adult outpatients suffering from adjustment disorder with anxiety (Nguyen et al., 2006; Stein, 2015). The impact of etifoxine (50 and 100 mg, single dose) on vigilance or psychomotor impairments in healthy volunteers aged from 18 to 35 years was studied in a placebo-controlled trial and etifoxine showed no deleterious impact on cognitive functions (Micallef et al., 2001). However, there is little data concerning the cognitive effects of etifoxine in elderly subjects over 65 years of age.

The present study, ETILANCE, was conducted to evaluate the effects of a single oral administration of the usual 100 mg dose of etifoxine on alertness and cognitive functions in healthy elderly subjects between 65 and 75 years of age. The primary objective was to measure the impact of etifoxine as compared to a placebo on alertness. The secondary objectives were to evaluate the cognitive performances of subjects and describe any adverse effects. The lorazepam arm of the study was used as a positive control due to its previous well-described psychomotor and amnesic effects (Pomara et al., 2015; Loring et al., 2012).

2. Experimental procedures

ETILANCE was a randomized, double-blind, placebo-controlled, 3-way crossover study performed between December 2013 and October 2015 at the Clinical Investigation Centre 1403 INSERM of the Lille University Hospital (France). Both the French Health Authority (*Agence Nationale de Sécurité des Médicaments*, ANSM) and the Nord-Ouest IV Ethics Committee approved the study (EudraCT number 2012-005530-11). ETILANCE was performed in accordance with the Declaration of Helsinki and Good Clinical Practices. The participants were informed about the risks and requirements of the study and gave their written informed consent before any study procedure was done. The study was also registered at ClinicalTrials.gov (NCT02147548).

2.1. Subject selection

Right-handed men and women (according to Edinburgh Handedness Inventory) aged from 65 to 75, with no progressive neurological or psychiatric condition, and not usually receiving neither psychotropic treatment nor any other psychoactive substances, were eligible. Main exclusion criteria were anxiety (a score > 7 on the Hamilton Anxiety Rating Scale and/or a score > 51 for men and > 61 for women on Spielberger's anxiety scale), current treatment with drugs known to interfere with the metabolism of study drugs, previous allergic reactions to medicines, smoking, or excessive consumption of coffee or tea (> 4 cups/day) or alcohol (> ½ liter of wine or equivalent/day). Subjects were also able to carry out the cognitive tests and to understand instructions.

2.2. Study procedures and treatment

Participants underwent a total of 3 one-day sessions, according to a comparative, randomized placebo-controlled,

double-blind, crossover design. The sessions were separated by a washout period of 14 days to one month.

At each session, participants arrived at the centre at about 8:00 am and were first tested to confirm there had been neither recent alcohol consumption (alcohol breath test) nor psychotropic substance abuse in the previous 48 hours (urine screening test: Multiscreen 6-Biomedical Diagnostics).

Subjects were assigned on a double-blind basis to receive, in a random order, etifoxine (2×50 mg, Stresam®, Biocodex), lorazepam (2×1 mg) or a placebo on 3 separate testing days. The 100 mg of etifoxine corresponds to the maximal dose that could be used for each intake. Since lorazepam was used as a positive control able to induce both alertness and cognitive dysfunction, the choice of the dose was based on previous publications where altered cognitive performances were observed (Pomara et al., 2015; Loring et al., 2012). Two hours after treatment intake, participants underwent cognitive tests using the Cambridge Neuropsychological Test Automated Battery (CANTAB®; Cambridge Cognition). A neuropsychologist also supervised the other cognitive evaluations. Subjects were given a 15 min break after 1 h of cognitive evaluations. The duration of participation per subject was a maximum of three months.

2.3. Neuropsychological tests

A neuropsychologist administered all neuropsychological tests and CANTAB® was used to examine some components of cognition. CANTAB® is a computer-based battery using a touch-tone screen and press pad with 2 buttons. This computerized platform is validated and widely used for assessing cognitive functions (Smith et al., 2013; Kim et al., 2014). Based on the study purpose, a battery of five tests was selected to evaluate alertness and cognitive functions. The Reaction Time (RTI) was selected as the primary efficacy criterion to observe the treatment effect on alertness. Rapid Visual Information Processing (RVP) was chosen to assess the effect of treatments on attention. Paired Associates Learning (PAL) and Spatial Recognition Memory (SRM) assessed visuospatial memory, and Spatial Working Memory (SWM) test evaluated working memory. All the participants performed the Motor Screening Test (MOT) before their inclusion to avoid any learning process and to ensure that the participants had no sensorimotor or other difficulties that may have hampered the collection of valid data for the subsequent tasks. These tests are described in Suppl. Table 1.

In addition to the CANTAB® tests, Stroop test, Rey Auditory Verbal Learning Test (RAVLT) and forward and backward Digit Span test (DS) were administrated to investigate treatment effect on attention, verbal memory and working memory. A full description is available in Suppl. Table 2.

Finally, adverse effects (AE) were monitored throughout the course of the study, especially any AE spontaneously reported by the subjects.

2.4. Statistical analysis

Efficacy analysis used an analysis of variance for Latin square study design with treatment, period, carryover and period by treatment interaction as fixed effects. Etifoxine and lorazepam were compared to placebo with a significance level of 2.5% to take into account multiple comparisons through a Bonferroni correction. If the treatment by period interaction or carryover effect were significant, data from the first treatment period were analysed by Mann Whitney test to compare etifoxine and lorazepam to placebo with a significance level of 2.5%.

The validity of the mixed model was then verified using the normal probability plot to conduct a graphical analysis of the residuals. In case of an error in the linear mixed model (non-normal distribution of residuals), a logarithmic data transformation was applied and the analysis repeated.

3. Results

3.1. Subjects' characteristics

From the 47 eligible subjects screened, 31 were included in the study and 30 participated in the 3 separate testing days (Fig. 1). One included subject withdrew prematurely from the study after the first period for personal reasons (death of a parent). The 30 other subjects completed the entire protocol without any major deviation. They received the study medication according to the randomization scheme.

The demographic characteristics are shown in Table 1. There were twice as many women ($n = 20$; 66.6%) as men, with a mean age of 68.1 (±2.9) years. All included subjects satisfied all inclusion criteria.

3.2. Efficacy results

A total of 90 measurements were analysed: 3 measurements corresponding to the 3 study periods for each of the 30 healthy volunteers. There was neither statistically significant treatment by period interaction nor carryover effect. According to the main objectives of the study, the results presented here are focus on etifoxine effects while details on lorazepam effects are given in Suppl. Tables 3 and 4.

Table 1 Demographic characteristics.

$N = 30$	
Men, n (%)	10 (33.3)
Mean age (± SD), years	68.1 (± 2.9)
Mean weight (± SD), kg	71.4 (± 14.5)
Mean height (± SD), meters	1.67 (± 0.1)
Mean years of schooling (± SD)	12.1 (± 2.3)
Occasional smokers, n (%)	1 (3.3)
Alcohol use, n (%)	
Occasionally	17 (56.7)
Regularly (< ½ liter/ day)	6 (20)
Current treatment* at screening, n (%)	26 (86.7)

* Aside from other psychoactive substances such as etifoxine or lorazepam.

n (%): number and percentage of subjects; SD: Standard Deviation.

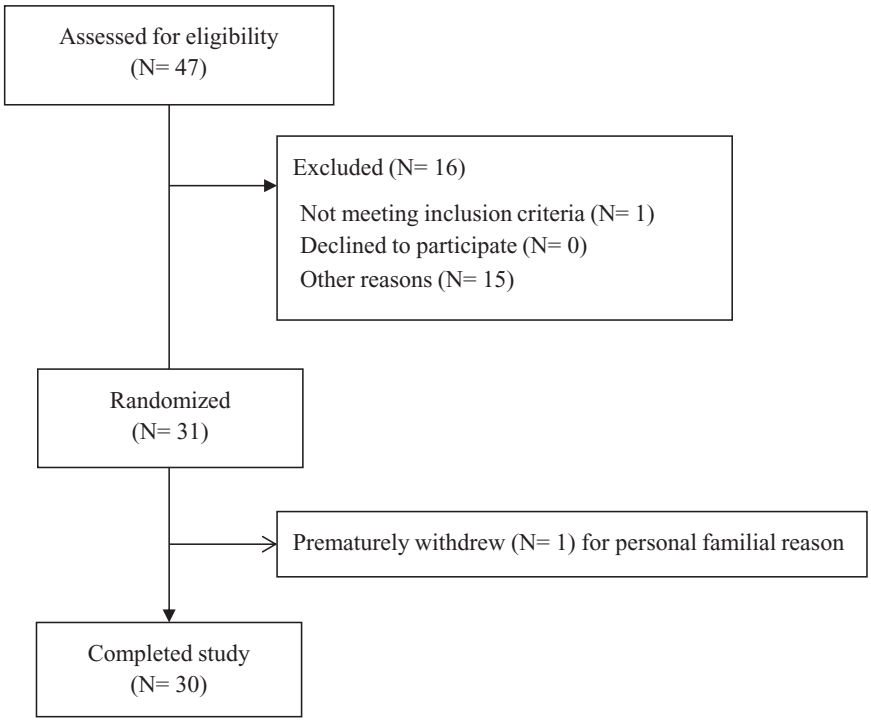

Fig. 1 Subjects' disposition.

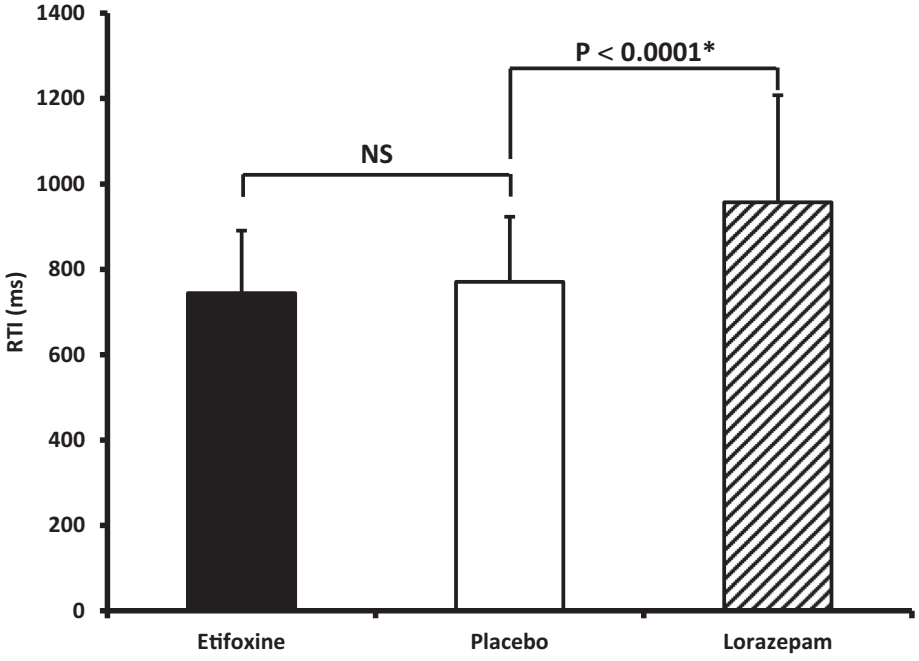

Fig. 2 Etifoxine and Lorazepam effects on alertness 2 h after administration as compared to placebo
RTI: Reaction Time expressed as mean ± standard deviation (30 subjects); ms: milliseconds. * Bonferroni correction for multiple comparisons *vs* placebo with signification level < 0.025; NS: not significant.

3.2.1. Main efficacy criterion: CANTAB® reaction time
Compared to placebo, a single dose of 100 mg of etifoxine has no deleterious effect on alertness as evidenced by a non-significant difference in reaction time to the CANTAB RTI test (RTI: 744.0 ± 146.8 ms *versus* 770.3 ± 153.1 ms under placebo; $p = 0.789$; Fig. 2). On the other hand, as a positive control, as compared to placebo, lorazepam significantly increases the reaction time (RTI: 956.9 ± 250.7 ms; $p < 0.0001$; Fig. 2).

Table 2 Etifoxine effects on attention 2 h after administration.

Parameters	Etifoxine $N=30$	Placebo $N=30$	Comparison[1]
Automated visual attention test			
RVP mean latency (milliseconds)	486.8 (95.9)	477.6 (98.4)	$P=1.0000$
RVP A (p) The probability of detecting the target sequence	0.9 (0.05)	0.9 (0.05)	$P=0.5624$
RVP probability of correct responses (%)	0.5 (0.2)	0.6 (0.2)	$P=0.3572$
RVP total false alarm (number)	4.0 (3.2)	4.9 (5.6)	$P=1.0000$
Stroop			
Stroop interference time (seconds)	122.4 (33.7)	115.1 (21.9)	$P=0.4574$
Stroop total errors (number)	2.9 (3.5)	2.1 (2.4)	$P=0.6240$

Results are presented as mean (standard deviation). RVP: Rapid Visual Information Processing; %: percentage; *p*: probability.
[1] Bonferroni correction for multiple comparisons *versus* placebo with $P<0.025$.

Table 3 Etifoxine effects on learning and memory performances 2 h after administration.

Parameters	Etifoxine $N=30$	Placebo $N=30$	Comparison[1]
Visuospatial memory			
PAL total errors 6 shapes adjusted (number)	8.3 (8.9)	6.5 (5.9)	$P=1.0000$
PAL first trial memory score (number)	9.6 (3.8)	10 (3.1)	$P=0.9886$
SRM mean latency (milliseconds)	2514.9 (653.1)	2606.9 (856.8)	$P=1.0000$
SRM correct responses (%)	70.7 (11.9)	72.7 (12.2)	$P=0.9056$
Verbal memory			
RAVLT score test 1 (number)	7.8 (2.5)	7.2 (1.9)	$P=0.6658$
RAVLT score test 2 (number)	11.2 (2.6)	10.2 (2.3)	$P=0.1164$
RAVLT score test 3 (number)	13.0 (2.0)	12.3 (2.3)	$P=0.3342$
RAVLT score test 4 (number)	13.2 (2.3)	13.1 (2.1)	$P=1.0000$
RAVLT score test 5 (number)	13.7 (1.7)	13.8 (1.5)	$P=1.0000$
RAVLT score test 6 (number)	12.7 (2.7)	12.1 (2.4)	$P=0.7060$
RAVLT total correct answers (number)	13.1 (1.8)	12 (2.6)	$P=0.1620$
Working memory			
SWM between errors 4 to 10 boxes (number)	50.9 (16.2)	53.9 (14.9)	$P=0.6634$
SWM strategy 6 to 10 boxes (number)	31.0 (5.1)	31.1 (4.6)	$P=1.0000$
DS forward score (number)	9.2 (1.9)	9.4 (2.6)	$P=1.0000$
DS backward score (number)	7.1 (1.9)	6.7 (2.1)	$P=0.4082$

Results are presented as mean (standard deviation). PAL: Paired Associates Learning; SRM: Spatial Recognition Memory; RAVLT: Rey Auditory Verbal Learning Test; SWM: Spatial Working Memory; DS: Digit Span; %: percentage.
[1] Bonferroni correction for multiple comparisons *versus* placebo with $P<0.025$.

3.2.2. Secondary endpoints

The two neuropsychological tests used to evaluate the attention showed that a single 100 mg dose of etifoxine has no deleterious effect on attention. The CANTAB® Rapid Visual Information Processing (RVP) and the Stroop test gave comparable results with etifoxine and placebo (Table 2). Compared to placebo, etifoxine caused no memory disorder (Table 3), neither on visuospatial, verbal nor on working memory. As expected, lorazepam, used as positive control, significantly impaired alertness, attention and both working and verbal memories. Nevertheless, such treatment did not alter visuospatial memory (details in Suppl. Tables 3 and 4).

3.3. Safety

A total of 87 adverse events (AEs) were reported within the 24 h following treatment administration. A similar percentage of AEs were observed with etifoxine ($n=12$; 13.8%) and placebo ($n=16$; 18.4%), while their incidence was higher with lorazepam ($n=59$, 67.8%). Most AEs were neurological, the most frequent being drowsiness (Table 4). Drowsiness was rated as severe once with etifoxine and four times with lorazepam. No serious adverse event occurred during the study; in particular we observed neither cutaneous disorder nor acute hypersensitivity reactions.

4. Discussion

Our study showed that single administration of etifoxine at the usual dose of 100 mg to healthy elderly subjects of 65 to 75 years of age, impairs neither alertness nor cognitive functions and is devoid of adverse effects as compared to placebo.

These results are in accordance with previous findings of Micallef et al., (2001), whose study in young healthy volunteers, showed that a single dose of 100 mg etifoxine has no harmful effects on alertness, attention or visuospatial, verbal and working memories. In the crossover ETILANCE study, elderly subjects received etifoxine as well as lorazepam and a placebo as respectively positive and negative controls.

Table 4 Overview of Adverse Events (AEs).

	Etifoxine ($N = 30$)	Placebo ($N = 30$)	Lorazepam ($N = 30$)
Number of reported adverse events	**12**	**16**	**59**
Type of AE			
Drowsiness	6	8	27
Headache	4	2	2
Nausea	1	1	4
Hypotension	1	-	4
Vision disorder	-	2	3
Fatigue	-	-	4
Impaired alertness	-	-	2
Dizziness	-	-	3
Lack of concentration	-	1	2
Other	-	2*	8**

* The following were reported once: sleep disorder; keratitis

** The following were reported once: disorientation in space, groggy feeling; insomnia; loss of balance; vertigo; neurasthenia; hypertension; bladder disorder

Cognitive functions were then assessed under each investigational condition by using the highly sensitive CANTAB®, a tool that has been validated in both healthy volunteers and patients aged between 4 and 90 years (Robbins et al., 1998; Louis et al., 1999; Roque et al., 2011). Besides not being influenced by cultural or socio-economic aspects, an important property of CANTAB® for an elderly population is that this screening tool is brief in application, requires simple responses from the participant and does not require any computer/technology knowledge that may influence subjects' performance on computerized test batteries (Falleti et al., 2006).

The timing of procedures and the washout duration were determined by taking into consideration the products' half-lives. 100 mg of etifoxine is the recommended dose per intake according to the product leaflet. Because effects of psychotropes can be observed as early as the first intake, the present results provide an accurate description of the acute impacts of etifoxine on alertness and cognitive functions. Moreover, very few AEs have been reported with etifoxine, particularly drowsiness, which occurred at the same rate as with placebo. The deleterious effects of 2 mg of lorazepam that are clearly confirmed here help to validate our study design. The deleterious acute effects of lorazepam on sedation and cognitive functions have been reported at the same dose in the elderly in naïve subjects and long-term users (Pomara et al., 2015; Loring et al., 2012). On the other hand, the acute administration of etifoxine at 100 mg in both healthy young volunteers (Micallef et al., 2001) and in elderly subjects in the present ETILANCE study, did not affect cognitive functions. Even if the observation of deleterious effects consecutive to acute administration is possibly not correlated to long-term effects, these results strongly contrast with both the acute and long-term effects of BZDs, which are highly suspected to favour the development of cognitive disorders and possibly dementia (Islam et al., 2016; Pariente et al., 2016; Picton et al., 2018).

The absence of deleterious effect of etifoxine on alertness and cognitive performance may be related to its pharmacological mechanism of action. Etifoxine directly interacts with the chloride channel of the Gamma Amino Butyric Acid A (GABA-A) receptor complex, potentiating GABAergic synaptic transmission (Verleye et al., 1999; Schlichter et al., 2000). It also enhances the synthesis of brain neurosteroids (pregnenolone, allopregnanolone), by acting on translocator protein (TSPO) (Schlichter et al., 2000; Liere et al., 2017). Etifoxine, as well as BZDs, facilitate the action of the major inhibitory GABA neurotransmitter in the central nervous system (Tan et al., 2011; Griffin et al., 2013; Choi and Kim, 2015; Islam et al., 2016; Pariente et al., 2016). However, etifoxine enhances GABAergic neurotransmission through allosteric interaction with the GABA-A receptor that is clearly different from BZDs (Bouillot et al., 2016). The anxiolytic effects of etifoxine are mainly produced by binding to $\beta 2$ or $\beta 3$ subunits while that of BZDs are known to be mainly mediated by $\alpha 2$ or $\alpha 3$ -containing GABA-A receptor complex (Hamon et al., 2003). Furthermore, the $\alpha 1$ and $\alpha 5$ subunit binding by classical BZDs, such as diazepam, bromazepam and lorazepam, may contribute to their unwanted effects including withdrawal symptoms, sedation, amnesia and cognitive impairments (Rudolph and Knoflach, 2011). The identification of GABA-A receptor subtypes and clarification of their function provide the hope that drug development will lead to GABA-A agonists and modulators which have fewer adverse effects, lower risk for dependence, and greater specificity of action.

The main limit of this study is that it was performed in a healthy population with neither psychiatric symptoms nor anxiety, and only involved a single dose intake of the drug. Therefore, the results are not fully generalizable to ageing patients with anxiety or other neuropsychiatric diseases. Moreover, because subjects were submitted to a single dose of each treatment, these results do not allow a definitive conclusion in normal practice where patients are usually treated with repeated dosages. Nevertheless, despite the use of a single dose in the present study, lorazepam is able to induce unmistakable cognitive dysfunctions as it was previously shown in both young and elderly subjects with similar dosages of the drug (Pomara et al., 2015; Loring et al., 2012). According to the number of patients actually

concerned, the potential of BZDs to favour cognitive dysfunction or dementia is an important issue with a possible deleterious effect of longer- rather than shorter-acting BZDs, longer rather than shorter durations of use, as well as earlier rather later exposure (Pariente et al., 2016; Picton et al., 2018). On the other hand, some serious adverse events were also described with the use of etifoxine in the clinical practice including severe toxidermia and hepatitis where contributing factors should be more clearly identified (Cottin et al., 2016). While the impact of the cognitive decline in a large number of patients receiving BZDs probably has important long-term consequences for both subjects and community, severe adverse events of etifoxine occur in a small number of patients that actually require medical attention during the first weeks to stop treatment if need.

5. Conclusion

The ETILANCE study showed, through standardized cognitive tests, that a single administration of the usual 100 mg dose of etifoxine has no effect on alertness and did not impair cognitive functions in a population of healthy elderly participants. The absence of evidence about long-term cognitive disorders with the use of etifoxine suggests this drug may be an alternative to classic BZDs, especially in elderly subjects when an anxiolytic treatment is necessary.

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The study sponsor, BIOCODEX, fully granted this study and also participated in the study design.

Conflict of interest

All authors declare that they have no conflicts of interest.

Authors contributions

D. Deplanque (DD), F. Machuron (FM), N. Waucquier (NW), E. Jozefowicz (EJ), S. Duhem (SD), S. Somers (SS), O. Colin (OC), A. Duhame (AD), R. Bordet (RB)
DD, AD and RB designed the study and wrote the protocol.
DD, SD, OC, RB managed the literature searches and analyses.
DD, NW, EJ, SD, SS and OC participated to the realization of the study including subjects' inclusion and follow-up.
DD, FM, AD undertook the statistical analysis.
DD, FM, AD and RB wrote the first draft of the manuscript.
All authors contributed to and have approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2018.05.011.

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