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An update on the anxiolytic and neuroprotective properties of etifoxine: from brain GABA modulation to a whole-body mode of action

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Abstract: Treating the signs and symptoms of anxiety is an everyday challenge in clinical practice. When choosing between treatment options, anxiety needs to be understood in the situational, psychiatric, and biological context in which it arises. Etifoxine, a non-benzodiazepine anxiolytic drug belonging to the benzoxazine class, is an effective treatment for anxiety in response to a stressful situation. In the present review, we focused on several aspects of the cerebral and somatic biological mechanisms involved in anxiety and investigated the extent to which etifoxine's mode of action can explain its anxiolytic activity. Its two mechanisms of action are the modulation of GABAergic neurotransmission and neurosteroid synthesis. Recent data suggest that the molecule possesses neuroprotective, neuroplastic, and anti-inflammatory properties. Etifoxine was first shown to be an effective anxiolytic in patients in clinical studies comparing it with clobazam, sulpiride, and placebo. Randomized controlled studies have demonstrated its anxiolytic efficacy in patients with adjustment disorders (ADs) with anxiety, showing it to be superior to buspirone and comparable to lorazepam and phenazepam, with a greater number of markedly improved responders and a better therapeutic index. Etifoxine's noninferiority to alprazolam has also been demonstrated in a comparative trial. Significantly less rebound anxiety was observed after abrupt cessation of etifoxine compared with lorazepam or alprazolam. Consistent with this finding, etifoxine appears to have a very low dependence potential. Unlike lorazepam, it has no effect on psychomotor performance, vigilance, or free recall. Severe adverse events are in general rare. Skin and subcutaneous disorders are the most frequently reported, but these generally resolve after drug cessation. Taken together, its dual mechanisms of action in anxiety and the positive data yielded by clinical trials support the use of etifoxine for treating the anxiety signs and symptoms of individuals with ADs.

Keywords: etifoxine, adjustment disorders, TSPO, translocator protein 18 kDa, 3 α , allopregnanolone, 5 α -THP, GABA, benzodiazepines, anxiety, neuroprotection

Introduction

Anxiety, an emotional experience characterized by a state of arousal and the expectation of danger, has been part of human experience throughout the ages. Over time, numerous conceptions of anxiety and classifications have been proposed, particularly in the medical field. Classifications of anxiety regularly redraw the boundaries between its different clinical manifestations, and new research continues to reveal further layers of complexity in its pathophysiological mechanisms. In the present review, we focused on the treatment of anxiety with etifoxine, a non-benzodiazepine (BZD) anxiolytic. Our aim was to provide an overall picture

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of the anxiolytic properties of etifoxine, both within the traditional conceptual framework of anxiety disorders and with respect to the new perspectives opened up by recent research.

We focused on the treatment of adjustment disorders (ADs), a category that was recently redefined in the DSM-5 and ICD-11. Previously, the emphasis was on subjective distress and emotional disturbances in ADs, principally in terms of anxious or depressive symptomatology, leading to the identification of ADs with anxiety (ADWA) and ADs with depression. ADWA were described as being more frequent than their depressive counterpart, mainly affecting young and professionally active individuals.¹ The manifestations of anxiety in ADWA were considered to be just as severe as those of generalized anxiety disorders.² Nonetheless, criticisms were voiced regarding the validity of the DSM-IV and ICD-10 diagnostic criteria for ADs. Some of these have been addressed in the newly published classifications, where there has been a shift toward conceptualizing ADs as trauma- and stressor-related disorders. DSM-5 diagnostic criteria for ADs include transient maladaptive or pathological reactions to identifiable stressors or changes in life circumstances, with symptoms emerging within 3 months of stress or onset. Anxiety, depression, and behavioral disturbances are now seen as potentially associated qualifiers, rather than as specifiers. Clinical manifestations are described as being out of all proportion with the event. In addition to its intrinsic nature, the stressor must be seen within the personal and interpersonal context in which it has occurred, and cultural norms. The ICD-11 classification goes one step further, by identifying core clinical manifestations, namely 1) “preoccupation with the stressor or its consequences, including excessive worry, recurrent and distressing thoughts about the stressor, or constant rumination about its implications”, and 2) “failure to adapt to the stressor that causes significant impairment in personal, family, social, educational, occupational, or other important areas of functioning”. If functioning is maintained, it is done so only through significant additional effort, and if impairment takes place, it must be far greater than it would be expected, given the individual’s prior functioning.

A better definition of ADs might make it possible to identify associated CNS and whole-body biomarkers, based on the psychobiology of trauma and stressor, and ultimately improve their treatment. In particular, it is important to study the role of GABA in AD³ along with neuroendocrine and whole-body processes such as inflammation, immunity, and oxidative stress.⁴

The traditional concept of the pathophysiology of anxiety has focused on structural and functional brain dysfunction.⁵ It regards anxiety as the result of an alteration of the coordinated activity of brain pathways, modulated by local and distant synaptic relays via neurotransmitters. Structurally, a set of limbic structures have been implicated in anxiety. These include the amygdala, which is tightly connected to the prefrontal cortex and appears to be critical for the regulation of negative emotion. Various neurotransmitters and modulators play an important functional role in modulating anxiety-related behaviors. These include mediators associated with the hypothalamic-pituitary-adrenal (HPA) axis,⁶ monoaminergic and GABAergic neurotransmission systems,^{7,8} neuropeptides such as cholecystokinin, and lipid neuromodulators.⁹

In addition to this brain-centered approach to the pathophysiology of anxiety, there is increasing evidence to suggest that anxiety states can also be modulated by the effect on the brain of somatic physiological processes such as inflammation, immunity, and oxidative stress, as well as gut microbiota.¹⁰ For instance, dysfunctional interactions involving the HPA axis and gut microbiota¹¹ have been described as contributing to the pathophysiology of anxiety. In humans, stress, a common feature of all anxiety disorders has been shown to be associated with several pro-inflammatory response phenotypes that may be unresponsive to the anti-inflammatory actions of glucocorticoids.¹² Moreover, several drugs known to reduce the clinical manifestations of anxiety (antidepressants, certain BZD, and non-BZD anxiolytics) have been shown to attenuate the above-mentioned abnormal physiological processes, pointing to a possible – and previously underestimated – aspect of the mechanism of action of anxiolytic drugs.¹³

Current understanding and treatment of anxiety disorders may thus need to be broadened in order to adopt a whole-body perspective. In particular, we need to reappraise our understanding of the mechanisms of action of anxiolytic drugs to include newly identified mechanisms within or without the CNS. Etifoxine, a non-BZD anxiolytic molecule that acts as a positive allosteric modulator of GABAergic transmission, is no exception to this rule. Recent studies have shown that etifoxine can exhibit considerable anti-inflammatory activity in the CNS.¹⁴ Effects on the immune system¹⁵ and neuroendocrine system, notably through binding to the mitochondrial outer membrane translocator protein (TSPO)¹⁶ and neurotrophic factor synthesis,¹⁷ may also contribute to etifoxine’s anxiolytic activity. This approach is opening up novel and exciting

avenues for exploring the mechanisms of action of this anxiolytic agent.

Strategies for treating anxiety disorders are inspired by evidenced-based studies, along with empirical experimentation with drugs. Given the wide variety of clinical settings in which the manifestations of anxiety can arise and the chronicity of these manifestations, it is unrealistic to expect to find a single, optimum evidence-based treatment for all clinical situations. Clinicians, therefore, need to gain a deeper understanding of the diverse mechanisms of action of anxiolytic agents, in order to select the most promising anxiolytic medication for their patients.

In this context, we conducted a detailed review of the mechanisms through which etifoxine exerts its anxiolytic activity. Looking beyond the classical GABA_A receptor interactions we present new research data about etifoxine's other putative anxiolytic mechanisms.

Interactions of etifoxine with the GABA_A receptor

Role of GABA_A neurotransmission in the pathophysiology of anxiety

Both animal research and brain imaging studies have demonstrated that prolonged dysregulation of brain networks involving cortical and specific subcortical areas (amygdala, hippocampus, thalamus, prefrontal, and cingulate cortex) contributes to the expression of anxiety symptoms.⁵ In particular, reduced inhibitory GABAergic transmission in the CNS has been shown to be critical for the manifestation of anxiety.¹⁸ In this respect, the structure and function of the GABA_A receptor have been under intense scrutiny.

The GABA_A receptor is a ligand-gated chloride-selective ion channel. It is a hetero-oligomeric protein made up of five subunits that cross the neuronal membrane. Most GABA_A receptors include two α subunits, two β subunits, and one γ subunit.¹⁹ The α and β subunits enable GABA binding, while the γ subunit confers BZD sensitivity, as these drugs bind within the interface between the α and γ subunits, enhancing the probability of a channel opening in response to GABA.²⁰ The opening of this chloride/bicarbonate-permeable channel²¹ by at least two GABA molecules induces an influx of negatively charged chloride ions, resulting in a transient reduction in the ability of the neuronal membrane to conduct action potentials, leading to phasic inhibition of the neuron. The anxiolytic effect of drugs binding to the GABA_A receptor is attributed to the

facilitation of chloride channel opening, thereby amplifying neuronal inhibition in response to GABA.

Over the last half-century, numerous GABA_A receptor ligands have been developed as therapeutic agents, including anxiolytics, hypnotics, muscle relaxants, and antiepileptics. One such anxiolytic drug is etifoxine (6-chloro-2-ethylamino-4-methyl-4-phenyl-4H-3,1-benzoxazine), a non-BZD anxiolytic drug belonging to the benzoxazine class.^{22–24} The affinity of etifoxine for the chloride channel coupled to the GABA_A receptor is in the micromolar range, whereas that of BZDs for this same channel are in the nanomolar range.²⁵ Etifoxine has a dual mechanism of action on GABAergic transmission, through both a direct effect on the GABA receptor and an indirect effect via neurosteroid synthesis allowing for allosteric modulation of the GABA_A receptor.^{26,27}

Direct action of etifoxine on the GABA_A receptor

In vitro studies have demonstrated that etifoxine can inhibit the binding of a specific GABA_A receptor ligand (t-butylbicyclophosphorothionate, TBPS) in the cerebral cortex of rodents, suggesting the presence of binding sites for etifoxine on the GABA_A receptor. In vivo evidence of a functional consequence of etifoxine binding to the GABA_A receptor has come from studies in mice, where etifoxine has been found to block the clonic seizures induced by TBPS, demonstrating an anticonvulsant effect mediated through the GABA_A receptor.²⁵

More detailed information on the nature of the interaction between etifoxine and the GABA_A receptor has been yielded by radioligand binding studies evaluating competition from etifoxine for the binding sites of the GABA agonist [³H]-muscimol and the BZD modulator [³H]-flunitrazepam on the GABA_A receptor. In vitro experiments on rat brain membrane preparations²⁸ have shown that the binding of these ligands is not hindered by etifoxine, indicating that its binding site is distinct from that of GABA and BZDs. Instead, the binding of these two radio-labeled ligands increases in the presence of etifoxine, demonstrating positive allosteric modulation. The in vivo observation that the anxiolytic action of etifoxine is not inhibited by flumazenil, a specific antagonist of the BZD binding site on the GABA_A receptor,²⁹ is also consistent with the notion that etifoxine and BZDs bind to different sites. This property may explain the lack of a detrimental effect of etifoxine on sedation and memory compared with BZDs (Figure 1).

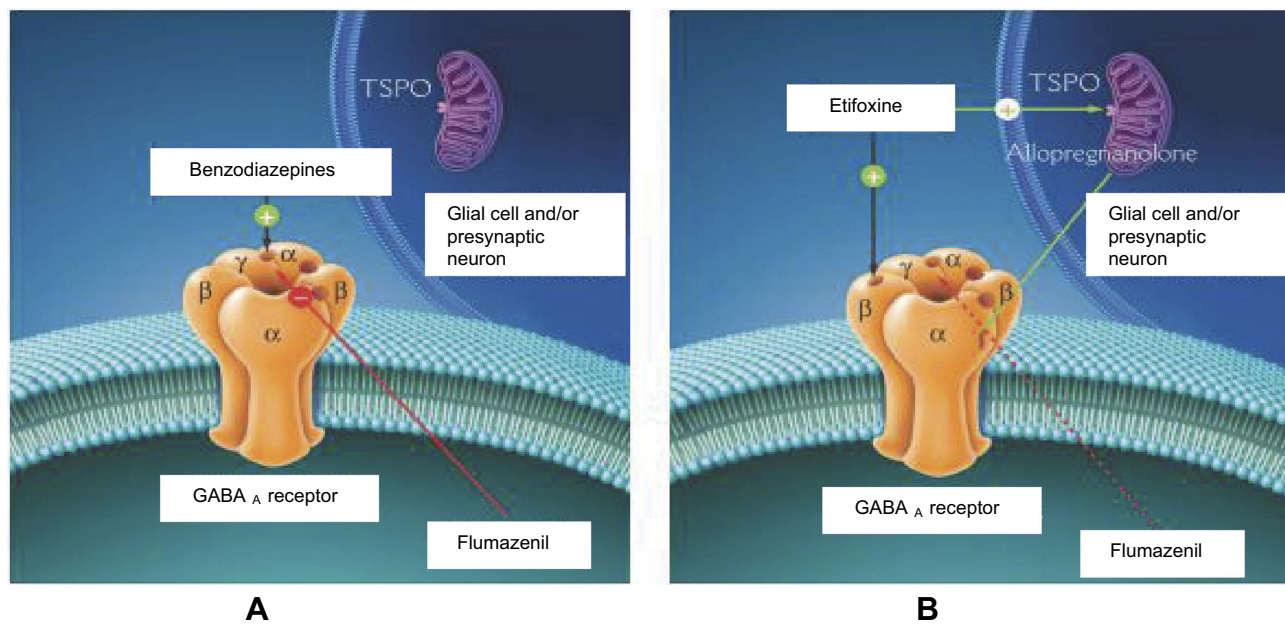


Figure 1 Comparison of the mechanism of action of etifoxine and benzodiazepines on the GABA_A receptor. **(A)** Benzodiazepines bind principally within the between the α and γ subunits of the GABA_A receptor. The nature of the α subunit influences the pharmacological properties of agents binding to it (sedation, myorelaxation, amnesia, etc). Flumazenil specifically inhibits binding of benzodiazepines to the GABA_A receptor. **(B)** Etifoxine acts on the GABA_A receptor, both by binding directly to the β_2/β_3 subunits and by indirectly stimulating neurosteroid production (allopregnanolone). Flumazenil does not affect the binding of etifoxine to the GABA_A receptor. Reproduced with kind permission from Biocodex.

Abbreviation: TSPO, translocator protein of 18 kDa.

Studies of recombinant GABA_A receptors have shown that etifoxine-stimulated GABAergic transmission persists in the absence of α or γ subunits, suggesting that it is the β subunit of the GABA_A receptor that is critical for etifoxine binding. The different subunits of the GABA_A receptor hetero-oligomer vary from one another in the composition of a limited set of amino acid sequences, each family is made up of a restricted number of variants. Several subtypes of the GABA_A receptor are present within the CNS, and these subtypes show specific anatomical and subcellular expression patterns, as well as functionally different properties. The apparent affinity of GABA_A receptors for GABA and etifoxine depends on the subunit composition and, more specifically, on α - β subunit dimers forming the agonist binding sites for GABA. In this context, etifoxine has a higher affinity for receptors containing β_2 or β_3 subunits than for ones containing β_1 subunits.³⁰ The effects of etifoxine are thus mainly determined by the presence of β subunits, which clearly distinguishes this anxiolytic drug from other positive allosteric modulators of the GABA_A receptor, such as BZDs whose activity depends primarily on the nature of the α and γ subunits.³¹ The binding of etifoxine to β subunits leads to a positive allosteric modulation of the chloride currents resulting from the opening of GABA_A receptors, associated with an increase in the current duration

and amplitude in the case of non-saturating GABA concentrations. Etifoxine has also been shown to increase the frequency of spontaneous miniature GABAergic inhibitory post-synaptic currents, without changing their amplitude or kinetic characteristics.³

The behavioral consequences of this subunit specificity were elegantly demonstrated by Verleye et al. Two different inbred mouse strains (BALB/cByJ and C57BL/6J) were compared on emotional and anxious behavior. An overexpression of the β_2 subunit in the CNS was found in the BALB/cByJ mice, compared with the C57BL/6J mice, and the former were more reactive to stressful stimuli than the latter.³² No differences in β_3 subunits were found between the two strains. The BALB/cByJ strain was also more responsive to the anxiolytic and antiepileptic effects of etifoxine, indicating a positive correlation between the proportion of β_2 -containing GABA_A receptor subunits and etifoxine efficacy.³³

Indirect action of etifoxine on the GABA_A receptor

In addition to its direct action on the GABA_A receptor through binding to the β -subunit, etifoxine can displace [³H]-PK11195, a highly specific TSPO ligand, in a concentration-dependent manner.^{16,34} The exact role of

TSPO in neurosteroid synthesis within the neurons and glial cells of the CNS – particularly that induced by etifoxine – is not as clear today as it used to be.³⁵ TSPO was initially thought to be located at the contact zone between the outer and inner mitochondrial membranes, and to be key in orchestrating mitochondrial cholesterol translocation, playing the role of the rate-limiting step of neurosteroidogenesis. However, a recent experiment showing that TSPO-/- mouse line is not modified in steroidogenesis^{36,37} and that PK11195 can stimulate steroidogenesis even in the absence of TSPO, points to the existence of another target molecule.³⁸ A study in frog hypothalamus explant published the same year demonstrated that etifoxine may act through a mechanism that is independent of TSPO, leading to an increase in neurosteroidogenesis.¹⁶

Certain neurosteroids produced in the mitochondria interact with the GABA_A receptor. Pregnenolone, which is synthesized from cholesterol in the mitochondria, is converted to progesterone by 3 α -hydroxysteroid dehydrogenase. In turn, progesterone is converted in the cytoplasm to its 3 α ,5 α -derivatives (3 α ,5 α -tetrahydroprogesterone or allopregnanolone, and allotetrahydrodeoxy corticosterone or alloTHDOC) by successive actions of 5 α -reductase and 3 α -hydroxysteroid dehydrogenase. Of interest, progesterone, deoxycorticosterone, and testosterone metabolites, particularly allopregnanolone, are the most potent known positive allosteric modulators of GABA_A receptors.³⁹ They increase the opening burst duration of the GABA_A receptor channel, as well as the mean open time.²¹

The increase in brain allopregnanolone levels after etifoxine administration observed in animal models is assumed to have a synergistic and facilitatory effect on GABAergic neurotransmission,²⁷ complementing the direct action of etifoxine on the β subunit of the GABA_A receptor. Etifoxine's molecular mechanism of action (Figure 2) is thus ascribed both to its direct effect on the GABA_A receptor and to an indirect effect on the receptor via increased synthesis of certain neurosteroids as a consequence of binding to and activating TSPO.^{40,41}

This dual mechanism of action has been correlated with the anxiolytic effect of etifoxine observed in animal models of anxiety.^{42,43} For instance, this effect was confirmed in a study of anxious BALB/cByJ mice subjected to acute immobilization stress. The effects of different substances blocking central GABAergic function or neuroactive steroid synthesis were also evaluated.⁴⁴ The authors concluded that by binding to distinct recognition sites on the GABA_A receptor, etifoxine, and allopregnanolone exert additive

effects in potentiating inhibitory GABAergic transmission, reflected in an increased anticonvulsive effect.⁴⁵

Etifoxine and the serotonergic system

Other neurotransmitter systems besides the GABAergic system, such as the serotonergic system, are also involved in anxious behavior. Given the numerous interactions between these two neurotransmission systems, it is relevant to investigate possible interactions between etifoxine and serotonergic receptor ligands. Bourin et al, demonstrated in a mouse model of anxiety that the anxiolytic effect of etifoxine is modulated by the co-administration of 5-HT_{2A} ligands.⁴⁶ A serotonergic mechanism is thus involved in the anxiolytic effect of etifoxine. As etifoxine has no direct interaction with the serotonergic system, these results suggest that the anxiolytic activity of etifoxine is subtended by a relationship between the serotonergic and GABAergic systems.

Behavioral pharmacology of etifoxine: manifestations of anxiety

Several studies have evaluated the direct or indirect GABAergic mechanisms through which etifoxine regulates autonomic responses associated with anxiety.

Etifoxine's effects on autonomic responses to stress have been investigated in rat models of anxiety (stress-induced hyperthermia, conditioned fear stress-induced freezing behavior, and activation of colon motility). Etifoxine treatment attenuated hyperthermia, and reduced freezing behavior and the frequency of caeco-colonic contractions in rats subjected to stressful events. The anxiolytic effects of etifoxine thus involve attenuation of both behavioral and autonomic manifestations of anxiety.⁴⁷

Another animal model, which used the cerebral injection of corticotrophin-releasing factor (CRF) to reproduce autonomic and behavioral responses to stress, showed that the anxiolytic properties of etifoxine are related to its effect on GABAergic neurotransmission, rather than to an interaction with CRF1 and CRF2 receptors.⁴⁸

GABAergic involvement in the anxiolytic and anticonvulsant properties of etifoxine has also been highlighted in a mouse alcohol withdrawal model, in which hyperexcitability and anxiety in mice with alcohol withdrawal symptoms were reduced by etifoxine.⁴⁹

In the four-plate test model of anxiety, the anxiolytic activity of both etifoxine and gabapentin was found to be comparable to that of a BZD (diazepam) or a serotonergic

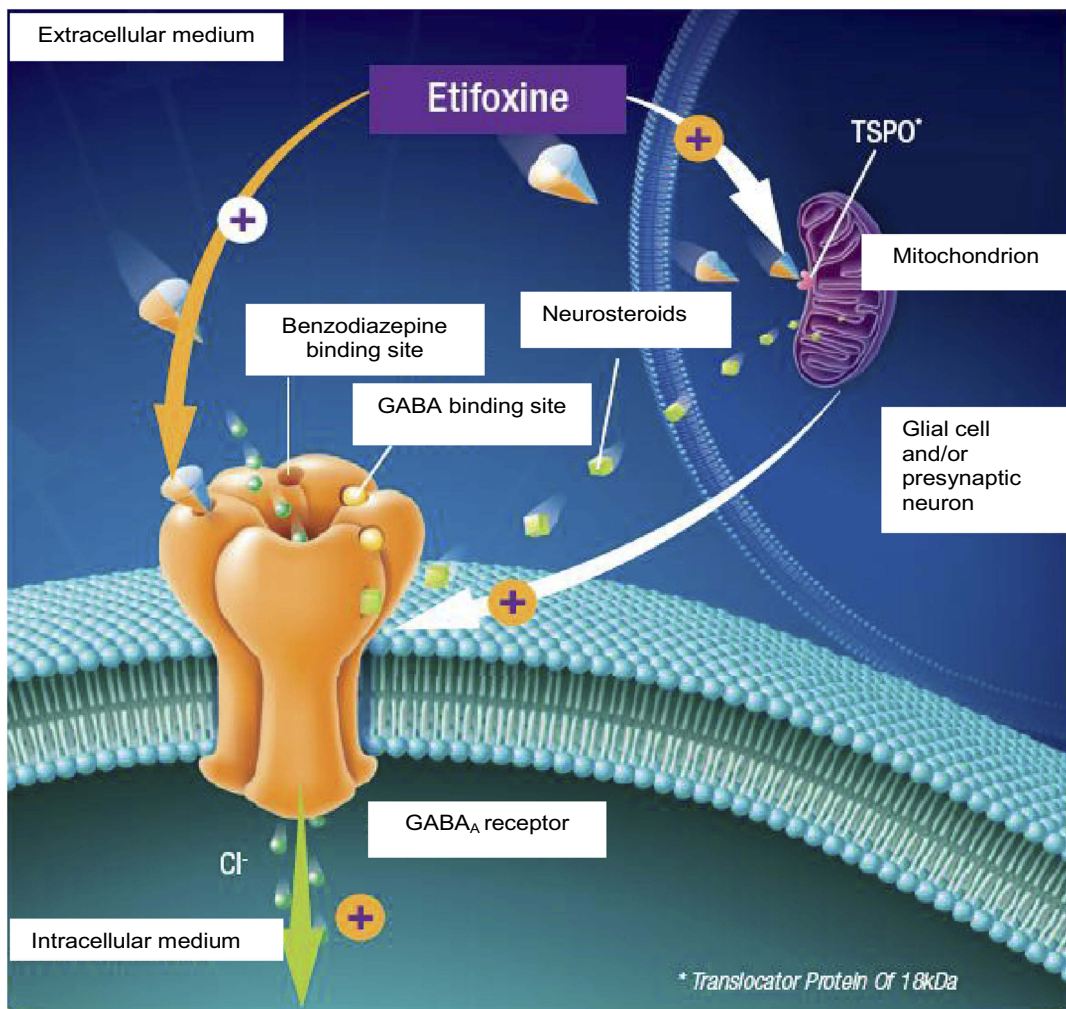


Figure 2 Mechanism of action of etifoxine. Etifoxine stimulates GABAergic transmission through two complementary mechanisms. Firstly, etifoxine binds directly to the β_2/β_3 subunits of the GABA_A receptor. Secondly, etifoxine reinforces GABAergic transmission via an indirect mechanism by binding to the TSPO receptor on mitochondria, thus facilitating the synthesis of neurosteroids, which are powerful positive allosteric modulators of the GABA_A receptor. Reproduced with kind permission from Biocodex.

agonist (DOI hydrochloride). The anxiolytic activity of etifoxine and gabapentin in this model, unlike that of diazepam, tended to persist during the test–retest procedure, albeit to a lesser extent than that of DOI hydrochloride.⁵⁰ These data suggest that etifoxine and gabapentin may be more effective in treating anxiety manifestations of stress and fear than BZD.

Anxiolytic activity of etifoxine: clinical trials and practice

Anxiolytic activity of etifoxine: studies in patients

Clinical pharmacology

Studies have been conducted in healthy volunteers to characterize the pharmacokinetic profile of etifoxine. Following administration of a single dose of etifoxine

(150 mg), the molecule 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. Time to maximum blood concentration is 2–3 hrs. It is rapidly metabolized in the liver to form several metabolites. One of these metabolites, diethyl-etifoxine, is active. It can also cross the placental barrier. Etifoxine's half-life is about 6 hrs, and that of its active metabolite is almost 20 hrs. It is mainly excreted in urine as metabolites, but is also excreted in bile. Small amounts are excreted in an unchanged form.⁵¹

Clinical efficacy

The first studies of etifoxine in the clinical development program to obtain marketing authorization were conducted

in patients presenting with anxiety and mood disorders. Compared with sulpiride and placebo, etifoxine demonstrated efficacy in reducing anxiety symptoms and cardiovascular signs such as dyspnea and tachycardia.

As the anxiolytic effects of etifoxine in animal models have been most robustly demonstrated in stress models, clinical development in recent years has focused on patients with ADs, and chiefly ADWA, as per DSM-III and DSM-IV classifications. The recent changes in AD categorization in both the DSM and ICD systems need to be taken into consideration when interpreting studies of etifoxine conducted using the previous DSM classification of ADWA.

Clinical studies in patients who have ADWA

The first multicenter, randomized, controlled, double-blind study evaluating the efficacy of etifoxine vs buspirone in 170 patients with a primary diagnosis of ADWA was carried out in France in 1998 (Table 1).⁵² Patients were treated for 4 weeks with either etifoxine (150–200 mg/day; n=83), or buspirone (15–20 mg/day; n=87). All patients presented with clinical anxiety at inclusion, according to their Hamilton Anxiety Rating Scale (HAM-A) score (≥ 18). The primary endpoint was the HAM-A score at 4 weeks, adjusted to the baseline value. Secondary endpoints were the Clinical Global Impression (CGI) Scale-Global Improvement score and the CGI-Efficacy Index (relationship between anxiolytic efficacy and undesirable effects).⁵³

Results showed the superiority of etifoxine over buspirone for the mean HAM-A score at 4 weeks ($p=0.05$). Moreover, the etifoxine group had a significantly better CGI-Global Improvement score than the buspirone group from Day 7 of treatment onwards ($p<0.001$ on Day 7, and $p=0.02$ on Days 14 and 28). Finally, the CGI-Efficacy Index on Days 14 and 28 was also better for etifoxine ($p=0.01$ and $p=0.05$). The treatment arms did not differ in the number of adverse events.⁵² CNS-related adverse events (somnolence, vertigo, and headache) were reported in 40.7% of the etifoxine-treated patients and 58.6% of the patients in the buspirone group.

In a second multicenter, controlled, randomized double-blind study, etifoxine was compared with lorazepam in outpatients with ADWA followed by general practitioners (Table 1).⁵⁴ Patients received either etifoxine (50 mg 3 times per day; n=93) or lorazepam (2 mg/day divided into three administrations: 0.5 mg morning and noon, and 1.0 mg in the evenings; n=96) for 28 days. All patients

presented with clinical anxiety at inclusion, according to their HAM-A score (≥ 20). The main efficacy assessment criterion was the HAM-A score on Day 28, adjusted to Day 0. Secondary endpoints included CGI, Sheehan Disability Scale⁵⁶ and Social Adjustment Scale Self-Report⁵⁷ scores. Both treatments were effective in reducing the HAM-A score from Day 7 onwards. The anxiolytic effect of etifoxine was noninferior to that of lorazepam (Schuirmann non-inferiority test: $p=0.0002$ for HAM-A score on Day 28, and $p=0.0001$ on Day 7). However, a higher number of patients responded to treatment, as expressed by a total decrease in the HAM-A score from baseline to Day 28 of $\geq 50\%$, in the etifoxine group (72% vs 56%; $p=0.0288$). The CGI score had improved in both treatment arms by Day 28, but more patients showed a marked improvement (CGI score < 3) in the etifoxine group than in the lorazepam group ($p=0.022$). The CGI-Efficacy Index on Day 28 was better for etifoxine ($p=0.038$). The agents displayed comparable efficacy in reducing disability and improving social adjustment.

There was no significant difference in the number of adverse events between the groups receiving etifoxine or lorazepam.⁵⁴ Somnolence was reported in 10.7% of the etifoxine-treated patients and in 18.7% of the lorazepam-treated patients. Performances on immediate and delayed free recall memory tests at 28 days were comparable in both treatment arms. Withdrawal symptoms were evaluated 1 week following treatment cessation. The number of patients who experienced rebound anxiety after treatment cessation was significantly greater ($p=0.034$) in the lorazepam group (eight patients) than in the etifoxine group (one patient).⁵⁴

In a study among patients with ADWA conducted in Russia,⁵⁸ the efficacy of etifoxine was compared with that of phenazepam, an anxiolytic BZD commonly used in Russia for the treatment of ADs (Table 1). This multicenter, open-label, randomized study recruited 90 patients, who received either etifoxine (150 mg/day) or phenazepam (1 mg/day) for 6 weeks. The primary endpoint was HAM-A on Day 42, adjusted to Day 0. Secondary evaluation criteria were CGI-Severity, CGI-Global Improvement, and CGI-Efficacy Index. Both treatments resulted in equivalent reductions in anxiety scores, according to the least-square mean estimate for noninferiority (95% etifoxine-phenazepam: -3.2 [-5.3 ; -1.1]). A second approach, however, indicated that etifoxine was superior to phenazepam ($p=0.003$ for HAM-A score on Day 42). More etifoxine recipients than phenazepam recipients showed a tendency to marked improvement (CGI score < 3)

Table 1 Ertifoxine efficacy and tolerability in patients

Study (year)	Design and sample size	Scale used	Sample	Results	Notes
Servant et al, (1998) ⁵²	DSM-IV criteria for adjustment disorders with anxiety 4-week double-blind RCT Multicenter Outpatients (GPs) N=170 ETX vs BUS Superiority test	Primary endpoint: improvement in HAM-A mean score at Week 4 Secondary endpoints: improvement in CGI mean score at Week 4 Efficacy/tolerability index: TI	Inclusion HAM-A score ≥18 Mean age: 44 yrs, female: 73% ETX (flexible) 150–200 mg/day) n=83. Mean (± SD) HAM-A inclusion score: 25.27 ±4.73 BUS (flexible 15–20 mg/day) n=87. Mean (± SD) HAM-A inclusion score: 27.17±5.29	HAM-A mean (± SD) total score at D28: ETX: 9.48±0.61 and BUS: 11.18±0.60 Greater improvement in HAM-A with ETX vs BUS at W4 (p<0.05) Greater improvement in CGI with ETX at D7 (p<0.001), D14 and D28 (p=0.002)	Greater and faster efficacy of ETX vs BUS with better tolerability TI improvement better with ETX at D14 (p=0.01) and D28 (p=0.05)
Nguyen et al, (2006) ⁵⁴	DSM-IV criteria for adjustment disorders with anxiety 4-week double-blind RCT Multicenter Outpatients (GPs) N=191 ETX vs LOR Noninferiority test	Primary endpoint: improvement in HAM-A mean score at Week 4 SAS-SR Secondary endpoints: improvement in CGI-Improvement, SDS, and SAS-SR mean scores at Week 4 Efficacy/tolerability index: TI	Inclusion HAM-A score ≥20 Mean age: 43 yrs, female: 66% ETX: 50 mg t.i.d (n=91) LOR: 2 mg/day (t.i.d) (n=96)	Baseline HAM-A (mean ± SD): 25.3±3.5 in ETX group vs 25.7±4.4 in LOR group At W4, decrease in HAM-A score: 54.6% for ETX vs 52.3% for LOR, noninferiority (p=0.0002)	Percentage of responders at W4 (≥50% decrease in HAM-A score) higher with ETX than with LOR (72% vs 56%, p=0.03) More ETX patients with marked improvement (CGI score <3) than LOR patients (p=0.022) TI higher in ETX group (78.9% vs 62.6%) than in LOR group (p=0.0383) At W1 after stopping treatment, rebound anxiety greater with LOR (p=0.034) 56.44% vs 45.35% decrease in HAM-A score for ETX vs PHE at Week 6 (p=0.003) Fewer adverse events leading to discontinuation for ETX group (p=0.002) at Week 6 Fewer withdrawal symptoms after treatment cessation for ETX (p<0.001) at Week 6
Aleksandrovsky et al, (2010) ⁵⁸	ICD-10 criteria for adjustment disorders 6-week open-label RCT Multicenter Outpatients (GPs) N=90 ETX or PHE Noninferiority test	HAM-A Primary endpoint: improvement in HAM-A mean score at Week 6 Secondary endpoint: improvement in CGI-Severity mean score at Week 6 Efficacy/tolerability index: TI	Mean age: 45 yrs, female: 66.6% two groups ETX (150 mg/day) PHE (1 mg/day) Baseline HAM-A: 29.73 ±7.62 for ETX group and 27.83±5.95 for PHE group	HAM-A mean score at Week 6 was 12.98 ±4.16 for ETX group and 15.21±6.02 for PHE group Noninferiority of ETX was proven with first least-square mean (95% CI ETX vs –3.2 PHE [–5.3; –1.1]) Greater decrease in CGI-Severity score at W6 for ETX than for PHE (p=0.004)	

(Continued)

Table 1 (Continued).

Study (year)	Design and sample size	Scale used	Sample	Results	Notes
Stein et al, ⁵⁵ (2015)	DSM-IV criteria for adjustment disorders with anxiety 4-week double-blind RCT Multicenter Outpatients (GPs) N=201 ETX vs ALP Noninferiority test	HAM-A Primary endpoint: improvement in HAM-A mean score at Week 4 Secondary endpoint: improvement in CGI-Improvement, SDS and SAS-SR mean scores at Week 4	Inclusion criteria: - HAM-A score ≥ 20 - Score ≥ 5 on at least one SDS subscale - MADRS score < 20 Mean age: 39.4 yrs, female: 73.1% ETX (150 mg/day) ALP (1.5 mg/day)	Decrease in mean HAM-A total score: 72.5% for ETX vs 79.7% for ALP. Noninferiority of ETX was not demonstrated At W5 (ie, 1 week after medication discontinuation), HAM-A continued to decrease for ETX (-0.6 ± 4.5), but increased ($+2.2 \pm 7.0$) for ALP ($p=0.019$)	All other outcome measures underwent similar improvements in the two treatment groups Faster improvement in somatic symptoms with ALP Adverse effects more often deemed to be treatment-related by investigators in the ALP group

on Day 42. The CGI-Severity score fell in both groups, with a significant difference favoring etifoxine on Day 42 ($p=0.004$). The CGI-Efficacy Index on Day 42 was also better for etifoxine ($p=0.004$).

In this study, 23 of the 24 patients in the phenazepam group reported adverse events. The most frequently reported one was somnolence (observed in 32.6% of the phenazepam recipients). A significant difference was observed between the two treatment arms with respect to the number of adverse effects leading to discontinuation (8 in the phenazepam group vs 0 in the etifoxine group; $p=0.002$).⁵⁸ Concerning withdrawal symptoms after treatment cessation, three patients in the etifoxine group vs 26 in the phenazepam group experienced rebound anxiety between Days 42 and 49, according to the irHAM-A scores ($p<0.001$).⁵⁹

A multicenter, double-blind, randomized clinical trial evaluating the efficacy of etifoxine vs alprazolam in 201 outpatients with ADWA was recently conducted in South Africa (Table 1).⁵⁵ Patients received either etifoxine (150 mg/day; $n=100$) or alprazolam (1.5 mg/day; $n=101$) for 4 weeks. All patients presented with clinical anxiety at inclusion, according to their HAM-A scores (≥ 20). The primary endpoint was the total HAM-A score at Day 28, adjusted for its value at Day 1. Secondary endpoints included CGI-Global Improvement and the percentage of responders (defined by $\geq 50\%$ decrease in HAM-A score between Days 1 and 28). Anxiety symptoms started to improve from the first week in both groups. By Day 28, the mean HAM-A total score had decreased by 72.5% in the etifoxine group and by 79.7% in the alprazolam group, while the adjusted mean difference in the HAM-A score was 1.78 (90% CI[0.23; 3.33]) in favor of alprazolam. As the upper limit of the 90%CI was greater than the 2.5 reference value, noninferiority of etifoxine to alprazolam was not demonstrated. One week after treatment discontinuation (Day 35), the HAM-A score in the etifoxine group was still decreasing, whereas it had started to climb in the alprazolam group, and the difference between the groups on the mean change between Days 28 and 35 was significant ($p=0.019$). Similarly, the CGI-Severity score decreased between Days 28 and 35 in the etifoxine group, whereas it increased in the alprazolam group ($p=0.004$). Regarding the secondary outcome measures, there were no significant differences between the two groups, neither CGI scores nor responder status at Day 28.

During this study, 35 patients (35%) in the etifoxine group experienced at least one adverse event, compared

with 48 (47.5%) in the alprazolam group. Adverse events were rated far more often as treatment-related by the investigators for the alprazolam group (62.3%; 13 possibly and 25 probably related) than for the etifoxine group (34.3%; 13 possibly and 11 probably related). Adverse events resulted in the withdrawal of seven patients from the etifoxine group and six patients from the alprazolam group, mainly owing to CNS or gastrointestinal symptoms. CNS symptoms (principally somnolence, sedation or fatigue) were reported by 16% of the etifoxine recipients and by 24.8% of the alprazolam recipients. Gastrointestinal symptoms were reported by 12 patients in the etifoxine group and eight in the alprazolam group. After treatment discontinuation, more patients (11%) experienced adverse events in the alprazolam group (16 events) than in the etifoxine group (4% of the patients and 4 events) ($p=0.063$). In the alprazolam group, 50% of these adverse events were treatment-related (five possible and three probable), compared with none in the etifoxine group.

These clinical studies clearly demonstrate the efficacy of etifoxine as an anxiolytic in patients with ADWA. They also highlight the good tolerability profile of etifoxine, particularly its preservation of cognitive function and vigilance. Moreover, etifoxine is not associated with either rebound anxiety or withdrawal symptoms following treatment cessation.⁶⁰

Pharmacovigilance

Over the 30 years since etifoxine was first licensed, drug safety monitoring has confirmed the low risk of drug dependence or withdrawal symptoms following treatment cessation.⁶¹ The few reported adverse events mostly concern skin and subcutaneous tissue disorders (eg, toxidermia), which generally resolve with treatment discontinuation. Hepatobiliary disorders such as elevated liver enzymes have been described, but their incidence is unknown. Elevated transaminase is generally reversible upon treatment discontinuation. As with any psychotropic drug, episodic liver function monitoring is recommended. Recent pharmacovigilance data are summarized in <https://www.has-sante.fr>.

Cognitive effects of etifoxine in healthy individuals

The psychomotor and memory effects of oral doses of etifoxine and lorazepam were compared in healthy participants in a randomized, double-blind, parallel-group placebo-controlled study⁶² (Table 2). A total of 48 healthy participants were assigned to one of four groups, to receive

either a single dose of etifoxine (50 mg or 100 mg), a single dose of lorazepam (2 mg), or placebo. Neuropsychological testing evaluated psychomotor performance (choice reaction time), attention (Barrage test), and memory (Digit Span, immediate and delayed free recall of a word list). A visual analog scale (VAS) was used to measure sedation and mood. Seven adverse events were reported by participants: five in the lorazepam group (sweating, intoxicated feeling, and three cases of somnolence), and one (somnolence) in the etifoxine group. Psychomotor performance at 2 hrs differed between the four groups. Reaction times in the lorazepam group were significantly longer than in the other three groups ($p<0.001$). In addition, lorazepam recipients gave fewer correct Barrage test answers than participants who had received 50 mg etifoxine or placebo ($p<0.002$). Both immediate and delayed free recall were significantly impaired by lorazepam ($p<0.001$). The VAS results showed that at 2 and 4 hrs, lorazepam-treated participants experienced significantly more fatigue, drowsiness, somnolence, and clumsiness and felt less energetic than those in the other groups.

This study provided no evidence that the single oral doses of etifoxine (50 and 100 mg) had a deleterious effect on psychomotor performance, attention or memory, in comparison with the lorazepam 2 mg used as a positive control.

In a recent publication,⁶³ 30 healthy older (65–75 years) volunteers were tested for alertness and cognitive functions in a study comparing etifoxine (2×50 mg), lorazepam (2×1 mg), and placebo (Table 2). The randomized placebo-controlled, double-blind, crossover design included three 1-day sessions separated by a washout period of 14–30 days. Testing occurred 2 hrs after treatment administration. Participants underwent cognitive tests comprising the Cambridge Neuropsychological Test Automated Batteries and other psychological tests (Stroop, Rey, Auditory Verbal Learning Test, Digit Span). Reaction time was the primary efficacy criterion. Compared with placebo, etifoxine has no deleterious effect on alertness whereas, as expected, lorazepam significantly reduced it. In addition, etifoxine administration had no deleterious effects on attention, rapid visual information processing, Stroop test, or visuospatial, verbal, or working memory measures. Similar percentages of adverse events were observed with etifoxine and with placebo. Most were found after lorazepam administration. The most frequent adverse event was drowsiness. Only one adverse event

Table 2 Etifoxine tolerability in healthy volunteers

Study (year)	Design and sample size	Scale used	Sample	Results	Notes
Micallef et al, ⁶² (2001)	Comparison of psychomotor and amnesic effects of single oral doses of ETX and LOR RCT N=48	VAS Barrage test CRT Digit span: immediate and delayed free recall of heard numbers Immediate and delayed free recall of pictures	Inclusion criteria: HAM-A < 2 with no history of substance abuse 24 women, 24 men Age: 18–35 years (M =24.9±3.5) 12 participants received a single dose of ETX (50 mg) 12 participants received a single dose of ETX (100 mg) 12 participants received a single dose of LOR (2 mg) 12 participants received a single dose of a placebo	LOR participants displayed longer mean CRTs ($p<0.001$) than the other groups At 2 hrs, LOR participants scored lower on the Barrage test ETX (50 mg) compared with placebo ($p=0.002$) The VAS showed a significant Group \times Time interaction, with LOR participants being more tired, clumsy, drowsy, and less energetic at 2 and 4 hrs LOR participants had significantly lower scores on immediate and delayed recall than the other groups	In contrast to LOR, ETX did not induce either psychomotor, attention, or memory effects Adverse events were more frequent (n=5) with LOR than with either ETX (n=1) or placebo (n=1)
Deplanque et al, ⁶³ (2018)	Comparison of alertness and cognitive effects of ETX (2 \times 50 mg), LOR (2 \times 1 mg), and placebo in older participants (65–75 years) Double-blind, crossover RCT N=30	Cambridge Neuropsychological Test Automated Battery Testing 2 hrs after treatment administration Primary endpoint: reaction time	N=30 (20 female) 3 testing days separated by a washout period of 14–30 days ETX (50 mg b.i.d.) LOR (1 mg b.i.d.) Placebo (b.i.d.)	ETX has no deleterious effects on alertness or cognition, compared with placebo (reaction time: 744 \pm 146 ms vs 770 \pm 153 ms; $p = 1.00$) LOR impaired alertness (reaction time: 957 \pm 251 ms) compared with placebo ($p < 0.0001$), and the most frequent adverse event involved cognitive functions LOR impaired alertness, attention, and both working and verbal memory	ETX and placebo had identical adverse events LOR adverse events were three times higher, with drowsiness being the most frequent one

was rated as severe in the etifoxine group, compared with four in the lorazepam group.

Neuroprotective activity of etifoxine in the central and peripheral nervous systems

Etifoxine has also been found to have protective effects in animal models of neuroinflammation, nociception, and neurodegeneration, which may partially account for its beneficial effects in neurological and psychiatric disorders.^{64,65} Of particular interest is its activity in increasing the synthesis of neurotrophic factors known to be involved in neuroplasticity, which occurs in response to the development and chronicity of neuropsychiatric disorders, especially at the synaptic level.^{66,67} These studies also provide further support for the favorable tolerability profile of etifoxine compared with BZD.⁶⁸

Etifoxine enhances the synthesis of neuroprotective factors

Several experimental procedures have been developed to examine the neuroprotective and neuroreparative properties of etifoxine. In a rat peripheral nerve lesion model (sciatic nerve cryolesion), Girard et al, demonstrated that etifoxine promotes peripheral nerve regeneration and axonal growth, leading to the accelerated and improved recovery of locomotion, motor coordination, and sensory functions.¹⁷ Etifoxine activity on neurite outgrowth has also been explored. Zhou et al, used a well-defined PC-12 cell model where etifoxine was found to promote the synthesis and release of glia-derived neurotrophic factor.⁶⁹ Dai et al, showed that etifoxine increases neuronal-like outgrowth in PC-12 cells in a concentration-dependent manner. They also demonstrated that etifoxine improves sciatic nerve regeneration, modulates immune responses, and boosts neurotrophin expression.⁷⁰ In a rat acellular nerve allograft model (for treating peripheral nerve injury), Zhou et al, reported that etifoxine increased the expression of neurofilaments in regenerated axons, improving sciatic nerve regeneration, increasing nerve conduction velocity, improving walking behaviors, and increasing neurotrophin expression.⁶⁹

Etifoxine has anti-inflammatory and immunomodulatory properties

Several brain injury models have been used to evaluate the anti-inflammatory, immunomodulatory and neuroprotective effects of etifoxine. A potential neuroprotective effect of etifoxine was evaluated by Li et al, using a mouse model of

middle cerebral artery occlusion (MCAO) and reperfusion. In this model, ischemia increased recruitment of certain microglial cell populations such as those expressing (ionized calcium-binding adaptor molecule 1 (Iba1+) and CD11b +CD45int. In these cells, TSPO activity was increased following ischemia. In this model, etifoxine significantly attenuated neurological deficits and infarct volume after MCAO and reperfusion. Etifoxine was shown to reduce the production of pro-inflammatory cytokines by microglia. In particular, decreases in interleukin-1 β , interleukin-6, tumor necrosis factor- α , and inducible nitric oxide synthase were observed in the etifoxine-treated animals.⁷¹ More recently, in two mouse models of intracerebral hemorrhage, etifoxine (50mg/kg/day, IP route) was shown to significantly reduce neurological deficits and perihematomal brain edema up to 3 days post hemorrhage. This protective effect of etifoxine was associated with reduced leucocyte infiltration into the brain and increased production of IL-6 and TNF α by microglial cells.⁷² Finally, in a model of traumatic brain injury, Simon-O'Brien et al, demonstrated that etifoxine (50 mg/kg/day/7 days, IP route) reduced the production of pro-inflammatory cytokines, macrophage infiltration, glial activation, and neuronal degeneration.¹⁴

In a mono-arthritic rat model of pain, 50 mg/kg of etifoxine efficiently reduced neuropathic pain symptoms, whether the etifoxine was administered before or after induction of arthritis. Etifoxine was found to strengthen overall inhibition in the dorsal horn of the spinal cord, reducing several spinal inflammatory processes and protecting against PGE2-induced glycinergic disinhibition.⁷³ Using an experimental model of multiple sclerosis (experimental autoimmune encephalomyelitis; EAE), Daugherty et al, showed that etifoxine can decrease the severity of inflammatory demyelination and reduce infiltration of peripheral immune cells into the spinal cord. Again, this anti-inflammatory effect could be seen whether etifoxine was administered before or after induction of EAE. Recovery was correlated with diminished inflammatory pathology in the lumbar spinal cord and increased oligodendroglial regeneration.⁷⁴ This effect of etifoxine may be mediated by modulation of TSPO activity, with etifoxine administration associated with an increase in 3 α -hydroxysteroid dehydrogenase (ark1c14) mRNA levels.

Protective effects of neurosteroidogenesis induced by etifoxine

Injections of 50 mg/kg of etifoxine in adult male rats were found increase concentrations of pregnenolone, progesterone

and its 5 α - and 3 α ,5 α -reduced metabolites in brain and plasma 30–60 mins after intraperitoneal administration. This response occurred within hours in the adrenal glands.⁷⁵ Given this neurosteroidogenic property of etifoxine, its potential modulatory effect was investigated in a rat model of neuropathic pain induced by the anti-cancer agent vincristine. Prior administration of etifoxine prevented pain sensitization by vincristine and reduce established hyperalgesia. Endogenous synthesis of 3 α ,5 α -reduced neurosteroids induced by etifoxine binding to TSPO appeared to be responsible for the observed anti-hyperalgesia effects.⁷⁶ In a chronic sciatic nerve constriction rat model, Aouad et al, demonstrated that etifoxine suppresses neuropathic pain symptoms. This effect was fully mediated by 3 α ,5 α -reduced neurosteroids, and probably also by allopregnanolone, which was found in high concentrations in the spinal cord of the treated animal.⁷⁷

Conclusion

Etifoxine is a non-BZD anxiolytic drug with selectivity for the β subunit of the GABA_A receptor. It possesses specific pharmacological properties, involving both direct and indirect (via neurosteroid synthesis) facilitation of GABAergic neurotransmission, leading to a potential indirect serotonergic activity. In addition, etifoxine attenuates CNS and whole-body inflammation and immunity processes known to be associated with anxiety.

Clinical studies have demonstrated the efficacy of etifoxine in the symptomatic treatment of anxiety, particularly in patients with ADWA, with daily doses of 150–200 mg. The tolerability profile of etifoxine is better than that of BZDs, notably because of a lack of effect on memory and vigilance. In addition, treatment cessation does not induce drug dependence, withdrawal, or rebound anxiety. The patients included in studies so far have mostly been women (2/3), which corresponds to the sex ratio for anxiety and ADs in the general population. However, a gender effect of etifoxine cannot be ruled out.

Of note, a 1990 European Council resolution underscored the danger of inappropriate or excessive prescription of hypnotic or anxiolytic BZDs.⁷⁸ This resolution recommended that prescribers restrict the use of anxiolytic BZDs to cases of severe or disabling anxiety and to limit treatment duration.

The anxiolytic efficacy of etifoxine, its good tolerability and the absence of drug dependence is strong arguments in favor of using etifoxine in the management of ADWA.

Disclosure

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