



## Commentary

Etifoxine (Stresam<sup>®</sup>) for chemotherapy-induced pain?

The majority of patients with cancer suffer from pain, in particular during advanced stages of the disease [6]. The pain can originate from the tumor itself, but in many cases it occurs as a consequence of cancer chemotherapy. In particular vinca alkaloids, taxanes and platinum drugs, which are often used for the treatment of solid tumors, cause severe and often dose-limiting painful neuropathies [2]. And the pain generally responds poorly to conventional analgesic treatment. The study by Aouad et al. [1] in this issue of PAIN is most exciting for all those who deal with cancer therapy-induced neuropathic pain, either as clinicians or as researchers. The authors demonstrate that the non-benzodiazepine anxiolytic, etifoxine, not only reverses vincristine-induced pain, but it can also prevent the development of neuropathic pain when given prophylactically—at least in rats.

These days, experimental research in the field of biomedicine is often performed with genetically modified, mainly knock-out, mice and very often authors cannot resist the temptation to speculate that the product of the gene under study is a potential new drug target. Later, it often turns out that the pharmacological intervention is not as effective as the respective gene deletion. In other cases, the protein under study may not be “druggable” and even if the protein is suitable for drug targeting, it may easily take a decade to bring a suitable drug candidate to the market. The present report is an exception. It not only studies the effect of a chemical compound, but this compound is already available as an anxiolytic drug, marketed by the French company Biocodex, under the proprietary name Stresam<sup>®</sup>. The drug should thus be readily available for clinical testing in patients with chemotherapy-induced neuropathic pain. If etifoxine not only shows high efficacy but is also well tolerated in cancer patients, these patients and their physician will have good reason to be happy with this development.

These results are very encouraging, but a host of questions must be answered before initiating further drug discovery and development programs. How does the drug act? What protein or molecule is targeted? Does the drug have to penetrate the blood brain barrier? The authors discuss some of these issues. Etifoxine, initially called Hoe36801, is a non-benzodiazepine anxiolytic that directly potentiates GABA<sub>A</sub> receptor activation through a site different from the classical benzodiazepine binding motif [5]. In addition, etifoxine modulates GABA<sub>A</sub> receptors via stimulation of neurosteroid production [9]. This occurs through the binding of etifoxine to the 18 kDa translocator protein, TSPO, of the outer mitochondrial membrane, previously known as the peripheral benzodiazepine receptor (PBR) [8]. One function of PBR is the transport of cholesterol into mito-

chondria, which increases the synthesis of neurosteroids, including the highly effective GABA<sub>A</sub> receptor modulator pregnanolone. The analgesic effect of etifoxine is indeed blocked by 6-medroxyprogesterone, an inhibitor of neurosteroid production [1], indicating that its analgesic action originates most likely from an interaction with TSPO. Both of these actions, direct activation or neurosteroid-mediated facilitation of GABA<sub>A</sub> receptors, could underlie the analgesic effect of etifoxine, especially as peripheral nerve damage has been shown to reduce GABAergic inhibition [3] and drugs that potentiate spinal GABA<sub>A</sub> receptors alleviate neuropathic pain [7].

However, the mechanism of etifoxine as an antineuropathic pain agent may be completely independent of GABA<sub>A</sub> receptors. A publication last year by Girard et al. [4] points in this direction. These authors did not study neuropathic pain or an analgesic action of etifoxine, but rather studied the effect of etifoxine on the regeneration of damaged peripheral nerves. They found that etifoxine strongly promoted the regeneration of peripheral nerve fibers after a freeze injury, an action that was mimicked by other ligands of 18 kDa TSPO, but was unaffected by antagonists of GABA<sub>A</sub> receptors. Importantly, etifoxine also stimulated neurite outgrowth in PC12 cells, which lack GABA<sub>A</sub> receptors, indicating that this regenerative action was independent of GABA<sub>A</sub> receptors. If the regenerative action of etifoxine underlies its analgesic effect against chemotherapy-induced neuropathic pain, then the analgesic action would also involve neurosteroid-dependent, but GABA<sub>A</sub> receptor independent effects. The etifoxine effect could very well involve a direct action on the peripheral nerve. Indeed, TSPO is induced in cell bodies of damaged nerve fibers and in macrophages that invade damaged nerves. As a result TSPO may contribute to either the pathology or the resolution of peripheral nerve damage. In fact, etifoxine reduces the number of invading macrophages and the release of proinflammatory mediators into the nerve, through as yet unidentified mechanisms [4]. The time courses of both the analgesic effect and the regenerative action support a mechanism that perhaps involves classical genomic effects. Identification of the underlying pathway could open a new avenue of future drug discovery.

Taking both studies together, it may be the case that the beneficial effect of etifoxine against neuropathic pain does not merely result from symptomatic pain relief, but might actually reflect the fact that the peripheral nerves are rendered less sensitive to potential toxins. The latter action could, in turn, promote the recovery of already damaged nerves. For all of these reasons, it is unlikely that I am the only one eagerly awaiting clinical trials of this drug in patients with painful neuropathies.

**References**

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Hanns Ulrich Zeilhofer

*Institute of Pharmacology and Toxicology, University of Zurich, and  
Institute of Pharmaceutical Sciences, Swiss Federal Institute of  
Technology (ETH) Zurich, Switzerland.*

*Tel.: +41 44 6355912; fax: +41 44 6355988.*

*E-mail address: zeilhofer@pharma.uzh.ch*