

TOPICAL REVIEW

Lamotrigine in the treatment of pain syndromes and neuropathic pain

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Abstract: Anti-epileptic drugs are increasingly used in the treatment of pain syndromes and neuropathic pain. Sodium channel blockers can be effective in the treatment of pain. The object of our interest is the efficiency of lamotrigine in treating the pain. A MEDLINE search was conducted to identify pertinent studies, case reports, letters, and reviews in English published from 1986 to May 2007. The search has indicated efficiency in treating a number of painful syndromes and neuropathic pain; central pain, trigeminal neuralgia and trigeminal neuralgia in multiple sclerosis, pain in multiple sclerosis, SUNCT syndrome, cluster headache, glossopharyngeal neuralgia, neuropathic pain, allodynia, neuralgia after nerve section, postherpetic neuralgia, HIV-associated neuropathy. Further researches are required on the role of lamotrigine in treating the spinal cord injury pain, neuralgia after nerve section, postoperative analgesic requirement, and in migraine (Tab. 1, Ref. 46). Full Text (Free, PDF) www.bmj.sk.
Key words: lamotrigine, pain, neuralgia.

Antiepileptic drugs (AEDs) are commonly utilized for non-epileptic condition, including pain syndromes and neuropathic pain. Lamotrigine is a novel antiepileptic agent with at least two antinociceptive properties: it stabilizes the neural membrane through blocking the activation of voltage-sensitive sodium channels, and inhibits the pre-synaptic release of glutamate (1). Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract; it is approximately 55% bound to plasma proteins and has a volume of distribution of about L/kg. The drug is extensively metabolized by conjugation with glucuronic acid. Lamotrigine elimination half-life is 25–30 h (2, 3). The treatment of pain syndromes and neuropathic pain is challenging, in part because of its multiple etiologies. The object of our interest is the efficiency of lamotrigine in the treatment of pain.

Materials and methods

We performed a systematic review of peer-reviewed publication identified through the MEDLINE databases (searched through May 2007). The search term was *lamotrigine, pain, headache*, and the search was limited to clinical trials and articles in English. The search was extended by review of bibliographies

from pertinent original reports of data and review articles. Unpublished trials and data presented only in abstracts were not included. The research included 220 references to lamotrigine and its influence to painful syndromes and neuropathic pain.

Review of literature

Central post-stroke pain is usually difficult to treat. Oral lamotrigine 200 mg daily is a well-tolerated and moderately effective treatment for central post-stroke pain and central pain (4–6). Trigeminal neuralgia is a chronic pain syndrome of still unestablished origin. Drug therapy initially helps a great majority of patients. Lamotrigine appears to be the most effective. Meta-analysis suggested; combination carbamazepine with lamotrigine or baclofen is the second-line treatment when monotherapy fails, but the evidence is weak (7–10). Neuropathic pain and paroxysmal symptoms are common in multiple sclerosis (MS) patients, although no double-blind clinical trial has been conducted to support the use of antiepileptic medications in MS (11). Several studies have been recently published addressing the prevalence of pain in MS subjects, finding a frequency of 40 %. The principal neuropathic pain syndromes common in MS are trigeminal neuralgia and dysesthetic pain syndrome. Treatment is based on antiepileptic medications acting on voltage-dependent sodium channels, such as carbamazepine and lamotrigine, or on tricyclic antidepressant (12). Cluster headache is episodic and unilateral, typically surrounds one of eyes, and lasts 15 to 180 minutes; the pain of trigeminal neuralgia lasts just for several seconds and is usually limited to the tissues overlying the maxillary and mandibular divisions of the trigeminal nerve. Cluster headache is

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Tab. 1. Lamotrigine in treatment of painful neuropathy.

Study (author, year)	Neuropathic pain	Conclusion – effect of lamotrigine
Eisenberg et al, 1998	diabetic neuropathy	potentially effective
McCleane, 1999	neuropathic pain	no effect
McCleane, 2000	neuropathic pain	may be effective
Eisenberg et al, 2001	diabetic neuropathy	effective
Vu, 2004	neuropathic pain	first-line or adjunctive therapy
Backonja and Serra, 2004	neuropathic pain	first-line therapy
Singleton et al, 2005	diabetic neuropathy	first-line therapy
Vinik et al, 2007	diabetic neuropathy	effective
Coderre et al, 2007	neuropathic pain	may reduce hyperalgesia
Chong and Hester, 2007	diabetic neuropathy	effective

unique because of its associated autonomic symptoms. The pathophysiology of cluster headache and trigeminal neuralgia are not completely understood. They both appear to have central primary processes, and these findings have prompted investigations of the effectiveness of new antiepileptic drugs for cluster headache prevention and for the treatment of trigeminal neuralgia. The new antiepileptic drugs such as lamotrigine are also used in preventing the cluster headache (13). The SUNCT syndrome is characterized by a short-lasting headache in the first division of the trigeminal nerve. It is associated with ipsilateral autonomic symptoms. It is highly refractory to prophylactic medication. Lamotrigine has recently been reported as an effective first-line therapy. It is effective in treating the SUNCT syndrome when used in high doses for a prolonged period of time (14–16). Neuralgia of the glossopharyngeal nerve is a rare disease entity, typically idiopathic, causing paroxysmal and excruciating pain. Lamotrigine is a potentially effective and safe compound in the treatment of painful glossopharyngeal neuralgia (17). Phantom limb pain and stump hypersensitivity post-herpetic neuralgia and causalgia respectively. The new antiepileptics, including lamotrigine, are most useful in the treatment of this type of neuralgia (18). Lamotrigine was well-tolerated and effective in HIV-associated neuropathic pain in patients receiving neurotoxic antiretroviral therapy (19). Neuropathic pain impacts many people around the world. Patients experience one of many symptoms, such as pain, paresthesia, dysesthesia, hyperalgesia, and allodynia for many years because of unavailable or inadequate treatment. Anticonvulsants, such as lamotrigine, have demonstrated efficacy in relieving the pain associated with diabetic neuropathy in several studies (20–29) (Tab. 1).

Lamotrigine therapy is described in treatment of individuals or smaller groups of subjects (patients) such as the treatment of migraine-related vertigo (30), neuralgia after nerve section (31), spinal cord injury pain (32), postoperative analgesia (33), intractable sciatica (34).

Discussion

Antiepileptic drugs (AEDs) are widely used today to treat epilepsy, migraine, neuropathic pain, and bipolar disorders. Other

disorders are also being investigated. The main targets for AEDs in the synapses include the enhancement of GABAergic inhibitory neurotransmission, decrease in glutamatergic excitatory neurotransmission directly or via inhibition of voltage-dependent sodium and calcium channels, and interference with intracellular signalling pathways. Lamotrigine decreases glutamatergic excitability (35). Lamotrigine inhibits excessive neuronal activity; this acute effect appears to be produced by several mechanisms, which fall into three major categories: 1) blockade of voltage-gated sodium channels; 2) indirect or direct enhancement of inhibitory gamma-aminobutyric acid (GABAergic) neurotransmission; or 3) inhibition of excitatory glutamatergic neurotransmission (36). The dose was gradually increased in steps of 25 mg up to the effective dose (mean 250 mg/d). Lamotrigine is effective in trigeminal neuralgia refractory to other treatments, post-herpetic neuralgia, painful peripheral neuropathy, HIV neuropathy, diabetic neuropathy, post-stroke pain, and has a significant effect on intractable neuropathic pain, pain related to spinal cord injury, glossopharyngeal neuralgia (17, 37–39). Lamotrigine is administered in various head and facial pains such as migraine, cluster headache, neuropathic trigeminal pain, atypical facial pain, and chronic tension-type headache. Lamotrigine was most effective in trigeminal neuralgia and dysesthesia, but had little effect on other head and facial pains (10, 16, 40–42). New AEDs have marked the new era in the treatment of neuropathic pain as the standards of their clinical trials were of higher quality. Lamotrigine is a fourth-line treatment in neuropathic pain, or in adjunctive therapy (43, 44). AEDs are potential alternatives in the treatment of diabetic neuropathy. Lamotrigine was inconsistently effective in pain associated with diabetic neuropathy but was generally safe and well-tolerated (27, 45, 46). All the above facts indicate that lamotrigine therapy is significantly efficient in the treatment of painful syndromes such as trigeminal neuralgia, pain in multiple sclerosis, SUNCT, post-stroke pain, HIV neuropathy, and diabetic neuropathy. Its efficiency when used only as an adjunctive therapy with other painful syndromes involving face and neck is somewhat lower. In cases of glossopharyngeal neuralgia, migraine, sciatic pain, spinal cord injury pain, neuralgia

after nerve section, and postoperative analgesic requirements, only isolated cases are described, wherefore further research is required.

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