

Anti-epileptic Drugs For Pain Management

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Abstract

Antiepileptic drugs (AED's) depress abnormal neuronal discharges and raise the threshold for neural impulse propagation. They have been found to have therapeutic efficacy in neuropathic pain states. Carbamazepine(CZ) and phenytoin (PT) were the drugs of choice for treating trigeminal neuralgia for 40 plus years. These two agents have been largely replaced due to the introduction of many newer, better-tolerated, and safer antiepileptic drugs.

CLINICAL USE/MECHANISM OF ACTION/SIDE EFFECTS:

There has been an explosion in the number of available AEDs. Many studies are ongoing to evaluate their efficacy in neuropathic pain states. Only CZ, PT, gabapentin (GB), and lamotrigine (LT) have been evaluated in double blind trials. (4,5,6)

Some tenets of use are common in all of these medications. Initial dosing should be done at a low dose administered at bedtime, increased slowly up to a therapeutic level over 4 to 8 weeks. These medications do not have a ceiling dose, but are usually more effective at higher doses. Clinically the dose should be titrated upwards until side effects are encountered, then back down a small amount. The pain relief obtained is gradual with most agreeing that an adequate trial of an AED for pain should last 4-8 weeks at therapeutic doses prior to calling a medication ineffective.

A brief summary of clinical uses, mechanism of action, and side effects will be presented for the following AEDs.

1. Carbamazepine (CZ): This medication has been used in trigeminal neuralgia and other lancinating pain syndromes since the early 1960s. Its efficacy has been shown in three well designed double blind, placebo controlled crossover studies. (2,7,8) It works by slowing the recovery rate of voltage gated Na⁺ channels from depolarization in a fashion similar to PT. The starting dose is 200mg bid, with effective dose ranging from 400 to 1000mg/day. The most common side effects are drowsiness, diplopia, and unsteadiness. Aplastic anemia can occur in 1:200,000 patients, more

commonly a reversible leukopenia and thrombocytopenia can be seen. It significantly induces the P450 cytochrome system. **(see related drug F oxcarbazepine.)

2. Phenytoin (PT): In the 1970s several trials were completed to evaluate the efficacy of phenytoin in painful diabetic neuropathy with mixed results. (9) Its mechanism of action is similar to CZ. The usual dose is 200 to 400 mg/day. The most common side effects are nausea, diplopia, dizziness, confusion, gingival hyperplasia, and rarely Stevens-Johnson syndrome. It also induces the P450 system.
3. Valproic Acid (VA): VA is a medication which has been shown to have therapeutic benefit in prophylaxis of migraine headache. (10) It blocks voltage gated Na⁺ channels similar to CZ and PT, but additionally increases levels of GABA by decreasing degradation. Side effects include nausea, vomiting, sedation, ataxia, rash, alopecia, and appetite stimulation. Commonly (40%), patients experience elevated transaminases with rare hepatic failure reported (1:50000).
4. Clonazepam(CP): CP is a benzodiazepine used for the treatment of certain types of seizure. Its use in painful conditions includes myoclonus/muscle spasms. The mechanism of action is enhancement of the GABA-induced increase in chloride conductance. Side effects include sedation, lethargy, ataxia, and dizziness.
5. Gabapentin (GP): GB has been in use since 1994 as an anticonvulsant. Two recent large clinical

trials have established its efficacy in the treatment of painful diabetic neuropathy and post herpetic neuralgia. (4,5) One recent comparative trial showed comparable efficacy of amitriptyline and gabapentin for painful diabetic neuropathy. (11) There are case reports on its treatment benefit in various types of neuropathic pain states including headache and many others. Its mechanism of action is uncertain, although the drug was synthesized as a GABA analog. The drug may have its effect at a central voltage dependent L-type Ca^{++} channel. The most common side effects are drowsiness, somnolence, nausea, and fatigue. These side effects are usually self-limited and subside after a couple of weeks allowing gradual dose escalation. Usual starting dose is 100-300 mg po at bedtime. Then a gradual increase to 1200 mg/day over 30 to 60 days. Some patients may require 3600mg/day or more for clinical effect. The dosing should be on a TID schedule. The drug is excreted unchanged in the urine, requiring adjustment of dosing in renal failure. GB does not have drug-drug interactions making it easy to use clinically. *(see related drug Pregabalin)

6. Pregabalin (PN): *(see related drug gabapentin) This is a drug not yet approved for clinical use, but it is a GP analog, which shows better treatment effectiveness in painful animal models than GP. (1)
7. Lamotrigine (LG): LG has been in use since 1993 and has been shown to have efficacy in the treatment of trigeminal neuralgia. Additionally, open label studies have shown promise in migraine headache and painful diabetic neuropathy. (12) LG is an inhibitor of voltage gated Na^{+} channels, but additionally may suppress glutamate release and inhibit serotonin reuptake. Side effects include dizziness, diplopia, drowsiness, and rash. The rash occurs in up to 10% of patients. Dosing is started at 25-50mg/day and increased by 50mg/d per week until analgesia is reached or reach an arbitrary maximum, usually around 900mg per day administered bid or tid.
8. Topiramate (TP): TP has been approved for use in 1997 and has shown promise in cluster headache and diabetic neuropathy. (13) Structurally it is a unique monosaccharide compound unlike other AEDs. It potentiates GABA responses,

significantly increasing CNS GABA levels, additionally it blocks the AMPA kainate excitatory receptor. It is also a weak carbonic anhydrase inhibitor. Effective dose ranges are 200-400 mg/day with bid dosing. Starting dose is 25mg bid increasing 50mg every week up to the dosing range. Side effects include unusual CNS effects such as abnormal thinking, delusional, and psychotic thinking. Also, rarely, a patient may develop renal stones. These side effects are rare <2-3%, but troubling to those patients.

9. Oxcarbazepine (OC) *(see related drug A carbamazepine.) OC is a keto-analog of CZ which should retain many of the therapeutic properties of CZ, while avoiding the toxicities. Published reports show efficacy in Trigeminal Neuralgia and there are ongoing open label trials in other neuropathic pain states. (14) The mechanism of action is also blockade of voltage gated Na^{+} channels. It probably modulates voltage activated Ca^{++} currents also. Starting dose is 300mg at bedtime, with weekly increases of 300-600mg/day up to a maximum of 1200-2400mg/day. This agent has been used in Europe since 1990 without a case of bone marrow suppression, also it does not induce the P450cytochrome system.
10. Felbamate (FM): FM is a unique agent in that it decreases glutamate synthesis and blocks NMDA receptors, but rare hepatotoxicity and aplastic anemia have limited its use. (15)
11. zonisamide (ZS): AED in use in Japan with mechanism of action being Na^{+} channel blockade in addition to T-type Ca^{++} channel blockade. It is also a carbonic anhydrase inhibitor. Studies in pain management are ongoing. (16)
12. tiagabine (TB): A GABA reuptake inhibitor with future potential for the treatment of painful conditions. (13)
13. vigabatrin (VB) : A GABA metabolism inhibitor with future potential for the treatment of painful conditions. (13)

CONCLUSION

AED's depress abnormal neuronal discharges and raise the threshold for neural impulse propagation. They have been

found to have therapeutic efficacy in neuropathic pain states. The older AED's have been largely replaced due to the introduction of many newer, better-tolerated, and safer antiepileptic drugs. (3) The AED of choice for different painful states has not yet been determined, nor has an algorithm of use been developed for the newer agents.

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