It is thought that they have dual modes of action:

(i) blockade of sodium channels

(ii) potentiation of GABAergic neurotransmitter system*

- the GABA system essentially "calms down" the nervous system. (is more inhibitory rather than excitatory)
- The dorsal horn neurones in the spinal cord contain cells which use GABA as their inhibitory neurotransmitter. These neurones are known to be involved in pain pathways.

Gabapentin does not appear to act at GABA receptor sites even though it was developed as a GABA analogue.

Hansen ( [i] ) suggests that allodynia may respond to gabapentin because of an effect on the GABAA receptor which inhibits large afferent (A beta) excitatory input.

Other research( [ii] ) has shown that gabapentin mimics GABAb receptor activation, but is active independently of the GABA receptor mechanism.

This is borne out clinically by the effect gabapentin has on reducing muscle spasm. Shimoyama et al( [iii] ) recently concluded from their animal studies that

"The antinociceptive effects of GBP may involve the inhibition of the release of excitatory amino acids from presynaptic terminals."

- Other new AEDs associated with the GABA-ergic system inlcude tiagabine and vigabatrin.
- Although topiramate and felbamate were shown to enhance GABA-mediated events, they have additional mechanisms of action, including blockade of voltage-dependent sodium channels and inhibition of glutamatergic neurotransmission.( [iv] )
- Lamotrigine affects glutamate release.( [v] ) It is also thought to inhibit voltage-sensitive sodium channels, thereby stabilising neuronal membranes.
- Valproate slows recovery rate of voltage-gated sodium channels and limits repetitive firing. It also increases GABA levels via its effects on various enzymes.
- Carbamazepine slows recovery of sodium channels and also has a minor anatagonistic effect on calcium channels. It is chemically related to tricyclic antidepressants.

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[i] Hansen HC *South Med J* 1999 92(7): 642-649 Treatment of Chronic Pain with Antiepileptic drugs: a new era.

[ii] Schlicker E, Reimann W, Gothert M *Drug Res* Gabapentin decreases monoamine release without affecting acetylcholine release in the brain.

[iii] Shimoyama M, Shimoyama N, Hori Y *Pain*

Gabapentin affects glutamatergic excitatory neurotransmission in the rat dorsal horn.

[iv] Czuczwar SJ *Neurol Neurochir Pol* 2000;33 Suppl 1:13-20 [GABA-ergic system and antiepileptic drugs].

[v] Teoh H, Fowler LJ, Bowery NG. *Neuropharmacol* 1995;34:1273-8 Effect of lamotrigine on the electrically-evoked release of amino acids from slices of dorsal horn of the rat spinal cord.