Anticonvulsants and Antidepressants in Chronic Pain Management

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Introduction:

Chronic pain is a global concern affecting people from all walks of life. As the epidemic of opiod misuse continues to grow, the need for balanced, multimodal approaches to the treatment of pain syndromes has become more apparent. These include medications which, though originally designed to treat other pathologies, have demonstrated benefits in the treatment of chronic pain. The following is a review of the pharmacodynamics of various classes of antidepressants and anticonvulsants, and the effects of these drugs on pain signalling and perception. Finally, recommendations for the use of such drugs in the patient with chronic pain are discussed.

Mechanism of anticonvulsants and antidepressants in chronic pain

Table 1: Mechanism of action of common anticonvulsants used in chronic pain

MECHANISM OF ACTION	DRUGS
Blockade of Sodium Channel	• Carbamazepine • Gabapentin
Blockade of Calcium Channel	• Gabapentin • Pregabalin
Enhancement of GABA	• Carbamazepine
Suppression of Glutamate	• Carbamazepine • Gabapentin • Pregabalin

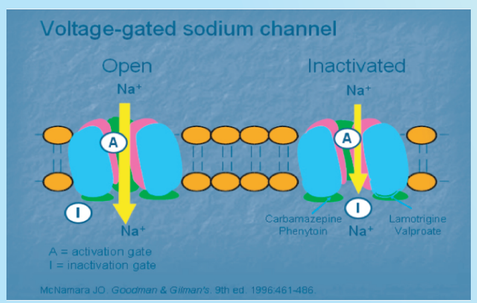

Figure 1: Mechanism of action of Carbamazepine

Ref: McNamara JO. Drugs effective in the therapy of the epilepsies. In: Hardman JG, Limbard LE, eds, Goodman and Gilman's the pharmacologocal basis of therapeutics, 9th ed. New York, McGraw Hill, 1996: 461-486

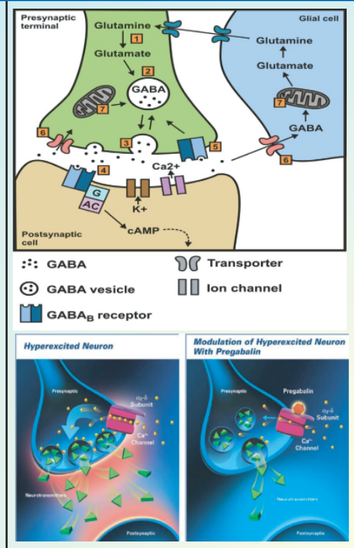

Figure 2 : Synthesis of γ-aminobutyric acid (GABA) fromglutamine/glutamate

Ref : Waxham MN. Amino acid neurotransmeters. In: Cellular and Molecular Neurobiology, The University of Texas Medical School, Houston, USA. Ebook, www. neuroscience.uth.tmc.edu

Figure 3: Mechanism of action of Pregabaline

Ref: Shim JH. Clinical application of α_2-δ ligand. Hanyang Medical Reviews 2011, 31: 55-62

Table 2 : Mechanism of action of common antidepressants used in chronic pain

MECHANISM OF ACTION	DRUGS	
Inhibition of Norepinephrine reuptake	Secondary amines	• Desipramine • Nortriptyline
Inhibition of Norepinephrine and Serotonin reuptake	Tertiary amines	• Amitriptyline • Imipramine
	SNRIs	• Duloxetine • Venlafexine

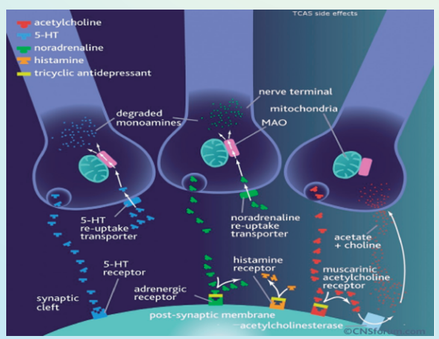

Figure 4: Mechanism of action of antidepressants and side effects

Ref: Drugs used in affective disorders. In: Pharmacology, 4th edition. Rang HP, Dale MM and Ritter JM. Edinburgh, UK: Harcourt Publishers Ltd, 2001:550-565.

Table 3 : Systematic Reviews of Anticonvulsants in chronic pain

Disease Condition	Study Drug (No. Trials)	NNT
Various neuropathic Conditions	Gabapentin (14) Pregabalin (14)	4.3-6.4 3.8-4.8
Trigeminal Neuralgia	Carbamazepine (2)	1.4-2.8
Postherpetic Neuralgia	Pregabalin [300-600 mg] (8) Gabapentin (4)	3.9-5.3 4.3-7.7
Diabetic Neuropathy	Pregabalin, 300-600 mg (17) Gabapentin (3)	5-11 4.7-28
Central Neuropathic Pain	Pregabalin, 600 mg (2)	3.5-14

† NNT values (for 50% pain reduction) are lower at higher doses; indicates NNT for PGIC "much or very much improved": NNTs are higher for "very much improved" only.
Ref: Ian Gilron,Treatment of Neuropathic Pain: Antiepileptic and Antidepressant Drugs. In: Pain 2014 Refresher Courses: 15th World Congress on Pain, IASP eBook, pp225-37

Table 4 : Systematic Reviews of Antidepressants in chronic pain

Disease Condition	Study Drug (No. Trials)	NNT
Various Neuropathic Conditions	Amitriptyline (10) Desipramine (2) Imipramine (3)	2.5-4.2 1.9-4.5 1.7-3.2
Various Neuropathic Conditions	TCAs (23) SSRIs (4) SNRIs (7)	1.9-3.8 3.9-27 3.4-14
Diabetic Neuropathy	Duloxetine (3)	5-10

Ref: Ian Gilron,Treatment of Neuropathic Pain: Antiepileptic and Antidepressant Drugs. In: Pain 2014 Refresher Courses: 15th World Congress on Pain, IASP eBook, pp225-37

Table 5 : Prescribing Recommendations for Anticonvulsants

Drug	Starting Dosage	Titration	Maximum Dosage	Duration of Adequate Trial
Gabapentin	100-300 mg at bedtime or 100-300 mg three times daily	Increase by100-300 mg three times	3600 mg daily	3-8 weeks
Pregabalin	50 mg thrice daily	Increase weekly by 150 mg	600 mg daily	4 weeks
Carbamazepine	100-200 mg daily	Increase weekly by 100-200 mg	1600 mg daily	6-8 weeks

Table 6 : Prescribing Recommendations for Antidepressants

Drug	Starting Dosage	Titration	Maximum Dosage	Duration of Adequate Trial
Nortriptyline	25 mg at bedtime	Increase by 25 mg weekly	150 mg daily	6-8 weeks
Desipramine	25 mg at bedtime	Increase by 25 mg weekly	150 mg daily	6-8 weeks
Duloxetine	30 mg once daily	Increase to 60 mg weekly	120 mg daily	4 weeks
Venlafaxine	37.5 mg once or twice daily	Increase to 75 mg weekly	225 mg daily	4-6 weeks

Conclusion

The mechanism of action of anticonvulsants and antidepressants clearly show its role in pain signalling and perception. Evidences regarding pharmacodynamics of these drugs in chronic pain appreciate their inclusion in the pool of multimodal approach of management of chronic pain.