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REVIEW ARTICLE

Anticonvulsants and Antidepressants in Chronic Pain Management

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ABSTRACT

Epidemiological studies have found that 10.1 to 55.2% of people in various countries have chronic pain. Various medicines are prescribed, depending on whether the pain originates from tissue damage or is neuropathic. Evidence suggests that chronic pain from tissue inflammation or damage as in rheumatoid arthritis and cancer pain is best treated with opioids and anti-inflammatory drugs, while for neuropathic pain where pain is caused by a damaged or dysfunctional nervous system other drugs may be more effective. Chronic pain is a global concern affecting people from all walks of life. As the epidemic of opioid 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. This article is a review of the pharmacodynamics of various classes of antidepressants and anticonvulsants and the effects of these drugs on pain signaling and perception. Finally, recommendations for the use of such drugs in the patient with chronic pain are discussed.

Keywords: Anticonvulsants, Antidepressants, Chronic pain.

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INTRODUCTION

Worldwide, 10.1 to 55.2% of people are suffering from chronic pain.[1] Chronic pain is a disease condition, whereas acute pain is a symptom. It includes different clinical conditions, such as cervical or lumbar radiculopathy, diabetic neuropathy, cancer pain, postherpetic neuralgia, pain due to spinal cord injury, multiple sclerosis, poststroke central pain, trigeminal neuralgia, posttraumatic or postsurgical neuropathic pain, complex regional pain syndrome, arthritis, phantom limb pain, scar pain, and human immunodeficiency virus (HIV)-related neuropathy. Chronic pain could be originated from activation of nociceptors by tissue damage or it could be from direct damage from nervous tissue or malfunction of the nervous system.[2]

The diversity of application of medicine in chronic pain is remarkable. It depends on the causes of chronic pain: whether the pain originates from tissue damage as in rheumatoid arthritis and cancer pain or nervous dysfunction as in radiculopathic pain, trigeminal neuralgia, diabetic neuropathy, and so on. Evidence suggests that chronic pain from tissue inflammation or damage is best treated with opioids and anti-inflammatory drugs, while chronic pain from dysfunctional nervous system may be treated with antidepressants and anticonvulsants.

Various medicines are prescribed for chronic pain. Though anticonvulsants and antidepressants are prescribed for various neurological conditions, evidence suggests their positive effectiveness in chronic pain. Historically, anticonvulsants were introduced in the 1850s and antidepressants in 1950s. They have been used in chronic pain since the last 50 to 60 years. But nowadays, judicious application in chronic pain is a vital issue. The objective of this article is to focus on the understanding of the mechanism of anticonvulsants and antidepressants in chronic pain, their efficacy, and recommendations for prescription in chronic pain.

ANTICONVULSANT DRUGS AND MECHANISM TO REDUCE CHRONIC PAIN

Anticonvulsants are the drugs that are used to treat seizures. They are classified as first-generation and second-generation anticonvulsants. Benzodiazepines, carbamazepine, phenobarbital, phenytoin, and valproic acid are well-prescribed first-generation anticonvulsants which were introduced between 1910 and 1970. Gabapentin, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, and zonisamide are second-generation anticonvulsants, which were introduced more recently.[3] Majority of anticonvulsants improve the quality of sleep

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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

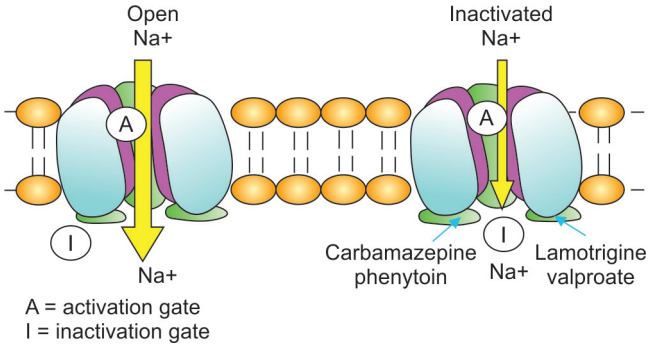

Fig. 1: Mechanism of action of carbamazepine[4]

and reduce anxiety in addition to pain. Multiple pharmacological mechanisms have been elucidated for most anticonvulsant drugs.[4-6] Gabapentin and carbamazepine act on sodium channel where they inhibit depolarization. Both gabapentin and pregabalin act on calcium channel and block it (Table 1). Carbamazepine enhances gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter (Fig. 1). Gabapentin, pregabalin, and carbamazepine suppress glutamate, which is an excitatory neurotransmitter in presynaptic level.[7]

ANTIDEPRESSANT DRUGS AND MECHANISM TO REDUCE CHRONIC PAIN

Antidepressants are the group of drugs that include a wide array of chemical agents that can be characterized by chemical structure and/or major pharmacological mechanism. They are classified as older antidepressants and newer antidepressants. Older antidepressants are the tricyclic antidepressants (TCAs) and the common newer antidepressants are monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) (Table 2). Tricyclic antidepressants inhibit the reuptake of norepinephrine, serotonin, and acetylcholine in presynaptic membrane which increases the serotonin level in synaptic cleft. They increase the acetylcholine level in synaptic cleft, which is why side effects are more.[8] Monoamine oxidase is the enzyme responsible for breaking down serotonin and thus MAOIs inhibit the action of monoamine oxidase enzyme, which ultimately helps to raise the serotonin level. Serotonin norepinephrine reuptake inhibitors are widely used antidepressants in chronic pain condition. These raise serotonin and norepinephrine levels in the synaptic cleft and make ready more serotonin for postsynaptic activities.[8] Serotonin norepinephrine reuptake inhibitors increase supraspinal availability of norepinephrine, which is thought to enhance descending inhibitory bulbospinal control.[9] Selective serotonin reuptake inhibitors selectively block the reuptake (absorption) of serotonin and raise the concentration in synaptic cleft.[8]

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
	• Venlafaxine

A large body of preclinical research has pointed to several putative analgesic mechanisms of antidepressant drugs. These include increased supraspinal availability of norepinephrine (thought to enhance descending inhibitory bulbospinal control), activation of endogenous mu- and delta-opioid receptors, sodium channel blockade, and *N*-methyl-D-aspartate receptor inhibition, among others.[9] Regardless of specific molecular mechanisms, the clinical rationale for using antidepressants in the management of chronic pain may also include treatment of comorbid depression and sleep disturbance as well as reduction of pain intensity.[10]

LITERATURE REVIEW FOR ANALGESIC EFFICACY OF ANTICONVULSANT DRUGS

Multiple high-quality randomized controlled trials (RCTs) on neuropathic pain are available for carbamazepine, oxcarbazepine, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, and valproate.[11] Meta-analysis of multiple RCTs on the action of carbamazepine and oxcarbamazepine showed estimated numbers needed to treat (NNTs) as 1.4 to 2.8.[12,13] Gabapentin showed interesting results in several RCTs of patients with fibromyalgia, diabetic neuropathy, postherpetic neuralgia, and other neuropathic conditions. It showed estimated NNT ranging from 4.3 to 6.4 in previous meta-analyses, but in a recent updated Cochrane review, reported NNTs are 9.6 (95% confidence interval: 7.4–14) for patient global impression of change (PGIC)

Table 3: Systematic reviews of anticonvulsants[30]

Disease condition	*Study drug (no. of trials)*	*NNT*
Various neuropathic conditions	Gabapentin (14)	4.3–6.4
	Pregabalin (14)	3.8–4.8
Trigeminal neuralgia	Carbamazepine (2)	1.4–2.8
Postherpetic neuralgia	Pregabalin, 300–600 mg (8)	3.9–5.3†
	Gabapentin (4)	4.3–7.7¶
Diabetic neuropathy	Pregabalin, 300–600 mg (17)	5–11†
	Gabapentin (3)	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

"very much improved" and 6.1 (4.9 to 8.0) for "much or very much improved."[14] Multiple RCTs have been conducted to see the efficacy of pregabalin on central neuropathic pain, diabetic neuropathy, and postherpetic neuralgia where it showed variable results.[15] A recent meta-analysis reported variable results depending on daily pregabalin doses. It showed NNTs of 3.9 to 5.3 for postherpetic neuralgia with daily dose of pregabalin 300 to 600 mg and 5 to 11 for diabetic neuropathy with the same dose.[16] One RCT showed estimated NNT of 5.6 when all central neuropathic pain patients were treated with 600 mg of pregabalin (Table 3).[16]

LITERATURE REVIEW FOR ANALGESIC EFFICACY OF ANTIDEPRESSANT DRUGS

A good number of RCTs were conducted to see the efficacy of TCAs on different chronic pain conditions where all RCTs support their efficacy. They showed estimated NNTs of 1.7 to 3.2 for imipramine, 1.9 to 4.5 for desipramine, and 2.5 to 4.2 for amitriptyline.[17-19] On the contrary, high-quality RCTs failed to demonstrate the efficacy of TCAs in HIV-related neuropathy[20,21] or in lumbar radiculopathy.[22] Another RCT showed the estimated NNT of SSRIs on neuropathic pain as 6.8, which indicates that SSRIs are less effective than TCAs.[11]

Table 4: Systematic reviews of antidepressants[30]

Disease condition	*Study drug (no. of trials)*	*NNT*
Various neuropathic conditions	Amitriptyline (10)	2.5–4.2
	Desipramine (2)	1.9–4.5
	Imipramine (3)	1.7–3.2
Various neuropathic conditions	TCAs (23)	1.9–3.8
	SSRIs (4)	3.9–27
	SNRIs (7)	3.4–14
Diabetic neuropathy	Duloxetine (3)	5–10

Paroxetine *vs* imipramine was compared to see the efficacy on neuropathic pain which also indicated lower efficacy.[23] More recently, SNRIs, such as venlafaxine and duloxetine, have been evaluated and were superior to placebo in several RCTs, with NNT estimates of 5 to 14 (Table 4).[23] The dopamine–norepinephrine reuptake blocker, bupropion, showed promising results in a single RCT involving mixed neuropathic pain conditions.[24] But bupropion failed to show a bupropion *vs* placebo difference in subsequent RCTs.[25]

PAIN TREATMENT GUIDELINES REGARDING ANTICONVULSANT DRUGS

The European Federation of Neurological Societies (EFNS), the Canadian Pain Society (CPS), and the International Association for the Study of Pain Neuropathic Pain Special Interest Group (NeuPSIG) recommend gabapentin and pregabalin as first-line therapy for neuropathic pain with the exception of trigeminal neuralgia.[26-28] The EFNS and CPS recommend carbamazepine as first-line therapy for trigeminal neuralgia (Table 5).[24,27,29]

PAIN TREATMENT GUIDELINES REGARDING ANTIDEPRESSANT DRUGS

The EFNS, CPS, and NeuPSIG recommend TCAs as first-line therapy for neuropathic pain with the exception of HIV-related neuropathy (Table 6).[24,27,29] Whereas

Table 5: Prescribing recommendations for anticonvulsants[30]

Drugs	*Starting dosage*	*Titration*	*Maximum dosage*	*Duration of adequate trial*
Gabapentin	100–300 mg at bedtime or 100–300 mg three times daily	Increase by 100–300 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[30]

Drugs	*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 by 75 mg weekly	225 mg daily	4–6 weeks

the Canadian and European guidelines recommended SNRI antidepressants as second-line therapy because of estimates suggesting somewhat lesser efficacy than TCAs, the most recent NeuPSIG guidelines consider them as first line, possibly due to a more favorable side-effect profile.

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