DRUG REVIEW

Antidepressants /Antiepileptic drugs - Chronic Low Back pain

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Low back pain is a very common problem.In general, the first steps in the treatment of uncomplicated low back pain include a few days of rest and anti-inflammatory medications. Other recommended treatments might include a short course of oral steroid, stronger pain medication, muscle relaxants, steroids injected into the epidurals (outside the covering of the nervous system) space, the use of a transcutaneous electrical nerve stimulator (TENS unit) . Since there is very little research data on the treatment of chronic low back pain, a single best treatment has yet to be determined particularly in chronic low back ache.(1)

The development of newer classes of antidepressants and second-generation antiepileptic drugs in has created unprecedented opportunities for the treatment of chronic pain.(2-5)

The evidences (2-5) are consistent indicating that antidepressants may have an antinociceptive effect in chronic pain, and that these drugs are effective for neuropathic pain. There are also some evidence that these drugs could be effective for psychogenic or somatoform disorder-associated pain. Antidepressants could be effective for pain associated with some specific pain syndromes, such as chronic low back pain, osteoarthritis or rheumatoid arthritis, fibrositis or fibromyalgia, and ulcer healing. These drugs modulate pain transmission by interacting with specific neurotransmitters and ion channels (Table 1).

Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, desipramine) and certain novel antidepressants (i.e., bupropion, venlafaxine, duloxetine) are effective in the treatment of neuropathic pain. The analgesic effect of these drugs is independent of their antidepressant effect and appears strongest in agents with mixed-receptor or predominantly noradrenergic activity, rather than serotoninergic activity.

Tricyclic antidepressants are thought to affect pain transmission in the spinal cord by inhibiting the reuptake of norepinephrine and serotonin, both of which influence descending pain pathways. In addition, histamine H1-receptor affinity (associated with sedation) may be correlated with the analgesic effect of antidepressants. Amitriptyline also has an analgesic effect in patients with acute pain.

Tricyclic antidepressants may be categorized as secondary or tertiary amines. Secondary amines such as nortriptyline & desipramine show relatively selective inhibition of norepinephrine reuptake. Tertiary amines such as amitriptyline and imipramine show more balanced inhibition of norepinephrine and serotonin, but they also have greater anticholinergic side effects.

The novel antidepressants venlafaxine and duloxetine have balanced inhibition of serotonin and norepinephrine reuptake without blockade of other neuroreceptors that are responsible for typical tricyclic side effects. The mechanism of action of bupropion is uncertain but involves blockade of dopamine uptake.

Depression and painful somatic symptoms commonly occur together. Depression and chronic pain can have devastating effects on a patient's health, productivity, and overall quality of life. When moderate-to-severe pain exists, it can impair patient function while making treatment more difficult or resistant, with increased severity in depressive symptoms and worse outcomes. The link between pain and depression lies in the central and peripheral nervous systems. The brain stem serves

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as an important connection between the higher brain centers and the spinal cord. In the brain stem, the neurotransmitters serotonin and norepinephrine modulate pain transmission through ascending and descending neural pathways. Both serotonin and norepinephrine are also key neurotransmitters involved with the pathophysiology of depression. (5)

Antiepileptic Drugs(2)

Antiepileptic drugs act at several sites that may be relevant to pain, but the precise mechanism of their analgesic effect remains unclear. These agents are thought to limit neuronal excitation and enhance inhibition. Relevant sites of action include voltage-gated ion channels (i.e., sodium and calcium channels), ligand-gated ion channels, the excitatory receptors for glutamate and N-methyl-D-aspartate, and the inhibitory receptors for GABA and glycine. Antiepileptic drugs may be categorized as first or second generation. The second-generation agents are better tolerated, cause less sedation, and have fewer CNS side effects.

Table 1: Mechanisms of Action for Antidepressants and Antiepileptic (2)

Inhibition of norepinephrine reuptake
Tricyclic antidepressants (secondary amines): desipramine , nortriptyline
Inhibition of norepinephrine and serotonin reuptake
Tricyclic antidepressants (tertiary amines): amitriptyline, imipramine
Novel antidepressants: venlafaxine , duloxetine
Cyclobenzaprine
Blockade of sodium channel
Antiepileptic drugs: carbamazepine, gabapentin, lamotrigine
Blockade of calcium channel
Antiepileptic drugs: gabapentin, pregabalin
Enhancement of g-aminobutyric acid
Antiepileptic drug: carbamazepine
Spasmolytic drug: baclofen

Clinical Considerations (6)

- Exercise is the primary therapy for chronic low back pain and fibromyalgia
- Begin treatment of low back pain with a nonsteroidal anti-inflammatory drug (not effective in the treatment of fibromyalgia).
- Consider use of a tricyclic antidepressant as a pain adjuvant to promote sleep and alleviate muscle spasm.
- Patients with associated anxiety, depression, or sleep disturbance may benefit from a tricyclic or novel antidepressant, although gabapentin and pregabalin also appear to reduce anxiety. Tricyclic antidepressants are significantly less expensive than second-generation antiepileptic drugs.
- A tricyclic antidepressant is the preferred initial therapy if the patient has coexisting insomnia, anxiety, or depression, or if cost is a consideration
- An antiepileptic drug (e.g., gabapentin) is preferred if the patient cannot tolerate the side effects of tricyclic antidepressants, has cardiac contraindications to the use of tricyclic antidepressants (e.g., conduction abnormalities, recent cardiac event).
- Titrate the selected medication to achieve clinical effect or to the maximum tolerated dosage.
- Monitor response to treatment.
- If monotherapy is tolerated but only partially effective, combine an antidepressant with an antiepileptic drug.
- If monotherapy is poorly tolerated or ineffective, choose a first-line agent from a different medication class or use a second-line agent (e.g., bupropion, venlafaxine).
- If pain relief remains inadequate, consider use of a short-acting or long-acting opioid or tramadol.

Table 2: Antidepressants and Antiepileptic Drugs in Chronic Pain (2,5)

Drug	*Dosage*	*Side effects*
Antidepressants		
Tricyclic antidepressants	-	dry mouth, constipation, urinary retention, sedation, weight gain
Amitriptyline	10 to 25 mg at bedtime	
imipramine	75 to 150 mg at bedtime	Tertiary amines have greater anticholinergic side effects; therefore, these agents should not be used in elderly patients.
Desipramine	25 mg in the morning , increase by 25 mg per week up to 150 mg per day	Secondary amines have fewer anticholinergic side effects.
nortriptyline		
Selective serotonin reuptake inhibitors		
Fluoxetine	10 to 20 mg per day; up to 80 mg per day for fibromyalgia.	nausea, sedation, decreased libido, sexual dysfunction, headache, weight gain.Efficacy in pain syndromes is relatively poor.
Paroxetine		
Novel antidepressants		
Bupropion	100 mg per day; increase by 100 mg per week up to 200 mg twice daily (400 mg per day).	anxiety, insomnia or sedation, weight loss, seizures
Venlafaxine	37.5 mg per day; increase by 37.5 mg per week up to 300 mg per day.	headache, nausea, sweating, sedation, hypertension, seizures
Duloxetine	20 to 60 mg per day taken once or twice daily in divided doses (for depression); 60 mg twice daily for fibromyalgia	nausea, dry mouth, constipation, dizziness, insomnia
Antiepileptic drugs		
First-generation agents		
Carbamazepine	200 mg per day; increase by 200 mg per week up to 400 mg three times daily (1,200 mg per day).	dizziness, diplopia, nausea Treatment can result in aplastic anemia.
Phenytoin	100 mg at bedtime; increase weekly up to 500 mg at bedtime.	dizziness, ataxia, slurred speech, confusion, nausea, rash Treatment can result in blood dyscrasias and hepatotoxicity.
Second-generation agents		
Gabapentin	100 to 300 mg at bedtime; increase by 100 mg every 3 days up to 1,800 to 3,600 mg per day taken in divided doses three times daily.	drowsiness, dizziness, fatigue, nausea, sedation, weight gain
Pregabalin	150 mg at bedtime	drowsiness, dizziness, fatigue, nausea, sedation, weight gain
Lamotrigine	50 mg per day; increase by 50 mg every 2 weeks up to 400 mg per day.	dizziness, constipation, nausea; rarely, life-threatening rashes

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