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ANTIDEPRESSANTS IN CHRONIC PAIN RELIEF- A REVIEW

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ABSTRACT: IASP (International Association for study of pain) defined pain as "an unpleasant, sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage". Chronic Pain can be more described as a disease rather than a symptom. Antidepressants are the drugs that can elevate the mood. Recent trials have elucidated that anti- depressants can be of worth in treating chronic pain conditions. However, the safe use of these drugs depends on upon the clinician or any other health professional and their ability to choose the right tolerated drug at safe doses. Any psychiatric comorbidity must be treated to avail best results with anti-depressant therapy.However, most of the trials focus upon only Tri-CyclicAntidepressants and Selective Serotonin Reuptake Inhibitors. Research into other novel Anti-depressant drugs may lead to best chances of recovery in patients with chronic pain.

Key words: Pain, Antidepressants, Tri Cyclic Antidepressants, Analgesic, Diabetic Neuropathy.

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Pain

IASP (International Association for study of pain) defined pain as "an unpleasant, sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"(Merskey H et al., 1994). Pain often is so subjective, however, that many physicians represent pain as whatever the patient says it is. The best care is achieved when the patient arrives first (Partners against Pain News., 2000).

Epidemiology

Fifty million Americans are partially or completely disabled because of pain (Joint Commission on Accreditation of Healthcare Organization., 2000). In one year, an estimated 25 million Americans have undergone acute pain due to injury or surgery, and one-third of Americans have experienced severe chronic pain at some point in their lives (Berry PH et al., 2006).

These numbers are expected to rise, as more Americans work past an age of 60 years and sustain into their 80's (Gallagher RM., 1999).Unfortunately, pain often remains ill-treated in hospitals, long-termfacilities, and the community. Seriously ill hospitalized patients have reported a 50% incidence of pain; 15% had extremely or moderately severe pain occurring at least 50% of the time, and 15% were dissatisfied with overall pain control (Desbiens NA et al., 1996).Approximately 20% of the adult European population have chronic pain (Breivik H et al., 2006).According to a study, the prevalence rate of chronic pain was 13% in India (Dureja GP et al., 2014).

Classification of Pain:

Pain is classified on basis of the following:

1. Pathophysiological Classification
2. Classification based upon the Pain duration
3. Etiological Classification
4. Anatomical Classification

Pathophysiological Classification:

There are two main types of pain according to the Pathophysiology:

1. Nociceptive Pain
2. Neuropathic Pain

Classification based upon the duration of Pain:

Based on the duration of the pain, Pain can be classified into:

1. Acute Pain
2. Chronic Pain
3. Episodic or recurrent Pain
4. Breakthrough Pain
5. Incident Pain
6. End of dose Pain

Etiological Classification:

This is little relevant to the mechanism and is categorized based on the underlying disease being malignant or non-malignant.

Anatomical Classification:

This is classified based upon the body location (e.g. head, back or neck) or the anatomic function of the affected tissue (e.g. myofascial, rheumatic, skeletal, neurological etc.) (WHO Guidelines on the pharmacological treatment of persisting pain in children with mental illness., 2012).

Pathophysiology of Pain:

The pathophysiology of pain involves a complex web of neural networks which are acted upon by afferent stimuli to produce the experience we know as pain. In acute pain, this modulation is short lived, but in some cases, this modulation persists and chronic pain develops (Loeser JD et al., 1999; Woolf CJ., 2004).

Nociceptive Pain:

Nociception can be subdivided in terms of:

- ❖ Stimulation
- ❖ Transmission
- ❖ Perception
- ❖ Modulation
- ❖ Adaptive inflammation

Stimulation

The first main step in the occurrence of thesensation of pain is the activation or sensitization of free nerve endings known as nociceptors by the mechanical, thermal and chemical impulses. The underlying mechanism in this process may be the release of bradykinins, prostaglandins, leukotrienes, substance P, potassium ions, and other allied substances. These chemicals sensitize the nociceptors and activate them. This further leads to propagation of action potentials along the afferent nerve fibers to the spinal cord.

Transmission

Nociceptive transmission occurs in large diameter, less myelinated Aδ fibers which give sharp, well-localized pain and in small diameter, unmyelinated C fibers which produce dull, aching, poorly localized pain. These afferent pain fibers connect in the laminae of spinal cord's dorsal horn and release diverse neurotransmitters like Substance P, Glutamate, and calcitonin gene-related peptide. A complex array of events occurs due to the interactions between these released neurotransmitters and the nociceptors. This complex array is the pathway for the pain initiation and transmission. This pain processes reaches the brain through at least five ascending spinal cord pathways including the spinothalamic tract. The thalamus acts as a booster station to pass the pain to the adjacent and central structures.

Pain perception

The brain can only lodge only a limited number of pain signals and these can be modified by cognitive and behavioral changes. Relaxation, distraction, and meditation can decrease the extent of pain whereas anxiety, depression can worsen the extent of pain.

Modulation

The body regulates pain through a number of complex processes. One of them is anendogenous opiate system which consists of neurotransmitters like enkephalins, dynorphins, β-endorphins and receptors throughout the central nervous system. Like exogenous opioids, these endogenous opioids also bind to opioid receptor sites and regulate the pain transmission. Other receptor types like NMDA (N- methyl D- aspartate) receptors found in the dorsal horn also influence the pain transmission. The central nervous system itself contains a highly organized descending system which inhibits the transmission of synaptic pain in thedorsal horn and controls the pain transmission. The neurotransmitters involved in this process include the endogenous opioids, serotonin, GABA (γ-amino butyric acid), norepinephrine and neurotensin (Pasero C et al., 1999).

Adaptive inflammation:

Inflammation occurs to reduce the threshold of pain and to promote the progression of healing of the injury. When this prolongs it may lead to maladaptive inflammation like in chronic diseases like rheumatoid arthritis. In response to tissue damage and inflammation, a significant alteration of neurons occurs which result in alteration of phenotypes of proteins thereby changing their transmission and transduction properties. An increase in excitability or responsiveness of neurons within the CNS may occur which is prominently referred to as central sensitization (McPherson ML., 2005).

Neuropathic Pain:

Neuropathic Pain is a result of nerve damage and is often under recognized and difficult to treat. Examples of neuropathic pain syndromes include Post herpetic neuralgia, Diabetic nephropathy etc. The mechanisms involved in neuropathic pain include ectopic excitability, enhanced sensory transmission, nerve structure reorganization and loss of modulatory pain inhibition. Pain circuits rewire themselves producing spontaneous nerve stimulation, autonomic neuronal pain stimulation and a progressive increase in the discharge of dorsal horn neurons. The changes in clinical presentation of patients over time help to find out the type of pain and nerve-related damage (Elliot KJ., 1994).

Clinical Presentation of Pain:

- In the case of acute pain, there is an obvious distress, whereas in chronic pain there is no noticeable distress (Twycross RG., 1978).
- General signs include Hypertension, Tachycardia, Diaphoresis, Mydriasis, and Pallor, but these signs are not diagnostic.
- Pain is always subjective and is best diagnosed by the patient description and history (American Pain Society., 2003).

Diagnostic scales:

These are also known as Pain Assessment tools. The National Initiative on Pain Control (NIPC) has provided several types of diagnostic tools or scales in order to estimate the severity and the type of pain experienced by the patients. Various Pain Assessment Scales include:

- Wong- Baker FACES Pain Rating Scale
- 0-10 Numeric Pain Rating Scale (McCaffery M et al., 1999)
- Pain Quality Assessment Scale (PQAS)
- Minnesota Multiphasic Personality Inventory (MMPI-2) data (Carlson C., 1997)

- Graphic Rating Scales
- Verbal Rating Scales
- Verbal Descriptor Scales
- Body Diagrams
- Computer Graphic Scales
- Picture Scales
- Coin Scales
- McGill Pain Questionnaire
- Brief Pain Inventory
- Behavioral Pain Scales
- Pain / Comfort Journal
- Multidimensional Pain Inventory
- Pain Information and Beliefs Questionnaire
- Pain and Impairment Relationship Scale
- Pain Cognition Questionnaire
- Pain Beliefs and Perceptions Inventory
- Coping Strategies Questionnaire
- Pain disability index
- Leeds assessment of Neuropathic Symptoms and Signs (Assessment of Pain from Nursing times., 2008)

Figure -1: Wong-BakerFACES Pain Rating Scale (Wong-Baker FACES Foundation., 1983).

Pain Management: The WHO devised a three-step ladder in an attempt to improve the worldwide management of pain.

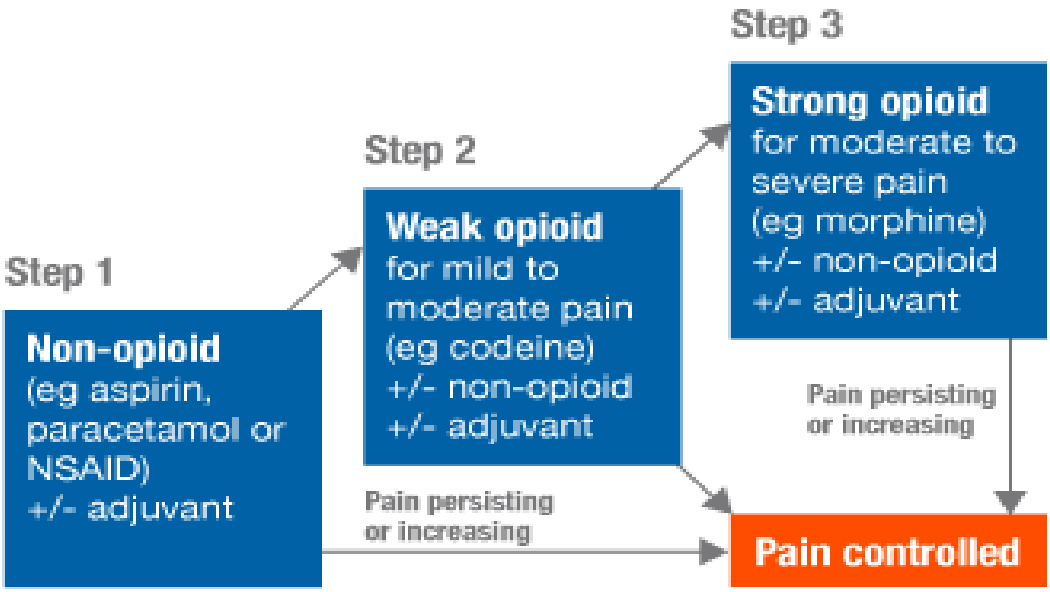

Figure-2: Pain Management (WHO Pain Relief Ladder) (Max MB, Lynch SA. (1992).

Anti- Depressants

These are the drugs that can elevate the mood in depressive illness. Normally, Antidepressants act on monoaminergic transmission in the brain.

Classification

1. Tricyclic and tetracyclic antidepressants:
   E.g. Imipramine, amitriptyline, clomipramine, Desipramine, Nortriptyline, Amoxpine, Protriptyline, Trimipramine, Maprotiline
2. Enzyme inhibition

a) Irreversible and nonselective classical MAO inhibitor
   E.g. Isocarboxazid, phenelzine, tranylcypromine

b) Reversible inhibitor of MAO-A (RIMA)
   E.g. Moclobemide

3. Serotonin selective reuptake inhibitors (SSRIs)
   E.g. Citalopram, Escitalopram, Fluvoxamine, Fluoxetine, paroxetine, Sertraline
4. Dual serotonin and norepinephrine reuptake inhibitors (SNRIs)
   E.g. Duloxetine, venlafaxine
5. Serotonin-2 antagonist and reuptake inhibitors (SARIs)
   E.g. Nefazodone, Trazadone
6. Noradrenergic and specific serotonergic antidepressant (NaSSA)
   E.g. Mirtazapine
7. Norepinephrine and dopamine reuptake inhibitor (NDRI)
   E.g. Bupropion
8. Noradrenaline reuptake inhibitors
   E.g. Reboxetine (Chan HN et al., 2009)

Evidence for the efficacy of Antidepressants in Chronic Pain:

Several open labelled studies, meta-analysis, randomised controlled trials and systemic reviews have proved as a valuable evidence for the efficacious treatment of chronic pain by anti-depressants.

Tri-Cyclic Anti- Depressants:

Corroborations gathered over several years suggest that Tri-Cyclic Anti- Depressants are gold standard Anti-Depressants for the treatment of persistent neuropathic pain (Bryson HM et al., 1996).These are most effective analgesics due to calcium antagonism property. Mostly used Anti-Depressants include Amitriptyline, Desipramine, and Imipramine etc. Evidence proves that Tri-Cyclic Anti- Depressants exhibit analgesic properties in conditions like Diabetic Nephropathy, Post herpetic Neuralgia, Post-Stroke pain, Tension-type of headache, Migraine, and Chronic Oral Facial Pain. The analgesic effect of Tri-Cyclic Anti- Depressants was pronounced in the absence of depression and at doses lower than those used for depression. The analgesic effect has an earlier onset of effect than that required for an anti-depressant effect. Tri-Cyclic Anti-Depressants relieves brief lacunating pain as well as steady constant pain (Mc Quay HJ et al., 1996).Tomkins et al. recently performed a meta-analysis by incorporating studies in all classes of anti- depressants in a migraine and tension-type headaches. He evaluated almost 19 Tri-Cyclic Anti- Depressants and recommended Amitriptyline as level 1 drug with a therapeutic dosage ranging from 30-150 mg/day (Tomkins GE et al., 2001).Tri-Cyclic Anti- Depressants may cause ocular glaucoma or incomplete bladder occlusion in predisposed patients and has less cardiovascular tolerability. Other potential side effects of these drugs include: sedation, drowsiness, and orthostatic hypotension (Colombo B et al., 2004).

Enzyme Inhibitors:

Classical Mono Amino Oxidase Inhibitors inhibit Mono Amino Oxidase type A and type B irreversibly but are infrequently used due to their extensive side effects and need for dietary restrictions (Chan HN et al., 2009).In a controlled trial involving 40 patients with atypical facial pain and depression, 45 mg of phenelzine led to significant improvement in the treatment of pain as well as depression (Lascelles RG., 1966).Moclobemide is a reversible inhibitor of Mono Amino Oxidase and is a safer alternative, but its use in treating chronic pain still remains limited. Adverse effects of Enzyme inhibitors range from headaches, dizziness, blurred vision, weight gain, weakness and sexual dysfunction (Chan HN et al., 2009).The dietary restrictions and variable drug interactions along with the substantial side effects limit the use of enzyme inhibitors as analgesics.

Selective Serotonin Reuptake Inhibitors:

Selective Serotonin Reuptake inhibitors wield their therapeutic effect by inhibiting the reuptake of serotonin. These drugs have milder side effect profile and are safer in overdoses when compared with Tri-Cyclic Anti-Depressants (Chan HN et al., 2009).Selective Serotonin Reuptake inhibitors are better tolerated but are inferior to Tri-Cyclic Anti-Depressants in controlling persistent pain occurred due to diabetic nephropathy and fibromyalgia. Five randomised controlled trials have proved that Selective Serotonin Reuptake Inhibitors are more efficacious than placebo in chronic pain conditions (Max MB et al., 1992).In fibromyalgia condition, Fluoxetine showed ahigher response to treatment of chronic pain when compared to Citalopram and Paroxetine. There is no evidence of theuse of these drugs in Rheumatoid and Osteo Arthritis (Perrot S et al., 2008).There is no proven analgesic effect of these drugs in low back pain (Wernicke JF et al., 2006).But there is an evidence of possible improvement in the well-being of patients with Irritable Bowel Syndrome (Creed F., 2006).Side effect profile includes Nausea, Vomiting, Diarrhoea and Sexual dysfunction. The use of Selective Serotonin Reuptake Inhibitors with Mono Amino Oxidase Inhibitors is contraindicated due to the risk of occurrence of serotonin syndrome (Chan HN et al., 2009).

Serotonin and Norepinephrine Reuptake Inhibitors:

Venlafaxine is one of the most investigated anti-depressants in pain management. It is effective in peripheral diabetic neuropathy and similar to the Tri-Cyclic Anti- Depressants in thecase of neuropathic pain with an added advantage of lesser intolerable side effects. It is considered as a second-line therapy after failure of all other therapies in pain management (Lithner F., 2000).Duloxetine and Milnacipran are found to have similar effects in the treatment of Fibromyalgia. In a 12 week randomized, double-blinded, placebo controlled trial; Duloxetine showed a significant reduction in pain scores (Arnold LM et al.,2004).There is no published evidence for the use of Serotonin and Norepinephrine Reuptake Inhibitors in thecase of Low Back Pain. However, Venlafaxine is effective and well tolerated in treating migraine condition (Ozyalcin SN et al., 2005).These drugs have a similar side effect profile consisting of dry mouth, dizziness, headaches, sexual dysfunction etc. and minimal drug interactions. But these drugs shouldn't be used in combination with Mono Amino Oxidase Inhibitors due to the risk of Serotonin syndrome (Chan HN et al., 2009).

Serotonin-2 Antagonist and Reuptake Inhibitors:

These drugs antagonise postsynaptic 5-HT-2 (5- Hydroxy Tryptamine-2) and inhibit the reuptake of serotonin. Trazadone is found to be ineffective in decreasing chronic low back pain based on a double blinded placebo controlled study conducted in 2006. Nefazodone is only tested on animals and is shown to produce analgesia. But it is not recommended because of its high risk of potential hepatotoxicity (Pick CG et al., 1992).

Common side effects of these drugs include Nausea, Headache, Dry mouth and Orthostasis. Rare cases of Priapism have been reported. These drugs should be prescribed with caution in patients with cardiac abnormalities. Trazadone was issued a black box warning by FDA (Food and Drug Administration) in 2002 as it is associated with liver failure (Chan HN et al., 2009).

Noradrenergic and Specific Serotonergic Anti-Depressants:

These drugs block the presynaptic Alpha-2 Adrenergic receptors thereby, increasing the levels of both norepinephrine and serotonin at the synapse (Chan HN et al., 2009).Mianserin is found to increase the anti-nociceptive effect of various analgesic agents in animal models. However, when a double-blinded, crossover study was performed in patients with diabetic neuropathy, the drug showed no analgesic effect. Similarly, Mirtazapine, an analogue of Mianserin, showed its effectiveness in a rat model of neuropathic pain but not efficacious in ahuman model of chronic pain with concurrent depression. At present, Mirtazapine is being evaluated for its efficacy in thetreatment of Fibromyalgia and chronic pain and is in Phase 4 Clinical trial (Freynhagen R et al., 2006).One randomised controlled trial with ashort duration of follow-up revealed that Mirtazapine has comparable effectiveness with Amitriptyline in treating chronic tension type of headaches. Another small placebo-controlled trial has found out that Mirtazapine significantly reduces the frequency, duration, and intensity ofa headache (Bendsten L et al., 2004).In another study, Mianserin showed asignificant effect in abdominal pain and Irritable Bowel Syndrome (Tanum L et al., 1996).General side effect profile of these drugs includes: over sedation, increased appetite with weight gain. It is generally safe in overdose and has minimal drug interactions (Chan HN et al., 2009).

Norepinephrine and Dopamine Reuptake Inhibitors:

These drugs predominantly block the reuptake of dopamine. Bupropion is the major drug and is also used in smoking cessation therapy as this is a weak norepinephrine and dopamine reuptake inhibitor (Chan HN et al., 2009).In a randomized, placebo-controlled trial conducted in patients with chronic low back pain, Bupropion showed no more effect than the placebo (Katz J et al., 2005).Bupropion has a low side effect profile with anabsence of sexual, cardiac and anticholinergic effects. However, high doses exceeding 450 mg per day may cause seizures (Chan HN et al., 2009).

CONCLUSION

Anti-depressants are becoming one of the best therapies used in relief of chronic pain. Recent trials have elucidated that anti- depressants can be of worth in treating chronic pain conditions. However, the safe use of these drugs depends on upon the clinician or any other health professional and their ability to choose the right tolerated drug at safe doses. Any psychiatric comorbidity must be treated to avail best results with anti-depressant therapy. Patients must also be educated by counselling on the safe use of these drugs. There are growing evidence and established guidelines for the treatment of chronic pain by anti-depressants. However, most of the trials focus upon only Tri-CyclicAntidepressants and Selective Serotonin Reuptake Inhibitors. Research into other novel Anti-depressant drugs may lead to best chances of recovery in patients with chronic pain.

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