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# ATYPICAL ANALGESICS IN CHRONIC PAIN MANAGEMENT

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**Abstract:** Chronic pain affects more than 15% of population and can be due to a variety of reasons such as osteoarthritis, cancer, degenerative diseases, or neuropathic mechanisms. Numerous mechanisms are involved in genesis of chronic pain like activation of NMDA receptors, the neurotransmitters substance P, neurokinin A and calcitonin gene related peptide, and other peptides such as nerve growth factor. Alterations in the pain inhibitory pathways such as decreased production of opioid peptides, decreased sensitivity of opioid receptors, and decreased activity of other inhibitory pathways such as GABA, serotonin, and nor epinephrine receptors also have significant contribution in chronic pain mechanism. Current treatment options for the management of pain include opioid analgesics like, morphine, hydromorphone, oxycodone and nonopioid analgesics like, acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs [NSAIDs]. But the management of chronic pain is different from routine pain management. The term '***atypical analgesic***', '***co analgesic***' or ***adjuvant analgesic*** describes any drug with a primary use other than pain, but due to its analgesic properties it can be use in some painful conditions. Although they can be used alone or co administered with analgesics NSAIDS or Opioids in chronic painful conditions.

**Keywords:** Chronic pain, Atypical analgesic, Opioids, Gabapentin

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**INTRODUCTION**

Chronic or persistent pain affects more than 15% of population and is major therapeutic challenge. For many patients pain produces severe distress, and disturbing their quality of life style. Chronic pain can be due to a variety of reasons such as osteoarthritis, cancer, degenerative

diseases, or neuropathic mechanisms .[1] Marked changes in the pain transmission pathways can occur via numerous mechanisms including, but not limited to: activation of NMDA receptors, the neurotransmitters substance P, neurokinin A and calcitonin gene related peptide, and other peptides such as nerve growth factor. [2] Additionally, alterations in the pain inhibitory pathways such as decreased production of opioid peptides, decreased sensitivity of opioid receptors, and decreased activity of other inhibitory pathways such as GABA, serotonin, and norepinephrine receptors.[3] Therefore the neurobiology of a chronic pain patient is much different and more complex than that of an acute pain patient.

Current treatment options for the management of pain include opioid analgesics like, morphine, hydromorphone, oxycodone and nonopioid analgesics like, acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs [NSAIDs]. Most NSAIDs are limited by a therapeutic ceiling and are appropriate for the relief of only mild to moderate pain. In addition, NSAIDs are contraindicated in patients with peptic ulcer disease, renal impairment, and any tendency for bleeding. Opioids are highly effective for acute and chronic pain, but their use is limited by nausea, vomiting, constipation, and sedation, as well as the possibility of addiction and dependence.

The term '***atypical analgesic***' describes any drug with a primary use other than pain, but due to its analgesic properties it can be use in some painful conditions.[4] Although they can be used alone or coadministered with analgesics NSAIDS or Opioids in chronic painful conditions. The term '***coanalgesic***' or ***adjuvant analgesic*** is sometimes used synonymously in this setting. Adjuvant analgesics are coadminstrated with opioid to enhance pain relief provided by the opioid, address pain that has not or has insufficiently responded, and allow the reduction of the opioid dose to reduce adverse effect balance between analgesia and side effects. Among these strategies is the use of atypical analgesics.

Atypical analgesics often are administered as first-line drugs in the treatment of chronic nonmalignant pain. In the cancer population, however, conventional practice has evolved to view opioids as first-line drugs, and atypical analgesics are considered after opioid therapy has been optimized. To better assess response and reduce the risk of additive toxicity, it usually is best to initiate treatment with one drug at a time.[5]

**ANTIDEPRESSANT DRUGS**

Antidepressants like ***Venlafaxine*** by virtue of their property of mood elevation due to increase in neurotransmitters carrying the pain sensation from nerve endings. It is also effective in chronic pain as an adjuvant drug treatment. Antidepressant acting through Inhibition of reuptake of monoamines leading to spinal inhibition of pain & might add a component of mood elevation to its analgesic effect thus making it a useful drug for patient with chronic pain.[6]

**Tricyclic antidepressants (Clomipramine, Amitriptyline).**

Tricyclic antidepressants (TCAs) have been used in the management of chronic pain in humans due to their activity as serotonin and norepinephrine reuptake inhibitors. Serotonin and norepinephrine act to modulate pain by enhancing the descending inhibitory pathways.[7] In humans, adverse effects are typically dose limiting, primarily due to their anticholinergic effects.

TCA's are a special type of medication that were among the first medications used to treat depression. It was discovered over time that TCA's were effective at helping control chronic pain. The types of pain that TCA's are most effective at controlling include migraine headache prevention, neuropathy (nerve pain), Fibromyalgia and several others.[8]

In summary, there is substantial evidence that antidepressant drugs have analgesic effects in diverse types of chronic nonmalignant pain. The sedating tricyclic antidepressants are often added when the patient complains of insomnia, the anxiolytic SSRIs can be useful in anxious patients[9], and bupropion[10] can be considered in sedated or fatigued patients**.**

**$\alpha_2$-ADRENERGIC AGONISTS**

Although clonidine and tizanidine are $\alpha_2$-adrenergic agonists and may be considered nonspecific multipurpose adjuvant analgesics, the supporting data are limited and the potential for side effects, most importantly somnolence and hypotension, is relatively great.

***Clonidine*** is a pain and blood pressure medication. It is a very unique drug. It was introduced and FDA approved as a blood pressure medication, but over time clonidine was found to block pain both at the peripheral nerves where the pain begins and also at the spinal cord where pain is transmitted. Clonidine also helps to relieve/prevent withdrawal symptoms from opioid/narcotic pain medications. Clonidine also has other potential uses including tremor and attention-deficit disorder, among others.[11]

***Tizanidine*** is approved as an antispasticity agent. Tizanidine is a medication that helps with muscle spasms and musculoskeletal pain syndromes; there is evidence that it helps in

neuropathic and musculoskeletal pain through alpha-2-receptor activity. Although the evidence of the analgesic efficacy of tizanidine is limited to the treatment of myofascial pain syndrome [12] and the prophylaxis of chronic daily headache a favorable clinical experience supports its use as a multipurpose adjuvant analgesic.

**ANTICONVULSANT DRUGS**

There is good evidence that the anticonvulsant drugs are useful in the management of neuropathic pain. The older drugs, which have been used for decades, are now complemented by a rapidly increasing number of newer agents. An expanding role for the anticonvulsants began with the introduction of gabapentin.

***Gabapentin*** in a γ-amino-butyric acid (GABA) analogue which may increase brain GABA concentrations in humans, but the precise mechanism of action has not been determined. Gabapentin does not appear to act directly on GABA receptors, but may increase GABA concentration by decreasing GABA metabolism, increase non-synaptic GABA release, or decrease reuptake. Gabapentin may also decrease the release of glutamate, a stimulatory neurotransmitter, in the spinal cord which may contribute to its analgesic effects. Gabapentin inhibits the voltage gated calcium channels in the spinal cord which may also contribute to its analgesic effects. Gabapentin is labeled for use in humans as an anticonvulsant and for the management of neuropathic pain .[13] Studies in humans have demonstrated variable efficacy of gabapentin for chronic and cancer pain. Gabapentin exhibits additive to synergistic effects when combined with tramadol in humans and rodents. Adverse effects in humans include sedation, ataxia, fatigue, tremors, and rebound seizures upon discontinuation of therapy. Gabapentin can be combined with NSAIDs, tramadol, and amantadine for the management of pain.

The analgesic efficacy of gabapentin has been established in several types of nonmalignant neuropathic pain and it is now widely used to treat cancer-related neuropathic pain ***Lamotrigine*** a new antiepileptic drug, has analgesic properties due to it stabilizes neural membrane through blocking the activation of voltage-sensitive sodium channel & inhibits presynaptic release of glutamate. It may prevent postoperative pain, neuropathic pain, neuralgia etc.[14]

***Oxcarbazepine*** is ketone derivative of carbamazepine has analgesic activity by inhibiting sodium channels, inhibition of high –threshold calcium channels, enhancement of potassium rectifiers currents and reduce glutaminergic transmission[15].

***Pregabalin*** is a medication used to treat pain and seizures. It is FDA approved for fibromyalgia pain, two types of neuropathic pain (diabetic neuropathy and post-shingles) and certain types

of seizures. Although the exact mechanism of action is unknown, the medication works on a specific sub unit of nerve calcium channels; this helps reduce pain and blocks seizures.

**_N_-METHYL-D-ASPARTATE RECEPTOR BLOCKERS**

Glutamate (Glu) is a major excitatory neurotransmitter in the mammalian central nervous system, acting both at ligand-gated (ionotropic) ion channels and G-protein-coupled metabotropic receptors. Ionotropic receptors are subdivided into NMDA (glutamine-N-methyl-Daspartic acid) and non-NMDA [á-amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid] receptors. However, only NMDA receptors are found within trigeminal ganglion cell.[16]

At the present time commercially available NMDA receptor antagonists in the .—the antitussive, ***dextromethorphan***; the dissociative anesthetic, ***ketamine***; the antiviral drug, ***amantadine*** and a drug approved for the treatment of Alzheimer's disease, ***memantine.***.

***Memantine*** is a non-competitive NMDA receptor antagonist that exhibits fast blocking and unblocking kinetics, and is more effective and better tolerated than other high affinity NMDA antagonists like ketamine and amantadine. It decreases the firing rate of neurons and works on central pain mechanisms.

***Ketamine***

Ketamine is a parenteral anesthetic agent that provides analgesic activity at sub-anesthetic doses. It is an N-methyl-D-aspartate (NMDA) receptor antagonist with opioid receptor activity. Use of this drug by the oral, intranasal, transdermal, rectal, and subcutaneous routes has been reported with analgesic efficacy in treating nociceptive and neuropathic pain. [17]

***Dextromethorphan*** In patients undergoing surgery for bone malignancy, dextromethorphan was shown to augment analgesia and lessen analgesic requirements .[18]

***Amantadine*** was originally introduced as an antiviral drug. However, it may be effective in treating chronic pain and as an adjunct in acute pain due to its activity as an n-methyl-daspartate (NMDA) receptor antagonist. Another effect of amantadine is as a dopamine agonist.

As an NMDA antagonist, amantadine's primary action is to decrease central sensitization (windup pain) and does not typically provide analgesia as a stand-alone treatment. Therefore amantadine is often used in combination with analgesics such as NSAIDs or opioids. Amantadine is a noncompetitive NMDA antagonist it might reduce pain, allodynia, and hyperalgesia in chronic neuropathic pain and surgical neuropathic cancer pain .[19]

The d-isomer of the opioid ***methadone*** also blocks the NMDA receptor. In the U.S., methadone is available as the racaemic mixture, 50% of which is the d-isomer. The contribution of this non-opioid molecule to the analgesia produced by methadone is uncertain, but growing clinical experience with this drug suggests that it may play a role.[20] There are no data, however, to support the conclusion that methadone is better than other opioids for the treatment of neuropathic pain.

**N-TYPE VOLTAGE SENSITIVE CALCIUM CHANNEL BLOCKERS**

Calcium channels are located at the presynaptic termini of neurons, where they are directly involved in the regulation of neurotransmitter release. Of particular interest, the transmission of pain signals from periphery to the central nervous system is mediated by N-type channels located at primary afferent terminals in the dorsal horn of the spinal cord. Over the last decade, synthetic efforts have focused on development of both peptidic and non-peptidic based small molecule N-type calcium channel blockers for analgesia or neuroprotection.

The therapeutic agents ***flunarizine*** [21]***, lomerizine*** [22] and ***ziconotide*** [23] exhibit inhibitory activities against a variety of ion channels and neurotransmitter receptors. We have optimized their scaffolds to obtain more selective N-type calcium channel blockers.

N-Type VSCCs [voltage sensitive calcium channels] produces analgesia in neuropathic, inflammatory, incisional pain, and other pain states that involve central (spinal) sensitization like allodynia, both primary and secondary hyperalgesia, and pain induced by mechanical, thermal, and noxious chemical stimuli. Clinical investigations have demonstrated that intrathecal and epidural injection produces analgesia in patients suffering from intractable neuropathic pain, cancer, and postoperative pain.

**NEUROLEPTICS**

In 1949, Laborit and Huygenard introduced the concept of an anesthetic technique that blocked not only cerebrocortical responses but also some cellular, endocrine, and autonomic mechanisms usually activated by surgical stimulation. This state was called "***ganglioplegia***" or "***neuroplegia***" (artificial hibernation). Neuroleptanalgesia is characterized by analgesia, absence of clinically apparent motor activity, suppression of autonomic reflexes, maintenance of cardiovascular stability, and amnesia in most, but not all, patients. The addition of an inhalation agent, usually $N_2O$, improves amnesia and has been called neuroleptanesthesia.

"Neuroleptic" drugs traditionally include the phenothiazines (e.g., chlorpromazine) and the butyrophenones (e.g., haloperidol and droperidol). Droperidol can also cause hypotension, but it is usually less severe and transient. The commercial preparation of droperidol-fentanyl (Innovar) is frequently the principal component of neuroleptic analgesic.[24]

The second-generation (atypical) agent ***olanzapine*** was reported to decrease pain intensity and opioid consumption, and improve cognitive function and anxiety, in a recent case series of cancer patients .[25]

**PSYCHOSTIMULANTS**

***(Methylphenidate, Amphetamine,Dextroamphetamine, Modafinil )***Stimulants are a group of medications used to treat a wide variety of disorders. They are FDA approved for the treatment of Attention Defecit Hyperactivity Disorder and narcolepsy (sudden and uncontrollable attacks of drowsiness and sleepiness). It is also used off label by providers to treat daytime drowsiness caused by shift-work or to fight the side effects of medications that cause drowsiness. One of the side effects of stimulants is weight loss and it can be used specifically for that side effects.

There is substantial evidence that psychostimulant drugs dextroamphetamine, methylphenidate and caffeine have analgesic effects.[26] although pain is not considered a primary indication for these drugs, the potential for analgesic effects may influence the decision to recommend a trial. In cancer patients, methylphenidate can reduce opioid-induced somnolence, improve cognition, treat depression, and alleviate fatigue.[27]

Modafinil, a newer psychostimulant with a unique mechanism, is also used to reduce opioid-induced somnolence in cancer patients.[28]

**CORTICOSTEROIDS**

Steroids are particularly useful as adjuvant therapy for metastatic bone pain[29], neuropathic pain, and visceral pain. As adjuvant agents, corticosteroids can directly reduce pain, reduce pain in concert with opioid use, allow for reduction of opioid dose, and have beneficial symptomatic effects outside of pain relief.

Glucocorticoids reduce pain by inhibiting prostaglandin synthesis, which leads to inflammation, and reducing vascular permeability that results in tissue edema. Glucocorticoids are also lipophilic molecules that can cross the blood-brain barrier. Research has shown that steroid receptors are found in the central and peripheral nervous systems and are responsible for growth, differentiation, development, and plasticity of neurons. In particular, corticosteroids have been shown to reduce spontaneous discharge in an injured nerve, which reduces neuropathic pain.[30]

Dexamethasone is the most commonly prescribed corticosteroid for pain, but prednisone or prednisolone can also be used. An advantage of prednisolone is that the side effect of myopathy is less common. Dexamethasone causes less fluid retention than other steroids owing to the fact that it has less mineral corticoid effect. It is also relatively more potent and,

owing to dexamethasone's longer half-life, it can be taken once daily. The most appropriate dose of dexamethasone has not been determined, but a range of 2 to 8 mg orally or subcutaneously once to 3 times daily is generally accepted .[31]

**HISTAMINE BLOCKERS**

Histaminergic mechanisms are known to be involved in the initiation, perception and also in the modulation of pain sensation. Histamine stimulates the cutaneous branch of the sensory nerve fibre and sends pain impulses to the central nervous system. [32] In the peripheral neurons the receptors for histamine are generally of H1 type. Substance P released from the peripheral nerve endings acts as a stimulus for histamine release by interacting with mast cell receptors to induce degranulation. The liberated histamine evokes a variety of responses including antidromic, vasodilatation, neurogenic plasma extravasation, reactive hyperemia and sensitizes the sensory nerve ending producing pain. Thus histamine released in the nerve endings evokes itch in the epidermis and pain in the dermis. Histaminergic mechanisms are also known to be involved in the modulation of pain sensation in the CNS. Hough (1988), has described that central histaminergic mechanisms involving both H1 and H2 receptors may be involved in the perception of pain.[33]

Cimetidine provided the dramatic relief of pain and erythema and was also found to be effective for rapid pain relief and prevention of post herpetic neuralgia in herpes zoster infection and effective in relieving neuralgic and neuropathic pain.[34]

**GABA-B RECEPTOR AGONIST**

***Baclofen***

It is an agonist at the gamma aminobutyric acid type B (GABA-B) receptor, has established efficacy in trigeminal neuralgia and is often considered for trial in any type of neuropathic pain.

Baclofen is a pain and muscle medication that helps with muscle spasms, cramps and abnormally increased tone. Originally, an anti-spasticity medication, it is frequently used in headache prevention and treatment, especially when the headaches are associated with neck muscle tightness or neck pain. Baclofen is used in pill form and in liquid form for implanted spinal pumps. Baclofen works in the spinal cord and cerebellum. In the spinal cord, baclofen blocks some of the signals that go to the muscles, making the muscles contract somewhat less, relieving spasms and cramps. Baclofen also may interfere with substance P, a pain-transmitting chemical in the spinal cord .[35]

**CANNABINOIDS**

cannabinoid receptors has been documented – CB1 (predominantly expressed by central and peripheral nervous system neurones) and CB2 (expressed by immune cells, including glia). Agonists at these receptors (cannabinoids) possess a wide range of pharmacological properties, including effects on immunomodulation, appetite, memory, body temperature regulation and pain .[36]

A framework of cannabinoid analgesia has been identified at brain, spinal cord and peripheral levels and both CB1 and CB2 are implicated. They are mainly present on the spinal cord and periphery, as this is the most plausible strategy for developing therapeutic cannabinoids with an acceptable therapeutic index, but it is emphasized that these sites cannot be seen in isolation – for instance brain stem CB1 receptors are involved in the descending control of spinal nociceptive traffic.

**BENZODIAZEPINES**

Analgesic effects from benzodiazepines is limited and provides little support for the conclusion that these drugs are analgesic for neuropathic pain. [37] Nonetheless, a trial of clonazepam can still be justified in refractory neuropathic pain on the basis of anecdotal experience, especially in the case of the common coexistence of pain and anxiety.[38]

If a muscle spasm is present and is believed to be responsible for the pain, drugs with established effects on skeletal muscle should be tried in place of the muscle relaxants these include diazepam or other benzodiazepines.

**ANTICHOLINERGIC DRUGS**

Anticholinergic drugs could theoretically relieve the symptoms of bowel obstruction by reducing propulsive and nonpropulsive gut motility and decreasing intraluminal secretions. Two small series demonstrated that a continuous infusion of hyoscine butylbromide (scopolamine) at a dose of 60 mg daily can control symptoms from nonoperable malignant bowel obstruction, including pain.[39] Glycopyrrolate has a pharmacological profile similar to that of hyoscine butylbromide, but may produce fewer side effects because of a relatively low penetration through the blood-brain barrier; this drug, however, has not been systematically evaluated in a population with symptomatic bowel obstruction.

**TOPICAL ANALGESICS**

***Lidocaine patch***

Lidocaine is a local anesthetic that can be used in a variety of ways. It is used in injectable form for pain relief during minor surgical procedures. It can be applied to the skin in the form of skins, gels and patches. It blocks pain by inhibiting the chemicals in the nerve so they cannot transmit pain impulses. The lidocaine patch is currently FDA approved for the treatment of post-herpetic neuralgia.[40] It may be used of label for treatment of other pain conditions.

***EMLA***, an eutectic mixture of local anesthetics (prilocaine and lidocaine), can produce dense local cutaneous anesthesia, which can be useful to prevent pain from needle punctures. Although it may be applied to larger areas for the treatment of neuropathic pain, its use typically is limited by cost.

***Capsaicin*** is the ingredient in chili pepper that produces its pungent taste. When applied topically, it causes the depolarization of the nociceptors and release of substance P. Regular use eventually leads to depletion of substance P from the terminals of afferent C-fibers, potentially leading to decreased pain perception. In cancer patients, capsaicin cream has been shown to be effective in reducing neuropathic postsurgical pain (such as postmastectomy pain).[41]

**CALCITONIN**

Calcitonin improved analgesic properties. The analgesic activity of calcitonin is both relatively rapid in onset and sustained, which appears to be independent of its action on bone .Clinical studies have also confirmed this, particularly in patients with osteoporosis, and also in Paget's disease and in cancer-related bone pain . [42] Extra-skeletal pain like, post-surgical pain, early phantom limb pain, trigeminal neuralgia and migraine, have also been found to respond to calcitonin treatment. The management of musculoskeletal pain with calcitonin in patients with metabolic bone diseases, especially in the osteoporotic ones, combines the anti-resorptive effect of calcitonin with analgesia.

Clinical observation that the analgesic effect of calcitonin lasts longer than its hypocalcemic effect, suggested that a different mechanism might be responsible, and these include both central and peripheral mechanisms: interaction with the serotoninergic and catecholaminergic systems, an effect on specific central nervous system (CNS) receptors (central), increased ß-endorphin release, inhibition of prostaglandin and other inflammation mediator synthesis (peripheral), and calcium flux modulation (central or peripheral). The possibility of a direct action on calcitonin receptors in the central neural system seems to be an attractive hypothesis.

**BISPHOSPHONATES**

Bisphosphonates are analogues of inorganic pyrophosphate that inhibit osteoclast activity and, consequently, reduce bone resorption in a variety of illnesses. ***Pamidronate*** has analgesic effects have been shown in breast cancer and multiple myeloma.[43]

**Zoledronic acid** is a new bisphosphonate that is approximately two to three times more potent than pamidronate. It has been shown to reduce pain and the occurrence of skeletal-related events in breast cancer, prostate cancer , and multiple myeloma, as well as a variety of solid tumors, including lung cancer . It is effective in both osteoblastic and osteolytic lesions. [44] Data on the analgesic effect of ***Clodronate*** are conflicting, but it has been shown to be effective in prostate cancer and multiple myeloma . The main advantage of clodronate over pamidronate is its good oral bioavailability.

**RADIOPHARMACEUTICALS**

***Radionuclides*** that are absorbed at areas of high bone turnover have been evaluated as potential therapies for metastatic bone disease. ***Strontium-89*** [45] and ***Samarium-153***[46], which are commercially available in the U.S., may be effective as monotherapy or as an adjunct to conventional radiation therapy . Given the potential for myelosuppression associated with their use, these drugs usually are considered when pain is refractory to other modalities.

**BOTUTINUM TOXIN TYPE A (BOTOX)**

Botox has been used for painful disorders associated with muscular contraction (e.g., cervical dystonia and facial spasticity) and glandular secretion (hyperhidrosis) . Acute and chronic pain syndromes are frequently associated with muscle spasm, and pre-clinical evidence using the rat formalin pain model supports the antinociceptive potential of Botox. Botox injected into the same site as formalin (subplantar surface) inhibited formalin-induced glutamate release from sensory neurons and reduced the expression of Fos-like immunoreactive cells in the dorsal horn . Botox reduced the release of substance P, calcitonin gene-related protein, and vanilloid receptors (such as $TRPV_1$).[47] In a case report, Botox injections into the trigger zone of individuals with trigeminal neuralgia reduce pain.[48]

**OCTREOTIDE**

The somatostatin analogue octreotide inhibits the secretion of gastric, pancreatic, and intestinal secretions, and reduces gastrointestinal motility. These actions, which can occur more rapidly than similar effects produced by anticholinergic drugs , probably underlie the analgesia and other favorable outcomes that have been reported in case series [49] and one randomized trial[50] in patients with bowel obstruction. Octreotide has a good safety profile, and its

considerable expense may be offset in some situations by the avoidance of gastrointestinal drainage procedures.

**CONCLUSION:**

Our article gives an overall idea about atypical analgesics including newer drugs. It will help budding researchers for future study of newer drugs that are under pipeline.

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