Treatment of Chronic Pain

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The International Association for Study of Pain defines it as “an unpleasant sensory and emotional experience associated with or resembling that associated with, actual or potential tissue damage” .

opioids psilocybin cannabidiol

1. The Ladder of Treatment for Chronic Pain

The World Health Organization (WHO) has developed an analgesic ladder with several steps to guide healthcare providers in treating patients with chronic pain [1]. The first step is using nonopioid analgesics such as NSAIDs, which reduce inflammation by inhibiting COX-1 and COX-2. COX-2 is chiefly responsible for inflammation and is thus the target of NSAIDs in pain relief. These must be prescribed with caution in large doses due to side effects, such as gastrointestinal ulcers. Selective COX-2 inhibitors such as celecoxib reduce the risk of the adverse effect of ulcers but may lead to increased incidence of thrombotic cardiovascular events [1].

The second step is using weak opioids, such as codeine, tramadol, and dihydrocodeine. These medications reduce chemicals that activate opioid receptors in the CNS and reduce the transmission of nociceptive signals. It should be noted that even “weak” opioids have the same side effect profile as more potent opioids and have not been shown to have a decreased risk of addiction when compared to their more potent counterparts [2].

The third step is the use of stronger opioids, such as hydrocodone. They activate G-protein-coupled opioid receptors, which promote K^+ entry and inhibit Ca^{2+} entry into the nerve cell. The side effect profile is more pronounced than in weak opioids. Respiratory depression, for instance, can be fatal even at therapeutic doses. Care must be taken to ensure the patient begins on a low dose. The higher the dose, the better the pain control, so the dose can be increased to combat tolerance and improve pain control. However, the side effects become more severe at higher doses. Reviews have shown short-term efficacy in musculoskeletal and neuropathic pain conditions, but use for periods lasting longer than six months is not recommended [1].

2. Side Effects of Opioids

Opioids are effective in the treatment of chronic pain; however, they are also associated with numerous side effects. There was an increased risk of experiencing adverse events with opioids than with placebo (relative risk = 1.42). These adverse events included constipation, dizziness, drowsiness, fatigue, hot flushes, diaphoresis,

nausea, vomiting, and pruritis. The study also demonstrated a 42% higher risk of adverse events and 175% increased risk of serious adverse events associated with opioids when compared to placebo [3]. Due to selective pain sensitization, long-term opioid use is also linked to opioid-induced hyperalgesia. This implies that opioids may intensify central sensitization (CS) by activating pronociceptive pathways [4]. CS is discussed in the next section.

Opioids have been shown to alter sleep regulation leading to sleep apnea and poor sleep quality. Furthermore, respiratory depression is associated with sleep-disordered breathing and may result in death since this can happen in opioid use. These agents have also been linked to depressive and anxiety disorders as well as sexual dysfunction. In addition, there is an increased risk of addiction to opioids with increasing dosages. Related to the side effect profile and risk of addiction and death, long-term use of opioids may only be recommended for a small subset of people living with chronic non-cancer pain [3]. This leads to a gap in the treatment of chronic pain if opioids are left out of the equation.

3. Central Sensitization Treatments

CS is a pain mechanism that amplifies signaling within the central nervous system, leading to pain hypersensitivity. This mechanism contributes to an augmented response to several types of stimuli such as mechanical pressure, chemicals, sound, and temperature. Drugs such as acetaminophen act centrally and thus may be used to treat CS pain in diseases, e.g., fibromyalgia, which is due to central pain processing abnormalities. SNRIs such as duloxetine have also shown promise in treating fibromyalgia and osteoarthritis. This may be due to a resulting decrease in CNS hyperexcitability; however, the actual mechanism is unclear [4].

Several other drug classes directly target the central nervous system and are recommended to treat CS pain. A new class of drugs known as the mu-opioid receptor agonist and norepinephrine reuptake inhibitor (MOR-NRI) has analgesic effects explained by a synergistic interaction between stimulation of the MOR and inhibition arising from norepinephrine reuptake inhibition. N-methyl-D-aspartate (NMDA) receptor antagonists have demonstrated effective analgesia by blocking neuronal excitation produced by NMDA receptor stimulation, which may block hyperalgesia. GABA agonists such as pregabalin work by binding to Ca^{2+} channels and blocking Ca^{2+} influx during depolarization, resulting in a reduction in glutamate, norepinephrine, and substance P release [4].

4. Multimodal Treatments

Another consideration in the treatment of chronic pain is combination drug therapy. This combination of drug therapies is known as multimodal treatments. Because pain has several mechanisms, prescribing different drugs that target each of those mechanisms is a possible strategy. Most pharmacologic agents alone provide a positive response in some people but since pain can be caused by many different mechanisms, a single agent may not completely target the cause of the pain or only partially relieve the pain. Therefore, combinations of drugs provide additive and/or synergistic effects to improve pain by targeting different mechanisms [5].

Combination drug therapy shows promise for numerous pain conditions, particularly neuropathic pain. For example, when gabapentenoids and tricyclic antidepressants are used in combination, they are more efficacious in the treatment of diabetic peripheral neuropathy and postherpetic neuralgia than with either drug alone [5]. Chronic low back pain is another condition that may benefit from combination drug therapy due to the presence of both neuropathic and nociceptive pain mechanisms. The Multimodal treatment model of chronic pain treatment also includes non-pharmacologic interventions as well. This can include both physical and occupational therapy. It can also include psychological interventions such as cognitive-behavioral therapy, yoga, or tai chi [6]. The addition of these treatments help address other factors that may be making the pain be perceived as more painful due to psychological factors such as depression or stress.

5. Alternative Medications

As the search for adequate chronic pain management continues, neuroactive substances such as some plant-based past drugs of abuse have been called into question as possible treatments for chronic pain. These drugs had previously been stigmatized for their abusive properties that cause hallucinogenic episodes. However, as the field of neuroplasticity has expanded, recent studies on alternative, plant-based drugs have revealed possible psychoplasmic capabilities that can lead to relief from chronic pain.

Compounds such as lysergic acid diethylamide (LSD) and 4-phosphorloxy-N, N-dimethyltryptamine (psilocybin) are serotonergic hallucinogens that are beginning to emerge as a promising target. These chemical compounds have been known to act on the serotonergic 5-HT_{2A} receptors. They play a role in learning, memory, hallucinations, and neurocognitive disorders. These activate many pathways which release oxytocin and acetylcholine [7]. Further investigation carried out by Ly et al. found that the neuronal remodeling is seen in these drugs through the activation of the 5-HT_{2A}, mTOR, and TrkB (tropomyosin receptor kinase B) receptors. mTOR activation is an important regulator of protein synthesis needed for neuronal growth [8][9]. TrkB receptors are linked to learning through long-term memory formation and plasticity in the hippocampus [10].

Alternative drugs, which have been used for other means, promise neuronal synaptic modulators. Ketamine is used for sedation maintenance and causes dissociative anesthesia. Ketamine is currently thought to preferentially block inhibitory GABAergic interneuron at the N-methyl-D-aspartate receptor (NMDAR). This blockage increases extracellular glutamate levels in the prefrontal cortex. It activates the release of BDNF (brain-derived neurotrophic factor), elongation factor 2 (eEF2), mTOR, and Glycogen synthase kinase-3 (GSK-3), which are key regulators of growth in the GABAergic neurons [11].

When looking at these electrophysiological changes in the brain, research groups have found that this drug administration causes broadband desynchronization and a disconnect in neurons in the sensorimotor cortex on EEG monitoring [12]. The results are an overall resetting due to decreased global activity and connectivity. This could perhaps lead to reset in the perception of pain or lead to a decrease in neuropathic pain.

Cannabidiol as a Possible Treatment

Related to the recent legalization of cannabis in several states in the United States, there has been growing interest in alternative therapies for chronic pain, including tetrahydrocannabinol (THC) and cannabidiol (CBD). Both THC and CBD come from the plant *Cannabis sativa*, with THC being the psychoactive component and CBD the non-psychoactive component. They both act on endocannabinoid receptors located in the brain [13]. THC has been associated with the high sensation that a person feels when consuming cannabis [14]. THC has also been associated with psychosis in some users. Studies suggest that smoking high potency marijuana (high in THC) every day could increase the chances of developing psychosis by nearly five times compared to those who have never used marijuana [15]. Research has suggested that CBD may have analgesic, anti-inflammatory, anticonvulsant, muscle relaxant, anxiolytic, and even antipsychotic activity [16].

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