



Summaries from the NFL/NFLPA Committee on Pain Management: 1) Alternatives to Opioids for Chronic Pain and 2) Cannabidiol and Cannabis

ALT-O: Alternatives to Opioids for Chronic Pain

Opioids are strong analgesics. Formerly known as narcotic analgesics, these are compounds similar to morphine. The primary reason why these are used is that pure agonists of this class do not have a ceiling effect, i.e. the higher the dose, the more analgesia provided. Unfortunately, this class of drugs suffers from high abuse potential, development of physical dependence and tolerance, and negative effect on performance. As the time the medication is used increases, tolerance leads to requiring higher doses to achieve the same level of pain relief.

However, there are safe and effective alternatives to opioid analgesics which should be preferentially used for chronic pain. Drug alternatives are salicylates, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, topical agents, antiepileptic drugs (AEDs), antidepressant-type medication, steroids, triptans and botulinum toxin (Botox) injections. All of these work through mechanisms that do not involve the endogenous opioid pathways. Non-drug treatments include transcutaneous electrical nerve stimulation (TENS), acupuncture, biofeedback, dry needling, and therapeutic massage.

Aspirin is the prototypic salicylate and is an NSAID. It is a cyclo-oxygenase inhibitor and thus works through a peripheral mechanism of action. Aspirin has a ceiling effect, as do the other NSAIDs, which means that higher doses above the recommended analgesic dosage do not confer any additional analgesic effect. Higher dosages will, however, increase the risk of side effects.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most-commonly used class of analgesics. The prototypic drug is ibuprofen (trade name Motrin). Others are indomethacin, naproxen, ketorolac (trade name Toradol), and celecoxib. They are especially useful for muscle and joint pain from conditions such as arthritis and post-concussion headache. In addition, NSAIDs also help lower fever and reduce swelling. Ketorolac is an especially-potent NSAID and is used to treat moderate to severe pain and inflammation. However, because of complications, including risks of bleeding and kidney issues, ketorolac is no longer routinely used to treat musculoskeletal (MSK) injuries in the NFL.

Several recent studies demonstrate the benefits of NSAIDs, and these studies suggest that opioids are no better than NSAIDs at reducing how much pain interferes with daily activities, such as working, walking or sleeping. Patients taking NSAIDs reported less pain than opioid users.

Acetaminophen is an effective analgesic for mild to moderate pain, including post-concussion headache. It is not an NSAID as it does not have anti-inflammatory properties. Its mechanism of action is complex. Like the NSAIDs, it works through the

cyclo-oxygenase pathway but is considered a weak agonist. It also involves the L-arginine/nitric oxide cannabinoid pathway. Like the NSAIDs, it also has an analgesic ceiling effect. Recent studies indicate that higher doses (1 gram no more than 4 times a day) are an effective alternative to opioids for MSK pain. A benefit of acetaminophen is that it will not irritate the stomach and intestinal lining. An important toxicity is that high dosage (> 4 grams/24 hours) can lead to severe hepatotoxicity, necessitating liver transplant. Because many lay users do not understand the ceiling effect, taking excessive doses is common. It is reported that 20% of liver transplants performed in the US are a result of acetaminophen overdose.

Lidocaine is a peripheral-acting anesthetic that is used systemically, locally and topically. Its mechanism of actions are inhibition of voltage-gated sodium channels and spinal cord dorsal horn neurons. Its use intravenously and as a regional anesthetic should be only done by properly-trained advanced medical providers, but lidocaine has been shown to be effective in severe pain, including with kidney stones. As a topical agent, it is used primarily for mild pain.

Topical Agents including capsaicin, and topical NSAIDs may be used to treat localized neuropathic pain, osteoarthritis, and localized MSK pain. Higher-dose capsaicin patches (8%) may require a prescription.

Anti-epilepsy drugs (AEDs) or also known as anticonvulsants, such as gabapentin, carbamazepine, and pregabalin are often prescribed for neuropathic pain. These are the AEDs that have the most evidence supporting their use for analgesia. Other agents in this group that also may be considered are phenobarbital, clonazepam, valproic acid, topiramate, and tiagabine.

Antidepressants may be used to treat nerve damage, arthritis, fibromyalgia, low back pain, and pelvic pain. Types of antidepressants include: tricyclic antidepressants (TCAs), such as amitriptyline; selective serotonin/norepinephrine reuptake inhibitors (SNRIs), such as duloxetine; and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine and sertraline. These agents have a slow onset of action and can take several weeks for clinically-relevant pain relief to develop.

Steroids (corticosteroids) are used to treat a variety of inflammatory diseases and conditions, such as arthritis, and can be administered topically (cream or ointment), orally, or by injection. For chronic conditions such as rheumatoid arthritis, oral steroids have been shown to effectively reduce pain. However, they are not as effective for localized joint or nerve pain. Corticosteroids tend to be used short-term. A common use is to treat flare-ups or episodes of acute pain associated with long-term conditions, such as osteoarthritis.

Triptans are serotonin or 5-hydroxytryptamine (5HT) antagonists, specifically 5HT_{1B} and 5HT_{1D} receptors. Drugs of this class are sumatriptan (trade name Imitrex), zolmitriptan, eletriptan, rizatriptan, almotriptan, frovatriptan and naratriptan. These drugs are used mainly for migraine and post-concussion headaches.

Nutritional supplements are often used to help treat pain. Chondroitin sulfate, glucosamine and bromelain are used for MSK pain. Whereas, 3-omega fatty acids, riboflavin and magnesium are used to reduce the frequency of post-concussion

headaches. It is important to know that the consistency of nutritional supplements can vary widely among manufacturers and batches of the same compound because this industry is not regulated by the FDA.

Botulinum toxin injections are also a minimally-invasive treatment for pain. Conditions for which this medication is used are migraine headaches, spasticity, chronic muscle pain, back pain, neck pain, and neuropathy. The injection may take 10 to 14 days to be effective, but can provide three to four months of pain relief. Between 5 and 10 injections in multiple areas may be needed to successfully relax tense muscles.

Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological intervention used for acute and chronic pain conditions. In this therapy, a small battery-powered device delivers alternating low-voltage electrical currents via cutaneous electrodes attached to the skin positioned near the painful area. TENS is particularly effective on muscle pain.

Acupuncture, where very thin needles are inserted at different places in the skin to interrupt pain signals, is another therapy that may provide relief. It is postulated that acupuncture works through the endogenous opioid system. It is effective for reducing back and neck pain, osteoarthritis, chronic headache, and shoulder pain.

Dry needling uses a thin filiform needle to penetrate the skin and stimulate underlying myofascial trigger points, muscles, and connective tissue locally and the nerves in the spinal cord and brain systemically to release natural pain-controlling chemicals. Dry needling has been found to be effective for decreasing trigger point-associated pain.

Therapeutic massage is a form of manual therapy and may relieve pain by physically relaxing painful muscles, tendons, and joints, and mentally reducing stress and anxiety. Fibromyalgia and arthritis are two conditions that can be positively impacted by massage therapy. However, the recommended 2 to 4 sessions per week may not be tenable for many patients.

Biofeedback and Cognitive Behavioral Therapy (CBT) teach relaxation techniques, patient coping strategies, and self-regulation skills to help manage pain and other life stressors. There are no associated risks with this therapy.

Depending on existing health conditions, exercise therapy (e.g., walking, swimming, yoga,) can address posture, weakness, or repetitive motions that contribute to musculoskeletal pain. In addition to physical function, exercise can improve mental health.

There are large number of additional therapies which can both decrease pain and in some cases increase performance, including laser therapies, myofascial cupping and extracorporeal shock wave therapy which show promise but require further study.

State of the Science: Cannabidiol (CBD) and Cannabis

In the context of changing cannabis policies, interest in the medical uses of cannabis and cannabinoids like cannabidiol (CBD) is growing. In the United States as

of July 2019, 33 states and the District of Columbia (DC) and 11 states and DC have passed laws for medical and recreational cannabis, respectively. Some players may see CBD and medical cannabis as possible solutions to their medical issues—especially pain-related issues—but the state of the science is complicated.

The cannabis plant contains hundreds of chemicals, including over 140 cannabinoids—chemicals only found in the cannabis plant. We are most familiar with two of these cannabinoids: delta-9-tetrahydrocannabinol (THC) and CBD. THC is responsible for the euphoria that users may experience as well as paranoia that some users experience as well. CBD does not make users high and it appears to have exciting anti-anxiety and anti-psychotic properties, functioning as a buffer of sorts to the effects of THC.

CBD is a promising compound, but the extent of its use in the United States outpaces the level of evidence. Most of the hype surrounding CBD are based upon results from non-human studies.¹ There are small clinical studies that suggest that it may be effective for treating neuropathic pain. Due to the fact that the majority of CBD products are purchased from unregulated sources, it is hard to know the purity and potency of these products. One study showed that only 30% of commercially-available CBD products contained the amount of CBD shown on the label.² Some of these products may contain THC, thus causing a positive urine drug screen. In addition, there may be drug-drug interactions caused by CBD or players may opt for CBD as a medical treatment in lieu of treatments with more scientific evidence supporting them.

The therapeutic use of cannabis has been studied more in recent years.³ Multiple positive randomized, controlled trials (RCTs) show cannabis and the first two FDA-approved cannabinoids, dronabinol and nabilone, to be effective treatments for chronic pain and neuropathic pain. However, there are several flaws in these trials including small sample sizes and short follow-up periods that lead many physicians to question the generalizability of the findings. Of course, cannabis remains a banned substance under the NFL Policy for Substances of Abuse. In addition, the potential problems associated with cannabis, from acute impairment of driving, addiction, and exacerbation of psychiatric disorders such as depression and anxiety, make it a substance to approach with extreme caution.

References

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