Clinical Review:

The Future of Pain Management

“ An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage,”- This is the way the International Association for the Study of Pain defines it[1] but really, pain is an especially broad concept and the word itself beings to mind various thoughts, perceptions and memories, most often from past experiences, and these notions vary vastly between individuals as well. Whichever way you look at it, pain is something we can all understand, at the very least, to some extent.

What exactly is pain, and why do we experience it? Pain is a physical and often emotional experience brought on by a pathway consisting of sequential steps to bring about the final result. The four steps of the pain pathway are: Transduction, Transmission, Modulation and Perception.

Transduction takes place when a primary afferent neuron receives a signal from an action potential that has been generated through an injury or damage to tissues in our body. Nocieptors in the tissues are either directly stimulated or sensitized to be more receptive to noxious stimuli. When tissues are damaged, the release of prostaglandins, potassium, adenosine triphosphate (ATP) and hydrogen ions from the damaged tissues stimulate or sensitize nociceptors. Stimulation of nociceptors causes an influx of sodium and calcium into the cytoplasm of cells through voltage-gated ion channels, which causes the membrane potential of the cell to increase until the threshold potential is reached, and an action potential is produced.

In the transition stage, this pain signal travels in the form of an action potential. As the action potential travels through the neuron through continued opening of voltage gated sodium channels, the action potential reaches the synapse between the primary afferent neuron and the secondary afferent neuron. The action potential within the secondary afferent neuron continues to propagate until it reaches the synapse between the secondary and tertiary afferent neurons. Once the action potential is generated in the tertiary afferent neuron in the thalamus, the stimulus travels to the somatosensory cortex, as well as the anterior cingulate cortex, the insular cortex, the ventrolateral orbital cortex and motor cortex. These areas are responsible for localizing the pain and product the emotional, autonomic and motor result associated with the pain that is experienced.

Aside from the already complex methods our bodies use to create and transfer signals of pain, our bodies are capable of altering or blocking the pain signals in times of need, as it travels through its pathway. This is called modulation. Pain signals travelling to the brain are decreased by a controlled, reduced release of pain-modulating substances from both pre-synaptic neuron terminals (glutamate, and substance P) and post synaptic neuron terminals (excitatory signals).

The part that actually causes the feeling of pain, is when the nociceptive signal, travelling as an action potential, reaches the cortexes in the brain involved in pain perception. At this point, our brains have received a signal and

made us aware of a damage/injury to tissue, and an emotional and motor reaction occurs. At this point, the body is conscious of pain, and it is no longer nociception, but rather, pain.

When looking at the various stages involved in the experience of pain, as well as the various parts of the nervous system involved, it is clear that various approaches to pain management are possible and often necessary depending on the severity, type and duration of pain experienced by patients. Some of the most popular approaches from pain management include analgesics such as NSAIDs, glucocorticoids, acetaminophen, opioids, local anesthetics, magnesium, alpha-1-agonists, ketamine, gabapentanoids, capsaicin, antidepressants as well as nonpharmacological methods. Each of these analgesics have different mechanisms of action:

NSAIDs inhibit the synthesis of prostaglandins through inhibition of cyclooxygenase-1 and 2 (COX-1 and COX-2) enzymes, thereby reducing pain from inflammation. Acetaminophen works to reduce inflammation by acting on a variation of COX-1 known as COX-3.

Glucocorticoids have several mechanisms of action for reducing inflammation, including blocking the formation of arachidonic acid, thereby inhibiting the production of both prostaglandins and leukotrienes, which are pro-inflammatory substances. In addition to this, by reducing the transcription of pro-inflammatory genes, increasing the transcription of anti-inflammatory genes, and reducing spontaneous action potential firing in damaged nerves, glucocorticoids assist in reducing the pain associated with inflammation.

Within our bodies, opioid receptors exist throughout the brain, spinal cord, GI tract and the peripheral nervous system, and these receptors play a role in pain modulation, as well as in nervous system functioning. Opioids bind to these various opioid receptors, and through various sequential steps and processes involving neurons, synapses and nerve fibers, endogenous opioids known as enkephalins are released. Enkephalins play a role in pain modulation by reducing the release of glutamate and substance P presynaptically, which in turn reduces the postsynaptic excitatory current released and this reduces or inhibits the pain signal travelling to the central nervous system allowing individuals to perceive pain. Due to the fact that exogenous opioids have the same effect of enkephalins, exogenous opioids are able to have the same effect in the same areas of the body that enkephalins act on.

The mechanism of action of local anesthetics is related to the blockage of action potential firing. Action potentials travel via the opening of voltage gated sodium channels within the neurons reaching threshold potential. When these sodium channels are either open or inactive, (where in this case, inactive is different to closed channels) local anesthetics are able to block the channels, preventing the travel of sodium through the channels, and therefore preventing the propagation of any action potentials. Blocking action potential firing means that any stimuli acting upon the sensory neurons cannot be transmitted through action potentials to the central nervous system for perception.

Apart from being a muscle relaxant, magnesium alleviates pain by blocking the propagation of nociceptive pain signals. This is achieved through the blockage of channels on the NM DA-receptor, which play a role in pain transmission. Even if NM DA-receptors are bound to glutamate, the presence of magnesium blocks the channels from being open for signal transmission. If magnesium is absent these channels would otherwise be opened once

glutamate binds to NM DA-receptors. When these channels are opened, nociceptive signals are able to pass through to secondary afferent neurons which propagate the signals. Increasing magnesium therefore assists with continued blocking of NM DA-type receptors, preventing the pain signals from travelling through to afferent neurons.

Ketamine's mechanism of action is also related to NM DA-receptors. By blocking NM DA-receptors in the central nervous system, brain excitation and nociceptive signal sensitivity is reduced. By reducing the reuptake of norepinephrine and serotonin, ketamine allows for the neurotransmitters to be more readily available to act as opioid agonists. Similarly, antidepressants reduce the reuptake of serotonin and norepinephrine which inhibits pain transmission.

Alpha-2-agonists, such as clonidine, help to reduce pain by binding to postsynaptic alpha receptors of interneurons. When this binding occurs, it promotes the release of enkephalins (endogenous opioids) which reduce pain in various areas of the body.

Gabapentinoids bind to voltage gated calcium channels, which, when stimulated, allow for an influx of calcium into presynaptic terminals, which allows for the release of neurotransmitters. When gabapentinoids bind to voltage-gated calcium channels (VGCC), the uncoupling of the subunits of the VGCC, leads to degradation of the calcium channels, decreasing the intracellular movement of calcium and the release of glutamate. Gabapentinoids are particularly helpful to use for neuropathic pain as VGCC are upregulated in damaged neurons, which leads to greater calcium influx and neurotransmitter release.

Capsaicin binds to the TRPV1 receptor responsible for responding to painful high temperatures. Initially, when capsaicin binds to this receptor, depolarization occurs, nociceptors are activated and an intense burning pain is felt. Thereafter, the TRPV1 receptor is deactivated and the nerve endings become resistant to stimuli, causing a prolonged analgesic effect[2].

In a 2014 study, the global burden of chronic pain was assessed, and results indicate that many as 10% of the global population reported being affected by a chronic pain condition. In addition to this, 1 in 10 individuals develop chronic pain every year. Another study of the National Institutes of Health's National Center for Complementary and Integrative Health, shows that nearly 50 million American adults have chronic or severe pain. Behind all of these numbers, lay the poorly affected lives of millions of individuals, and a yearning to regain the quality of life they once had[3].

Chronic pain is considered a disease state, which may arise from psychological states, and it has no clear endpoint, and furthermore serves no biological purpose. In contrast, acute pain does serve a useful biological purpose, is self-limited, and is provoked by a specific injury or disease to tissues. Acute pain therapy therefore focuses on interrupting nociceptive signals and treating the underlying cause of the pain. Chronic pain therapy however often involves more than one therapeutic approach and is often multi-faceted[4].

So, what is the solution to the plague of pain experienced by billons of individuals across the globe? Currently, pain management approaches are usually centered around oral dosage forms. The search for a superior pain management approach is underway to mitigate the negative effects of the current pain management approach

such as the high potential for drug abuse, negative side effects, risk of overdose, patient non-adherence to treatments, and a lack of targeted efficacy for particular conditions.

Compounding is one such solution that encompasses benefits such as personalized dosage forms and strengths tailored to specific patient needs, the ability to combine multiple active pharmaceutical ingredients (APIs), each with different mechanisms of action; into one convenient dosage form, as well as the mitigation of negative side effects through tailored dosage forms which promotes patient adherence.

For instance; topical transdermal pain management solutions, are proving to be an attractive alternative to oral regimens, which often include several different pain management solutions (NSAIDs, opioids, acetaminophen, etc.) taken several times a day. Oral systemic use of pain medications may result in_a variety of side effects such as GI upset, possible GI perforation and bleeding, nephrotoxicity, cardiovascular disease, cartilage degeneration, acute liver failure, increased sedation, dizziness and drowsiness, as well as constipation, dry mouth and tachycardia depending on the API.

As opposed to oral pain management regimens, topical transdermal pain management solutions have the benefit of conveniently dosing multiple APIs in one dosage form as well as potentially reducing the need for more frequent dosing. This in turn may lead to greater patient compliance and better treatment outcomes. The ability to apply the pain treatment topically also allows for patients to apply transdermal treatments directly to the site of pain where appropriate. The avoidance of oral dosing may assist in mitigating some of the adverse effects associated with oral systemic use.

Compounded pain creams have the potential to reduce systemic absorption of the medicines used for pain management. A study performed on patients suffering from osteoarthritis of the knee, demonstrated that high-dose topical ibuprofen treatment managed to achieve therapeutic concentration in the targeted tissues without elevating serum levels of ibuprofen. The synovial fluid as well as plasma were analyzed for the presence of ibuprofen, and the concentrations were low. A similar study investigating the use of topical NSAID pain creams demonstrated that there was a maximum plasma concentration of less than 15% of the concentration that results after oral NSAIDs are used. Ketoprofen used topically in arthritic patients, has been shown to result in high tissue concentrations of ketoprofen, with low serum concentrations which significantly reduces systemic side effects experienced by patients using the topical treatment.

Non-adherence to treatment regimens can contribute to the inefficient management of pain, especially for those using treatment regimens encompassing various types of pain management medicines, with multiple doses at various times_of the day. Using a compounded preparation which contains multiple APIs used for pain management in one convenient dosage form that can be applied directly to the site of action, with the potential to be dosed less frequently, likelihood of patient compliance to the treatment regimen as it is far more convenient may increase the likelihood This is also of particular importance to consider for those patients who have difficulty ingesting oral forms of medication due to difficulties swallowing.

For those patients who are struggling with drug addiction, it is of particular importance for them to avoid using medicines that could potentially become habit forming or provoke the use of other addictive substances. In this

sense, customized, compounded preparations are useful in that specific pain management medicines can be combined to produce an effective pain-relieving solution, that excludes any habit-forming substances.

Compounding also provides opportunities to approach conditions that are usually difficult to treat, in a new light, using different combinations of APIs. An example of this is the study conducted by Lynch et al, where 2% amitriptyline and 1% ketamine were combined into a topical delivery system and used in an off-label study as a means to treat neuropathic pain, which is notoriously difficult to treat. At the end of the twelve-month study, 40% of the patients reported a minimum of a 50% reduction in their pain. Studies by Tam and Furlan, further investigated the potential of compounded transdermal preparations for neuropathic pain. Combinations of ketamine and lidocaine were studied in twenty-one patients and the results indicated that 83% of participants reported to have benefited from the treatment[2].

In addition to neuropathic pain, compounded topical preparations have been used to successfully manage a variety of other types of pain such as vulvodynia and proctodynia. A retrospective study regarding vulvodynia in 51 patients suffering from this condition revealed that those treated for 8 weeks or longer, reported a 50% or greater reduction in pain [5]. One study found application of amitriptyline 2% and baclofen 2% to effective for topical use for vaginal pain conditions[6]. Compounded topical transdermal treatments have been studied and their efficacy has been demonstrated in the treatment of neuropathic, musculoskeletal, arthritic and postoperative pain as well as other pain-related conditions. The ability to customize treatment plans into a potentially safer, more localized and more convenient formulation, with the added benefit of potentially reducing side effects and the risk of abuse and addiction (or assisting in the management thereof) serves as an important tool for practitioners and may offer an alternative to conventional treatment for both chronic and acute pain conditions experienced by patients.

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