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Innovations in Pain Management: From Traditional Analgesics to Novel Therapeutic Modalities

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Abstract

Pain medicine has demonstrated its significance from brief surgical procedures to managing chronic illnesses. Historically, a range of analgesic and opioid agents have been utilized as treatment options, and although effective to a certain extent, traditional approaches exhibit limitations. Restricted by the constraints of technology, current approaches fall short in specificity and unintended effects. This review article delves into the evolving landscape of pain management, focusing on emerging treatment modalities within and beyond the pharmaceutical setting. Non-pharmaceutical treatment modalities, including myofascial release, transcutaneous electrical nerve stimulation (TENS), photobiomodulation, and passive treatment, such as capsaicin patches, introduce promising, non-invasive treatment options for those experiencing chronic pain. The advent of nanotechnology has also introduced an exciting new avenue that may herald a new era in personalized medicine. With many promising treatment modalities currently under investigation, this review article aims to examine and highlight the advancements in pain medicine. It is imperative to understand the potential remedies these novel modalities may have in a multitude of neurodegenerative disorders, cancer, and other diseases.

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1. Introduction

Pain serves as the body's protective response to external stimuli that pose potential harm. While essential for signaling bodily distress, persistent or chronic pain can persist even after the underlying issues have been resolved, significantly hindering the quality of life for those affected.

1.1 Pathways of Pain

Pain can be classified as either chronic (long-term) or acute pain (short-term). The fundamental mechanisms causing this pain can be categorized into two main groups: nociceptive and neuropathic pain[1]. Nociceptive pain is caused by the activation of nociceptors in response to surface-level tissue damage, representing the most immediate level of pain perception. Examples of nociceptive pain include minor injuries such as bruising, scratches, and cuts, as well as some deeper tissue damage like fasciitis, tendonitis, and fractures. Nociceptive pain normally subsides with time, although various physical therapies and pharmacological remedies offer immediate pain alleviation. Neuropathic pain arises from dysfunction or damage to the nervous system, specifically nerves responsible for transmitting pain signals to the spinal cord or brain.

Consequently, pain is perceived even in the absence of external stimuli. Whether caused by injury, disease, or other factors, damage to nerve fibers disrupt their ability to transmit accurate signals from the periphery to the central nervous system. Neuropathic pain syndromes can include post-stroke pain, spinal cord injury, multiple sclerosis (MS), and they have also been associated with other pain groups. Currently, the first line of treatment for neuropathic pain is using pharmaceuticals which include tricyclic antidepressants (TCA), gabapentin, anticonvulsants, and antidepressants[2]. In addition, there have been recent studies to show botulinum toxin has helped by inhibiting proinflammatory mediators[3]. Recognizing the interconnectedness of nociceptive and neuropathic pain is vital for developing comprehensive approaches to pain management. Acute pain typically subsides when the primary stimulus is removed, whereas chronic pain persists even after the primary stimulus is no longer present.

Classifying pain in two broad categories requires some more specificity to obtain effective characterization. The different conditions can be broken down into different categories in terms of chronic pain. These groups are inflammatory, musculoskeletal, and psychological pain[4]. Inflammatory pain is characterized by heightened sensitivity of nociceptive pain receptors due to inflammation[5]. Hallmark symptoms of this type of pain include increased pain perception, which is the result of the higher influx of pain mediators that localize with the increase in blood flow. This heightened sensitivity can manifest as allodynia, where pain occurs in response to stimuli that would not normally induce pain, or hyperalgesia, an exaggerated response to painful stimuli. Common examples of conditions associated with inflammatory pain include arthritis and various infections. Surgery and opioid use can also trigger hyperalgesia by increasing the concentration of calcium and upregulating calcium-dependent kinases, serving as a trigger for the release of neurotransmitters.

The next classification of pain to consider is musculoskeletal pain. It is highly prevalent in the general population, affecting approximately 37% of the United States population, with an economic burden of $635 billion per year[6]. Musculoskeletal pain is discomfort that arises in muscles, bones, ligaments, tendons, and various supportive tissues in the body, as a result of defects of certain receptors. The most common agitators for this type of pain include overuse, poor posture, and various underlying medical conditions, leading to other ailments including both osteoarthritis and rheumatoid arthritis[7]. It remains closely connected with inflammatory pain, as damaging the tissue as a result of bad posture or overuse, may cause inflammation.

During inflammation or tissue injury, damaged cells and immune cells release a variety of substances known as inflammatory mediators, such as bradykinin, nerve growth factor (NGF), prostaglandin E2 (PGE2), pro-inflammatory cytokines [e.g. interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α)] and chemokines (e.g. chemokine ligand 2). These inflammatory mediators act both directly on peripheral nociceptors, eliciting sensitization, and indirectly by promoting inflammation and the release of prostaglandins[8].

Psychological pain is relatively a new term and is still being discussed as to what the full criteria are. It is generally being discussed as relating to either psychological disorders such as severe depression or relating to physical pain like migraines and headaches[9]. In addition, due to the developing research on this type of pain, there is no definite way to treat this type of pain and no concrete definition of this pain yet.

Across various pain classifications, a shared pathway of pain reception emerges, initiated by A-delta and C-fibers – A-delta fibers emit rapid and localized signals, while C-fibers transmit non-localized pain signals[10]. These primary afferent axons serve as modalities for sensory perception, transducing pain signals from chemical to electrical within neurons. The electrical signals are transmitted along neuronal pathways to the central nervous system. Upon reaching synapses, axons convert electrical signals into chemical signals, which are then reconverted into electrical signals upon reception by dendritic cells. The presence of myelinated sheaths serves to expedite conduction speed along these pathways. Notably, ions such as calcium, potassium, and sodium play crucial roles in the transmission of these neurotransmitters. At a broader level, stimulatory molecules, including various growth factors, prostaglandins, and proteases are released upon contact with noxious stimuli. These molecules then access various channels, which facilitates the release of more pain mediators from nerve terminals, such as glutamate and interleukins. The signals are then sent to the central nervous system, specifically the spinal cord or dorsal horn, where they are interpreted in the primary sensory cortex. Understanding the intricacies of this pain perception pathway is essential for elucidating mechanisms behind pain perception and advancing targeted therapeutic modalities.

1.2 Physiology of Pain

Having understood the pain reception mechanisms and pathways, the next step in designing an effective pain medicine is identifying proper targets. Some of the mediators previously discussed, like glutamate, have significant interactions with NMDA pain receptors, primarily situated in the central nervous system. This interaction heightens sensitivity to pain while

simultaneously reducing the effectiveness of opioid receptor agents. Therefore, N-methyl-D-aspartate (NMDA) receptor-targeted modalities involve much of the research in pain medicine[11]. Another receptor of interest, dopamine, is classified into different types, each with distinct roles in pain modulation. D1 dopamine receptors, for instance, trigger the production of higher levels of cAMP (cyclic-adenosine-monophosphate), which in turn enhances PKA (protein kinase A) activity. In contrast, D2 dopamine receptors inhibit cAMP and PKA activity, exerting an opposing effect on D1 receptors. D1 receptors play a role in pain development and maintenance, while D2 receptors act to block pain signals. Shifting our focus to opioids; there are three main types of opioid receptors: delta-opioid peptide/receptor (DOP), kappa-opioid peptide/receptor (KOP), and mu-opioid peptide/receptor (MOP), each with their subtypes. In addition, there is a fourth receptor named nociception receptor (NOP) that is considered a non-opioid receptor of the opioid receptor family. NOP works similarly to the opioid receptors but does not bind or become affected by naloxone, the common opioid antagonist. Due to its lack of response to naloxone, it is frequently questioned if the classification of the opioid receptor is correct. Activation of DOP receptors may lead to spinal analgesia and reduced gastric motility[12]. KOP receptor activation also induces spinal analgesia but may increase urination and raise the risk of depression. MOP receptor activation provides analgesic effects but can lead to respiratory depression, sedation, cardiovascular complications, and nausea. Though these interactions serve as promising pain remedies, it is important to understand the unintended effects they may cause. Drugs that are capable of capitalizing on these reception functionalities will be reviewed later in the document.

1.3 Comorbidities

Pain is most commonly encountered in conjunction with its comorbidities, which is where most of the dedicated research efforts have been focused. Neurodegenerative disorders are normally associated with loss of coordination, memory, and motor movements. Understandably, treatment for these neurodegenerative disorders is focused on either restoring or retarding the progression of the disorders. However, patients report great levels of pain; thirty-eight to seventy-five percent in Alzheimer's disease and

other dementias, forty to eighty-six percent in Parkinson's disease and related disorders, and nineteen to eighty-five percent in motor neuron diseases report a high prevalence of pain[13]. Scientists are currently struggling to classify the type of pain experienced by patients, due to poor diagnostics, difficulties in patient self-reporting, and complex neuronal pathways. This article will be analyzing the ongoing research on the modalities of pain in Parkinson's Disease (PD), the most rapidly growing neurodegenerative disorder, which can be applied to other neurodegenerative disorders. In a study conducted by Cattaneo et al., a classification of pain at four levels was reported. The first level of this grouping isolates pain into PD-related and non-PD-related (level 1: relationship to PD). This idea stems from correlation, as many patients with PD are elderly. In the subsequent level, the two aforementioned types of pain are classified as nociceptive or neuropathic; if it is not clear which of the two classifications ought to be picked, pain is included in the "miscellaneous" classification (level 2: the broader categorical system). In the third level, the different types of pain are categorized according to the categories: musculoskeletal, visceral, cutaneous, peripheral, or central (tier 3: broad type). In the last (fourth) level, different aspects from a clinical, pathogenetic, and therapeutic point of view are specified (tier 4: specific structures and pathology). Another important classification method that is frequently used is that of Ford, which considers five categories: musculoskeletal, dystonic, neuropathic/radicular, central/primary, and akathisia[14].

A significant proportion of diabetes patients experience chronic pain. Musculoskeletal pain and neuropathy are the common symptoms of pain, stemming from alterations in the structural matrix and mechanical properties of periarticular connective tissues, owing to an unusual deposition of collagen[15]. These defects further lead to rheumatic problems such as the reduced mobility of joints, stiff hand and carpal tunnel syndromes, shoulder capsulitis, and tenosynovitis[16]. These trends may reflect correlation rather than causation. But according to a study sampling populations with nondiabetics, diabetics, and prediabetics, the results showed that, compared to prediabetic and nondiabetic individuals, diabetic subjects have a higher prevalence of lower limb pain (11.1%), back pain (8.9%), abdominal pain (6.7%), and neck pain (4.4%). A chi-squared test confirmed that diabetic and prediabetic patients had a significantly higher

prevalence of chronic pain[17]. If this problem is not properly dealt with, chronic pain may spiral into larger health problems, causing a greater disruption in the lives of many.

Cancer-related chronic pain affects about 40-70% of patients with cancer diagnostics and 33-40% of long-term cancer survivors suffer from chronic pain[18]. There exist numerous sources of pain, including the tumor itself, chemotherapeutic agents, and surgical interventions. All of these factors can not only cause physical pain, but also significant psychological pain. Delivery of therapeutics is currently a hot area of research in cancer research and will be covered in this article.

2. Previous Treatment Modalities

2.1 Nonopioid Drugs

Popular pharmaceutical drugs fall into three primary categories: nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and adjuvant analgesics. NSAIDs work primarily by inhibiting the activity of the COX-1 and COX-2 enzymes, which are subsets of the calcium-dependent kinases mentioned earlier[19]. This inhibition leads to reduced prostaglandin expression, resulting in analgesic effects and decreased inflammation. However, a significant drawback of NSAIDs is the increased risk of cardiovascular issues and gastrointestinal complications. NSAIDs are responsible for 30% of adverse drug reactions such as strokes, heart attacks, renal damage, and bleeding. Common examples of NSAIDs include aspirin, ibuprofen, and naproxen. The other common drug, acetaminophen, commonly recognized as Tylenol, operates similarly to NSAIDs. However, unlike NSAIDs, it does not interfere with the COX pathway in the peripheral nervous system; instead, its effects are limited to the central nervous system. As a result, Tylenol effectively alleviates pain perception and reduces fever but lacks efficacy in diminishing inflammation. When used in appropriate doses, Tylenol is generally considered safe. However, prolonged or excessive usage can lead to liver damage, occasionally fatal.

Adjuvant analgesics include most non-opioid drugs that are not classified as acetaminophen and NSAIDs. Adjuvant analgesics refer to medicine that

was originally engineered for purposes other than pain management; popular agents include antidepressants and anticonvulsants. Because of the nervous system's interconnectedness, drugs that operate in the nervous system for conditions such as depression or convulsions affect pathways involved in pain reception. Specifically, their effects on the spinal cord and dorsal horn overlap. Antidepressants suppress neuropathic pain by enhancing noradrenaline influx in the spinal cord[20]. This neurotransmitter binds to α2-adrenergic receptors, initiating downstream signaling cascades that inhibit calcium channel activity in the dorsal horn and dampen neurotransmitter transmission, thereby inhibiting hyperalgesia and allodynia.

Additionally, antidepressants hold therapeutic effects on the locus coeruleus, a brain region rich in noradrenergic nerve cells. Following injury, the locus coeruleus releases noradrenaline in response to noxious stimuli, contributing to nociceptive analgesia. However, with prolonged injury, this response diminishes, compromising the descending noradrenergic inhibitory system. Antidepressants intervene by restoring locus coeruleus function and increasing noradrenaline levels[21]. Moreover, they elevate levels of brain-derived neurotrophic factor (BDNF), crucial for AMPA receptor-mediated activation in the locus coeruleus, further promoting analgesic effects. Another common class of adjuvant analgesics, anticonvulsants, exert their analgesic effects by modulating neurotransmission to prevent seizure activity. The drug acts on the brain to serve its primary pharmaceutical purpose, which also inhibits neurotransmission in pain reception. Though the listed adjuvant analgesics manage pain well, they do have side effects; headaches, decreased alertness, and bleeding are just some of the problems that can arise.

2.2 Opioid Drugs

The most hazardous class of medications is opioids. Among the commonly known opioids are morphine, oxycodone, codeine, dihydrocodeine, and loperamide, some of which are available over the counter without prescriptions. Despite the wide array of opioid-based drugs available, they all share a common mechanism of action, targeting the mu, kappa, and delta receptors in the nervous system. In the context of pain medicine, the mu

receptor is of interest for its ability to elicit analgesic effects. Opioids bind to the mu receptor, decreasing the excitability of nociceptors and the release of pro-inflammatory peptides[22]. However, this is not all the drug does. The kappa receptor induces the commonly known drug effects, like euphoria and depression of bodily function. The addictiveness of the euphoria makes this combination especially dangerous. As depressants, opioids effectively slow down bodily functions, including respiration, which can lead to respiratory depression and neuronal damage. The unreliability of this drug makes it undesirable as a pain medicine. Nanoparticles, which will be discussed further on, hold promise for providing synergistic effects with opioids, making them safer to use.

Additionally, it is important to note that many of the commonly used opioids do not act on all of the opioid receptors. Although the majority of them act mainly on the mu receptor, they do not act on the other two receptors. For example, oxycodone, codeine, and loperamide are all opioids that are agonists on the mu receptor. Morphine affects each of the receptors but binds mainly to the mu receptor. When morphine binds with these receptors it leads to an activation of the descending inhibitory pathways of the central nervous system resulting in reduced nociceptive signal transmission[23]. Although morphine has been shown to decrease blood pressure and heart rate, it has some unfavorable effects such as constipation, nausea, depression, and vomiting. Pentazocine is not as commonly used at present but is a synthetic opioid used as an agonist on the kappa (κ) receptor[24]. Pentazocine does have the chance of common adverse effects of opioids such as nausea, respiratory depression, vomiting, and constipation. The final opioid receptor, the delta receptor, is known to associate with the drug named buprenorphine. Buprenorphine is also known to be a partial agonist to mu receptors and a weak antagonist at kappa receptors, but its effects on delta receptors are also weak . It is a synthetic opioid that is used for pain treatment and opioid use disorders (OUD). It acts differently from normal opioids by exhibiting slow dissociation kinetics, allowing for fewer adverse effects.

Though current drugs on the market have proven their use over the years, there are many avenues of innovation in the field of medicine that can elevate the current drugs on the market as well as provide alternate approaches to pain remedies.

3. Pharmaceutical Remedies Advancements

3.1 Nanoparticles

In contrast to the pharmaceutical remedies mentioned earlier, nanoparticles demonstrate therapeutic effects stemming from the emerging field of nanotechnology. The wide attributes and modifications for nanoparticles enable treatment for a diverse spectrum of diseases, as well as an avenue to the next age of precision medicine. This review article will explore the various avenues and types of nanoparticles that are relevant in a pharmaceutical context.

3.2 ZnO & MgO NP

Starting with zinc oxide, its wide range of capabilities places it at the forefront of scientific research. Zinc, recognized as an essential trace element, plays a crucial role in pain perception modulation, proving its ability to analgesia through various pathways[25]. Zinc ions have been shown to inhibit the release of glutamate, a previously mentioned neurotransmitter by producing more GABA, an inhibitory neurotransmitter. Furthermore, zinc ions noncompetitively inhibit the NMDA receptor, which diminishes the activation of the central nervous system, the perception pathway for pain. What differentiates the nanoparticle from the microparticle form is the penetration efficiency; nanoparticles are three orders of magnitude smaller, contributing to their greater motility through various tissues[26]. As a result, smaller doses of zinc oxide are required to induce saturation.

Furthermore, zinc oxide demonstrates photocatalytic capabilities, due to the high reactivity of surface oxygen atoms. It has proven to oxidize stimulants on peripheral receptors, and various tumors in cancer therapy. Magnesium oxide serves a similar role, as it is another vital cation in the human body that offers promising avenues for pain relief. By preventing the calcium ions from entering cells through blocking NMDA receptors, it serves as another

analgesic agent. One study[27] was conducted to test this reaction on mice. Varying doses of zinc oxide nanoparticles were injected into rats (0, 1, 5, 10, 20 mg/kg) and the latency in pain was measured. As shown in Figure 1, the latency period was longest at about 10 mg/kg, meaning pain was delayed for about 90 minutes. Just like zinc, magnesium reduces the need for relaxant drugs, intraoperative anesthetics, and morphine.

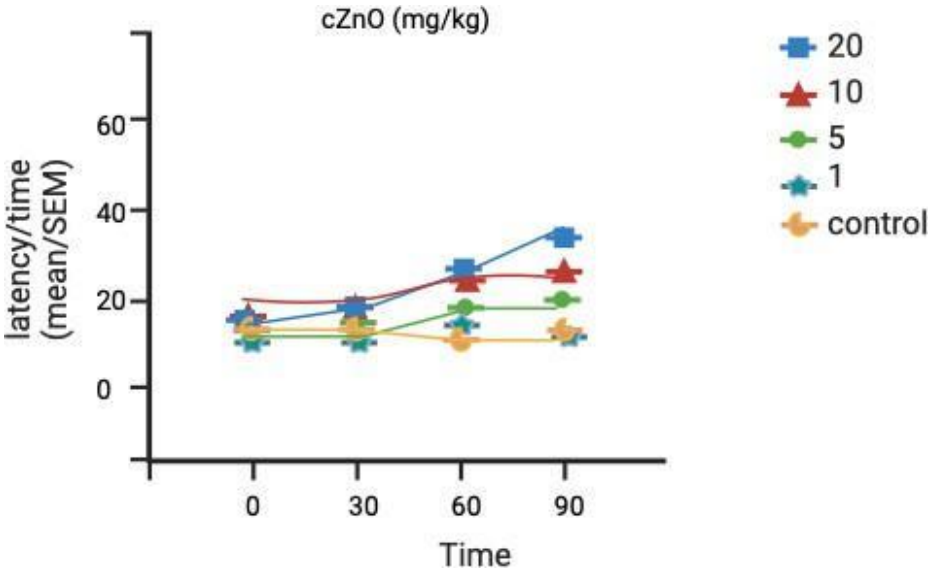

Figure 1. Results from Zinc Oxide Nanoparticles on Rats

3.3 Magnetite Nanoparticles

Magnetic metal oxides represent a distinct class of nanoparticles. Ferromagnetic compounds, including magnetite (Fe3O4), have shown ferromagnetism, meaning that they readily interact with applied external magnetic fields. Similar to zinc and magnesium oxide, magnetite has demonstrated potential in directly alleviating pain. Therapeutic effects that the nanoparticle possesses were revealed by a study that concluded diminished macrophage activity and diminished expression of inflammatory biomarkers with the treatment of ferromagnetic particles. However, the most intriguing aspect of magnetite is unveiled by its name: magnetism. It has been widely used as a nanocarrier because of its capability to control the vesicle externally through magnetic fields. The strong interaction between the nanoparticle and the external magnetic fields enhances the targeting efficacy of this method, contributing to precise delivery. Just like zinc oxide nanoparticles, the nanoparticles themselves hold therapeutic effects.

In a mice study[28], iron oxide nanoparticles were injected, and the prevalence of biomarkers was checked. These biomarkers include reactive oxygen species, CD68, and MPO (a neutrophil marker). Pain levels were also measured through von Frey filaments, a band that measures mice's paw withdrawal response, an indicator of pain perception. After the injection of treatment into inflamed tissue, there were signs of suppressed expression of the previously expressed proinflammatory biomarkers. Further taking advantage of the magnetic properties of magnetite, they are currently being studied in the field of nanoparticle-induced magnetic hyperthermia. Bioactive glass doped with magnetite nanoparticles can generate heat in the presence of an alternating magnetic field[29]. When the magnetic field alternates, the magnetism of the nanoparticle also alternates, but at a delay, a phenomenon called magnetic hysteresis. As a result, heat is capable of being generated in a highly specific area.

3.4 Gold Nanoparticles

Another metallic nanoparticle worth covering is gold nanoparticles. Currently, at the forefront of cancer research, gold nanoparticles boast a myriad of conformations and high membrane customizability. One of its most notable features is the surface plasmon resonance (SPR), a phenomenon that occurs when electron oscillatory frequencies align with the frequency of incoming light, allowing the generation of a magnetic field[30]. Though showing great promise, its toxicity must be considered when evaluating its efficacy. Gold nanoparticles can alter DNA function and bioaccumulate. Depending on the intended application, coatings added onto these nanoparticles, such as folic acid, polyacrylamide, polyvinylpyrrolidone, and polyacrylic acid can serve to either mask their cytotoxicity or exploit it when targeting cancer cells for treatment. For instance, in a study[31] that tested the absorption of gold nanoparticles, antibody-modified gold nanoparticles demonstrated a 600% increased retention to tumor cells, allowing greater release of cytotoxicity into the cell.

Looking into the therapies driven by gold nanoparticles, photothermal and radiofrequency therapy stand as promising candidates. As previously mentioned, the ability of nanoparticles to absorb and scatter electromagnetic radiation has captured significant interest in the realm of

photothermal therapy. The application of this phenomenon has been studied in localized hyperthermia, as well as radiofrequency therapy, as its great specificity and morphology control have contributed to great levels of localization. Its impact has also been seen in neurodegenerative disorders, such as Parkinson's Disease, Multiple Sclerosis, and Lou Gehrig's Disease. The commonality amongst these painful illnesses includes the decline of the NAD+/NADH ratio in the brain. Reversing this energy deficit promises slower neurodegenerative decline and even partial recovery. In the phase 2 clinical trial conducted in 2024[32], gold nanoparticles demonstrated their capability to improve this NAD+/NADH balance. 11 participants with relapsing Multiple Sclerosis and 13 with Parkinson's Disease were the subjects of this clinical trial and took CNM-AU8 (the gold nanoparticle-based therapeutic agent) for 12 weeks. The result included an average of 10.4% improvement in NAD+/NADH ratios. Further validated testing was performed to test the motor skills of these patients and improved motor skills were demonstrated by the patients. Without diagnosing any adverse effects of this treatment, the gold nanoparticles have cemented themselves as a promising candidate for neurodegenerative disorders.

The next class of nanoparticles this review article will be covering includes nanocarriers, one of the most active areas of research in nanotechnology. The capability to fine-tune the solubility and mimic human cells grants them easy entry into specific cells, while their ability to vary delivery mechanisms based on environmental factors ensures controlled and precise drug release. By doping the nanoparticles with various membranes or certain receptors, there are many ways to specify the targeted location of the cell. Beyond their ability to precisely target cells, their modifications enhance drug stability and cellular compatibility. With high modification potential, nanocarriers hold immense promise for personalized medicine and theranostic applications. We will be taking a look at a few nanocarriers that are currently being researched in the field of nanotechnology[33].

3.5 Liposomes

Liposomes are mainly composed of cholesterols and phospholipids, boasting great biocompatibility, biodegradability, high loading capacity, and permeability. Over the past decades, liposomes have gradually been

improved to localize more precisely, with improved responsiveness to pH and temperature as conditions, though they still encounter issues. Some of its applications have been heavily explored in co-morbidities with chronic pain, including cancer. In a clinical study[34] conducted in 2022 on the efficacy of liposomes in children's anticancer therapy 74 trials were conducted with 70 being intervention trials and 4 being observational trials, with 28.6% being in Phase 3 trials, 30.0% in Phase 1 trials, and 24.3% in Phase 2 trials. In total, 17 liposomal drugs for 123 types of cancer were investigated, consisting mainly of organic chemicals. Of these cancers, the highest proportion was leukemia (15.4%), followed by lymphoma (9.8%) and ovarian cancer (8.9%).

It is worth noting that accurate statistical masking is required to produce accurate results, and only 30% of the data collected was properly masked. Ultimately, many challenges were found to be associated with this treatment modality. Leakage, uncontrollable drug release, instability in storage, and difficulty in drug loading limited the use of liposomes in cancer therapy. However, they did demonstrate high loading capacity for hydrophobic substances. Ultimately, liposomes are still an active area of research for scientists and possess many challenges that must be overcome.

3.6 Solid Lipid Carriers and Nanostructured Lipid Carriers

Solid lipid nanocarriers have been around for decades and have been extensively researched. Many versions of this nanoparticle have been produced. A solid lipid nanocarrier, at its core, is a solid lipid (lipid that is solid at room temperature) that is commonly composed of triglycerides, fatty acids, waxes, and phospholipids[35]. These lipids form a matrix of crystalline structure that encapsulates the drug to be delivered. Surrounding this solid lipid nanocarrier core exists a surfactant layer. In chemistry, surfactants decrease the surface tension between adjacent surfaces and are amphiphiles. The hydrophilic portion of the surfactant faces outward toward the aqueous environment, while the lipophilic portion interacts with the lipid core, which acts as a stabilizer for the solid lipid core, preventing aggregation or coalescence. The first generation of this nanocarrier was used as a vesicle to deliver topical anti-inflammatory drugs. Great success was found in the controlled release of the drug, allowing for

bioaccumulation in the stratum corneum, the outermost layer in the epidermis. It has also served as an effective nanocarrier for various pain drugs.

Epalrestat[36], a treatment for streptozotocin-induced diabetic neuropathic pain, was delivered with solid lipid nanocarriers, and the effect was measured in a rat-modeled study. The study tested the efficacy of epalrestat encapsulated nanoparticles at varying concentrations (0.25, 0.50, 1, and 5 mg/kg) on streptozotocin-injected rats. The various parameters linked with peripheral neuropathy were subsequently measured. The results were promising. Solid lipid nanoparticles demonstrated a large encapsulation efficacy at 88 ± 2%. Analyzing the results, the tail-flick latency time and hot plate response time, improved linearly with greater doses of solid lipid nanoparticles.

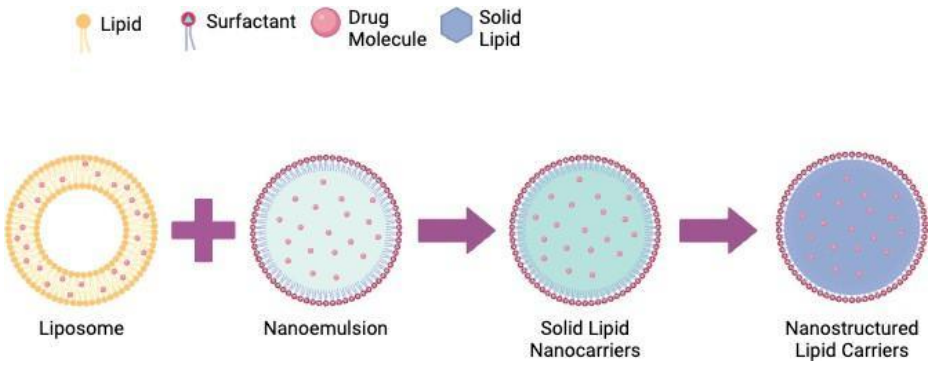

Figure 2. The formation of solid lipid nanocarriers.

The second generation of this nanocarrier saw the advent of nanostructured lipid carriers (NLCs). The main differentiating factor between these nanocarriers and solid lipid nanocarriers lies in the liquidized lipid core[37]. The oils in the core function by decreasing the crystallinity of the lipid core, preventing drug expulsion from the matrix, enhancing drug loading capacity, and stability, and ensuring long-term physical and chemical stability. As a result, its loading capacity saw an increase, and its encapsulation rate rose to 99.5%. Now solving many of the problems that plagued the solid lipid nanocarrier, one of its applications was the delivery enhancement of topical therapeutic agents like butyl-substituted benzocaine analog butamben, a local anesthetic. It proved to decrease

toxicity and improve analgesic effects. Building off of all the applications of solid lipid nanoparticles, it has been explored in the delivery of gene therapy, chemotherapy, and other treatments.

3.7 Hydrogels

Hydrogels in their simplest form are networks of water-absorbing polymers. Some commonly used polymers include Polyethylene glycol (PEG), Poly(acrylic acid) (PAA), Polyvinyl alcohol (PVA), Hydroxypropyl methylcellulose (HPMC), Alginate, Collagen, and Chitosan; some of these hydrophilic polymers are naturally forming polymers. In the world of anesthetics, the brief lifetime of the anesthetics and toxicity has been at the center of focus when attempting to engineer effective therapeutics. Hydrogels have demonstrated great promise in combination therapy with traditional anesthetics in blocking peripheral nerve blocks. A study[38] tested the logistics of polycaprolactone (PCL) hydrogels in delivering topical agents. The study determined that drugs enriched in a PCL core and chitosan shell demonstrated a steady release of drugs. They also tried determining the optimal ropivacaine (RPV) and dexamethasone (DEM) nanoparticle composition and determined that RPV/DEM CH-PCL NPs-3 delivered the best effects, the mix with the largest nanoparticle size.

Hydrogels have also been extensively researched in the field of oncology, as a result of their impressive biodegradability and biocompatibility[39]. Specifically, it has shown great promise in the field of immunotherapy. With difficulties arising in the delivery of monoclonal antibodies (immune checkpoint inhibitors), hydrogels serve as the perfect transport vesicle. (Li et al., 2023)[40] reported that the alginate hydrogel with protoporphyrin IX (PpIX)-modified iron oxide (Fe3O4) nanoparticles demonstrated high control over the performance of photodynamic and chemodynamic therapies[41]. Another study conducted by Li et al., 2021) demonstrated how a hybrid peptide hydrogel of melittin (RADA-320, titanium, and doxorubicin (DOX) controlled the release of

therapeutics-that activated immune cells, depleting the M2-like tumor-associated macrophages, effectively reshaping the immunosuppressive tumor microenvironment[42]. Altering the

microenvironment of melanoma gives promise to the capability to alter other tumor microenvironments present in other cancers.

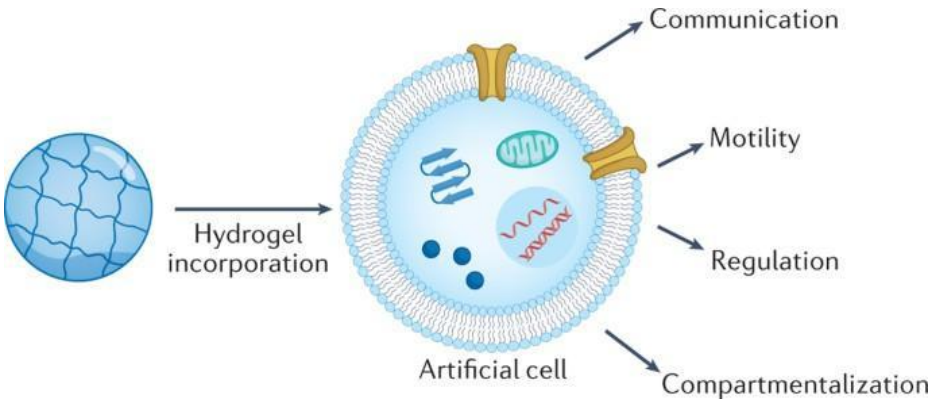

Figure 3. Hydrogel into a Cell

3.8 Micelles

In its simplest form, micelles are aggregates of amphiphilic molecules that have self-assembled into a spherical geometry. They are formed by submerging common amphiphiles, like surfactants, in an aqueous solution, where the hydrophilic heads shield the hydrophobic tails from the polar aqueous environment. This structure mirrors that of the phospholipid bilayer of cells, as there exists a hydrophilic head with hydrophobic tails. When applied to the field of therapeutics development, micelles can encapsulate drugs in their inner compartment. What differentiates micelles from other nanocarriers is their minute size, being sub 50 nanometers in size. Combined with their cell-like coatings, these particles have accessibility to deeper tissue locations, increasing the range of drug delivery distance. Micelles are also easily manufactured, increasing their accessibility relative to the previously discussed nanocarriers. Though there are many benefits to this nanocarrier, a major drawback includes instability in fluctuating environments. As a result, it may disintegrate in variable environments, like the bloodstream, thereby reducing therapeutic effectiveness of the nanocarrier. Current research efforts are investigating the possibility of crosslinking various structures to prevent premature release of therapeutic agents[43]. Like any other nanocarriers, micelles are currently being investigated for their role in delivering therapeutic agents to tumors. Their small size allows them to permeate well through certain systems, like the kidney, and evade elimination by the liver or spleen. Their minute size allows precise localization in certain tissues, improving therapeutics delivery.

By modifying the surface of micelles with ligands that can specifically recognize and bind to receptors overexpressed on the tumor cells, a targeting modality is established. This is evident in approved polymeric nano micelle-based drugs on the market for cancer treatment[44].

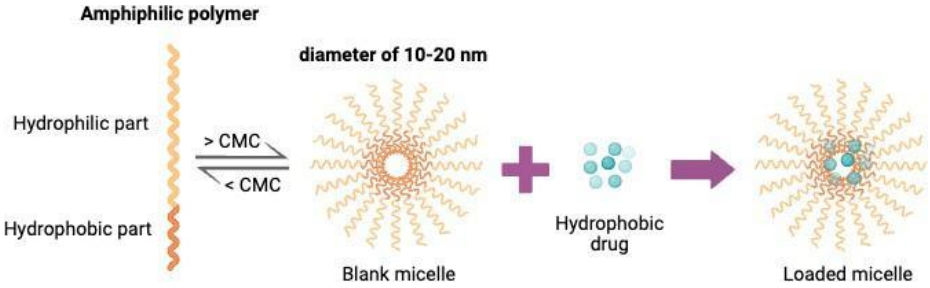

Figure 4. Loading of a micellar nanocarrier

Genexol-PM, a micelle-based drug, has been approved for the treatment of breast cancer, non-small-cell lung cancer, and ovarian cancer. It is also undergoing clinical trials for a variety of cancers. In a Phase II study of Genexol-PM in patients with locally advanced or metastatic pancreatic cancer, common side effects were comparable to those of Taxol in a dose of 300 mg/m2 every three weeks. The general reaction rate was 6.7%, with 1 patient in complete reaction and 2 patients in halfway reactions, and the infectious prevention rate was 60%. The median PFS was 2.8 months, and the median overall survival was 6.5 months. Neutropenia (40.0%), fatigue (17.8%), infection (13.3%), dehydration (13.3%), neuropathy (13.3%), and abdominal pain (11.1%) were the most common grade 3 toxicities. Genexol-PM had sufficient antitumor activity as second-line chemotherapy in patients with urothelial cancer after Gemcitabine-Platinum failure in a Phase II study in 37 patients with advanced urothelial cancer who had previously received Gemcitabine and Platinum combination chemotherapy[45]. Of 34 evaluable patients, the general reaction rate was 21%, with 1 patient in complete reaction. The median PFS was 2.7 months, and the median overall survival was 6.5 months. Grade 3/4 non-hematologic poison levels included neutropenia (14.7%) and contamination (5.9%). Hematologic toxicities of grade 3/4 were observed in only one patient. The low rates of high-grade toxicities give promising results prospects for micelles in the field of oncology.

3.9 Dendrimers

Dendrimers are large branched molecules that are composed of generation zero (the core molecule) with branched polymer chains synthesized onto the central molecule. Drugs can be integrated into the various branches of this molecule through reactions. Their differentiating characteristics from other nanocarriers include hyperbranching, well-defined spherical structure, and high compatibility with biological systems. Beyond operating as a nanocarrier, dendrimers can also be used to enhance drug solubility and as a stabilizing agent for various drugs. These two attributes are synergized when finding applications of dendrimers. The most well-known dendrimers incorporate poly(amidoamine) (PAMAM) dendrimers, polypropylene dendrimers, polyesters, and triazines. Dendrimers can be conjugated to various molecules in addition to the functional groups that are found on their external surface. Dendrimers are a productive solvency enhancer of NSAIDs, which is enhanced by weak hydrogen bonds provided by branch units, and electrostatic action from surface groups.

Koc et al. investigated the solubility of PAMAM dendritic macromolecules loaded with NSAIDs (ketoprofen, ibuprofen, and diflunisal) in a buffer solution[46]. The outcomes showed that the solvency improvement execution of hydrophobic medications in PAMAM dendritic atoms was several times greater than ethylenediamine-cored PAMAM dendritic macromolecules because of their original polypropylene oxide cores. As a result, dendrimer carrier optimization and application have significant potential for pain-induced inflammation treatment.

3.10 Poly(Lactic-co-Glycolic Acid) NPs (PLGA) Nanoparticles

PLGA nanoparticles are synthesized from lactic and glycolic acids, with customizability deriving from the myriad of lactic and glycolic acid concentrations. The differentiating factor of this nanocarrier lies in its simple preparation, biodegradability, and high drug-loading capacity. It also demonstrates great control over drug release. A study conducted on the release of ketamine through PLGA nanoparticles was conducted by Han et al; biocompatible and biodegradable ketamine-loaded polyethylene-glycol - PLGA nanoparticles were tested in pain treatment in the context of pain medicine[47]. The results demonstrated a 41.8% drug loading, with preservation of the drug for up to 7 days and controlled release for up to 21

days. Furthermore, the decay of ketamine below the lower limit of quantitation rose to ~103 hours and ~80 hours with PLGA in comparison to only 24 hours when injected intravenously without a nanocarrier. Further optimization of drug distribution in the polymer matrix as well as PLGA composition is being performed to better formulate drugs with broader and more effective applications.

3.11 Other Nanocarriers

There remains a multitude of nanocarriers currently being explored for their therapeutic applications. To list a few, thermogels, emulgels, various films, and silicon nanoparticles are currently being researched. It is important to note the limitations when it comes to nanotechnology, including stability, cytotoxicity, and solubility, as they pose great barriers to delivering many drugs.

4. Pharmaceutical Remedies Advancements

4.1 Myofascial Release

Myofascial release is an external method that refers to the manual application of a low-load, long-duration stretch of the myofascial complex. Its objective is to restore the ideal length of the fascial tissue to decrease perceived pain and enhance mobility. This method targets fascia tissue and other associated soft tissues. Fascia tissue is considered connective tissue and it is not just the muscular aspect but the connective tissue that also surrounds organs[48]. Overall fascia tissue goes under a lot of stress from the body and may become increasingly rigid over time. In addition, fascia tissue can be elastic and go in and out of the normal shape, but over time the overuse may gradually deform the tissue, allowing the rigidness to take place[49]. Tissue rigidity or deformity may contribute pain for an individual. The method of myofascial release is to target those tightened points of fascia tissue and either the individual or clinician will add pressure to the pain point and hold the pressure until there is no longer any resistance

from the tissue[50]. When myofascial release is used by the individual, the tools commonly used are a foam roller and roller massager[51]. Variety of motions and movements used with each of these tools target specific painful areas.

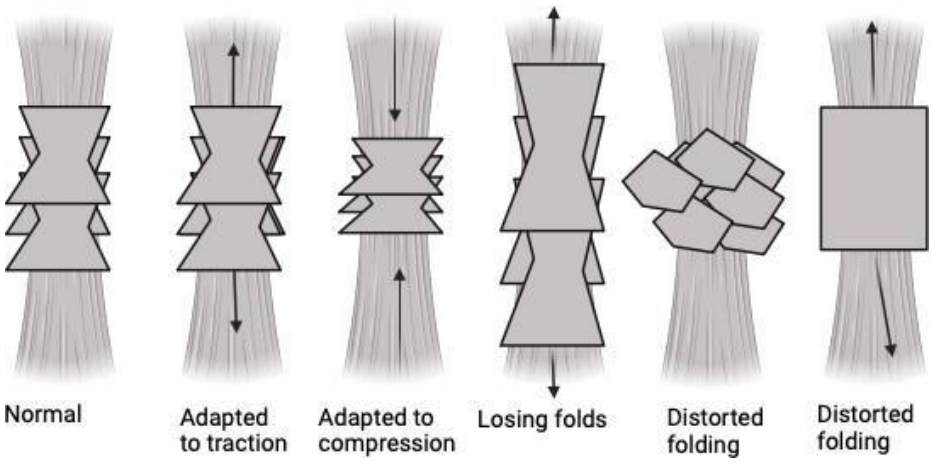

Figure 5. Fascia Tissue Normal vs Abnormal shape

A clinical, double-blind, parallel sham-controlled trial with a balanced randomization trial performed in 2021 investigated the magnitude of myofascial release's relief on chronic lower back pain (CLBP)[52]. In this trial, fifty-four participants between the ages of eighteen and sixty years old diagnosed with nonspecific CLBP for at least three months were chosen. These participants were then divided into two groups: myofascial release (n=27) and sham (n=27) with a random number generator. Patients' pain was measured through the Short Form McGill Pain Questionnaire (SF-MPQ) and visual analog scale (VAS) and disability was measured with the Roland Morris Questionnaire. The trial showed a significant improvement in pain, as displayed with the SF-MPQ compared to the sham group while showing no significant difference in VAS.

4.2 TENS

Transcutaneous electrical nerve stimulation (TENS) is an external non-invasive treatment used to treat neuropathic and nociceptive pain[53]. TENS, in practice, is an inexpensive mode of electrically stimulating targeted tissues that excite a neuronal complex. The most common form of TENS can be found as a small battery-run device that can be self-administered, with the dosage of electrical currents being delivered through electrical pads that are attached to the skin. In addition, there are three different techniques of TENS that are used with this type of device to evoke different nerve fibers to treat different types of pain. The three different techniques are conventional TENS, acupuncture TENS, and intense TENS.

Conventional TENS is the most commonly used technique and is characterized by a low-intensity and high-frequency stimulation[54]. The overall purpose of this approach is to target afferents (A-beta fibers) that are connected to the central nervous system and are related to pain. Conventional TENS stimulation affects a broader neural area and can inhibit nociceptive transmission[55]. Acupuncture TENS (AL-TENS) is considered a high-intensity low frequency technique used for hyperstimulation. AL-TENS targets a smaller area and aims for higher threshold peripheral afferents (A-delta). During this technique, patients may have painless muscle twitches because of the placement of the electrode pads. Intense TENS is viewed as a high intensity high frequency technique that is used as a "counter-irritant" to stop nociceptive transmission in the peripheral nerves before it reaches the central nervous system. This technique is different compared to the other two because this method can only be used for a small amount of time compared to the conventional method, which can be used as long as the patient desires.

The overall method of TENS affects the surrounding area by reducing the transmission of nociceptive neurons. TENS can also activate extra-segmental areas including the midbrain and the medulla. The activation in the midbrain and medulla complexes then triggers descending inhibitory systems which reduces hyperalgesia, an increased sensitivity to pain, or an extreme response to pain. Although the main intent of TENS is through electrical stimulation, some neurochemicals help further the effects of TENS. Low frequency stimulation has demonstrated the involvement of the mu opioid receptor and high frequency has displayed the use of the delta opioid receptors. TENS is still being researched and garnering more information but has shown promising results in multiple clinical trials.

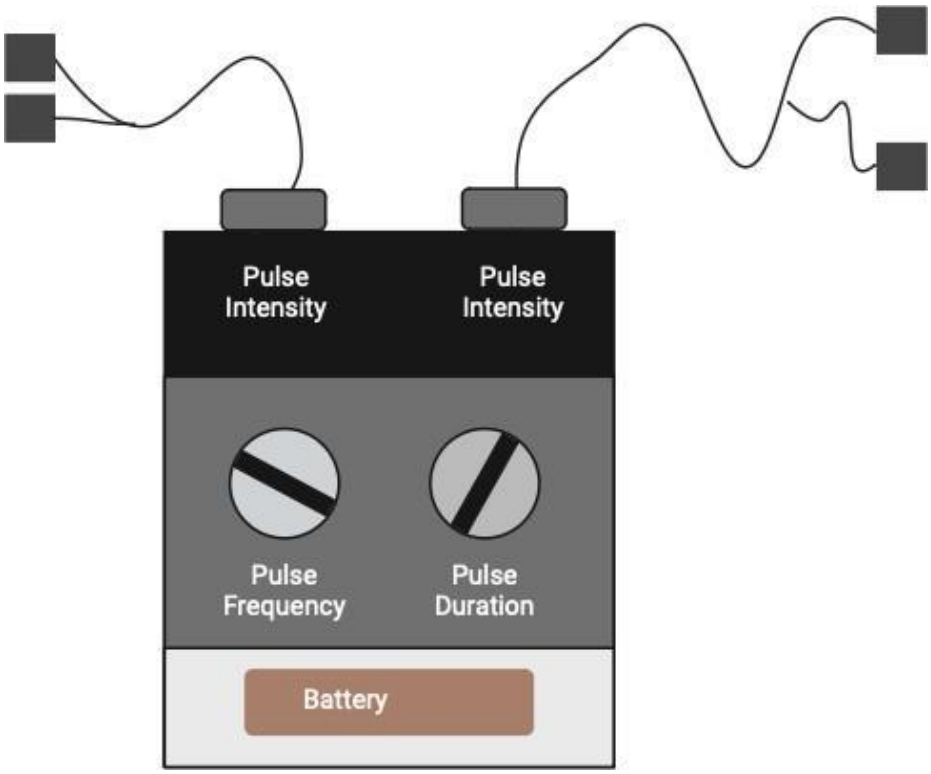

Figure 6. Common TENS device

A heat application studied in clinical trials garnered positive effects[56]. When applying TENS and heat stimulation in a 2021 clinical trial, the results showed a significant improvement in average pain experienced by those affected by chronic lower back pain. The clinical trial was a randomized, double-blinded controlled trial to test the early intervention of TENS for a spinal injury. A treatment of 30 minutes of TENS therapy twice a week for 8 weeks or a sham TENS therapy was supplied as a placebo (n=26). There were 4 pads applied, 2 located paraspinally to the spinal injury and the other 2 located ventrally within the dermatome of the injury. The overall end showed one patient from the TENS treatment and 2 from the sham treatment having adverse reactions related to the study.

With many clinical trials showing promising results, they have also shown some complications with interactions with pre-dispositioned illness. People with epilepsy, who are pregnant or have a pacemaker have been shown to have more risk of complications. In addition, there have been negative effects due to inappropriate positioning of the electrode pads. Current common errors in placement of the pads include over the chest near the heart, eyes, and internally unless specified for internal use. Overall the use of

TENS has been shown to be safe with little to no side effects for most people.

4.3 Photobiomodulation

Photobiomodulation is an external treatment that uses laser and LED light to affect the action potentials of the pain pathway. The method uses low-intensity red or near-infrared light that is brought near the surface of the skin, relative to other energy densities in laser therapy used for ablation, cutting, and the thermal coagulation of tissue[57]. It interferes with the stimulation of action potentials within the mitochondria by initially interacting with the peripheral nerves and having the electrons join part of the photoreceptor on the skin. These photoreceptors stimulate membrane potential and cause extra absorption into the potassium and sodium channels. This increases the reabsorption power of sodium and potassium which keeps the action potential from crossing the threshold needed. The electron transfer by photons in the visible and near-infrared light spectrum through the modulation of cytochrome c-oxidase activity, increasing ATP production, modulation of redox states, and inducing transcription factors[58]. Due to limited understanding of its effects on the molecular, cellular, and tissular mechanisms, photobiomodulation has not been widely accepted in clinical settings. In recent years, the effects of photobiomodulation have been further studied[59].

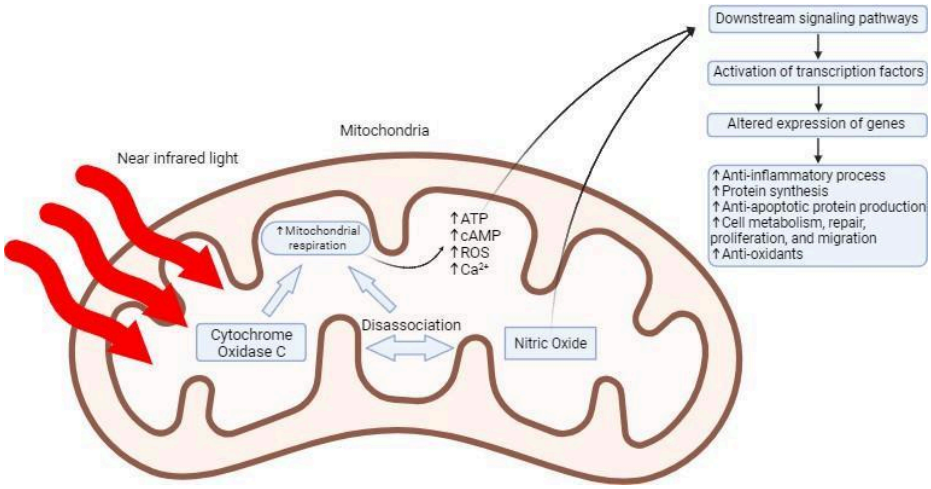

Figure 7. Photobiomodulation mechanism of action

A double-armed, randomized, sham-controlled, double-blinded clinical trial of photobiomodulation therapy with a 3:4 ratio (n=70) to treatment or

sham arms was conducive to less neuropathic pain in treating chemotherapy-associated peripheral neuropathy. Each patient was given 18 treatments of 30-minute duration three times a week, which included laser exposure to areas of pain which included the legs, feet, cervical spine region, and lumbar spine region for anywhere between 3 to 30 minutes, based on the severity of the symptoms. The change in mean for the pain score between the time of randomization and by the end of the experiment for photobiomodulation therapy and sham treatment were -6.8 and 0.2 respectively. The higher magnitude in a change of mean for photobiomodulation therapy demonstrates its efficacy in attenuating neuropathic pain symptoms.

Heat is a limitation in receiving optimal results as the skin surface temperature increases, and the effects of photobiomodulation decrease. Heat can be generated through the absorption of radiation by cells and tissue targeted by the laser. However, this energy transfer from the photons produced by the laser that the skin absorbs is allocated to non-targeted tissues that surround the targeted tissues, leading to the unwanted production of heat that reduces the efficacy of photobiomodulation. Absorption of light is a characteristic that is attributed to any material and, thus, is impossible to completely eradicate. Therefore, an external procedure that decreases the temperature of the surface of the targeted tissue must be performed to induce a substantial response toward photobiomodulation.

Other limiting factors include reflection and scattering[60]. Reflection of light from the targeted tissue implies that the energy provided by the light is not being completely absorbed and that energy is erroneously expended towards non-targeted tissues. Scattering on the other hand disperses light in different directions due to wave-particle interactions. This is significant to photobiomodulation efficiency because varying wavelengths of light pertain to different scattering properties when penetrating tissue, diffusing collimated beams into a cloud of photons. This dilutes the potency of the light because rather than focusing on a single area, surrounding non-target tissue receives unnecessary treatment. Recent debates on using pulsed waves instead of continuous waves to maximize therapeutic efficiency have emerged because pulsed waves are less thermally strenuous to irradiated

tissues which may improve deep tissue penetration, but this is only conjecture since evidence for this hypothesis is scarce.

Photobiomodulation has also been studied in the context of its promising effects on the musculoskeletal system. Due to its cellular activity enhancement capabilities, photobiomodulation is often used in recovering athletes affected by musculoskeletal-related issues. It has been found that when using an 810 nm laser on athletes to observe muscle performance and postexercise recovery, 50 J is the optimum dosage. The study only focused on three different doses at 10 J, 30 J, and 50 J, which implies that an upper limit is still unknown and that a higher dose may be conducive to more benefits. Similarly, an 830 nm laser was used on another group of athletes before and after exercise divided into three groups: placebo, pre-fatigue laser, and post-fatigue laser. This wavelength of light reduced serum lactate and creatine kinase levels in both pre-fatigue laser and post-fatigue laser groups. However, a more significant reduction was observed in the post-fatigue laser group. It has also been found that the source of light is responsible for the resulting beneficial effects of photobiomodulation. In a study observing musculoskeletal performance and postexercise recovery in healthy males, a 30 J dose provided the best results by decreasing delayed-onset muscle soreness and improving biochemical markers related to musculoskeletal damage[61]. Therefore, maximum musculoskeletal system recovery benefits stemming from photobiomodulation therapy are empirically attainable through optimizing wavelength, light source, and application during fatigue.

4.4 Passive Treatment

Capsaicin patch is an effective and accessible treatment for neuropathic pain. Capsaicin is a compound that when used topically, attenuates cutaneous hypersensitivity to heat and mechanical stimuli through the degeneration of nerve fibers. TRPV1, a cationic channel that is activated by capsaicin, stimulates the increased movement of sodium and calcium ions into sensory cells that depolarize nociceptive neurons and cause action potential firing. This creates an analgesic effect that desensitizes the nociceptive areas to which the patch or topical treatment is applied to.

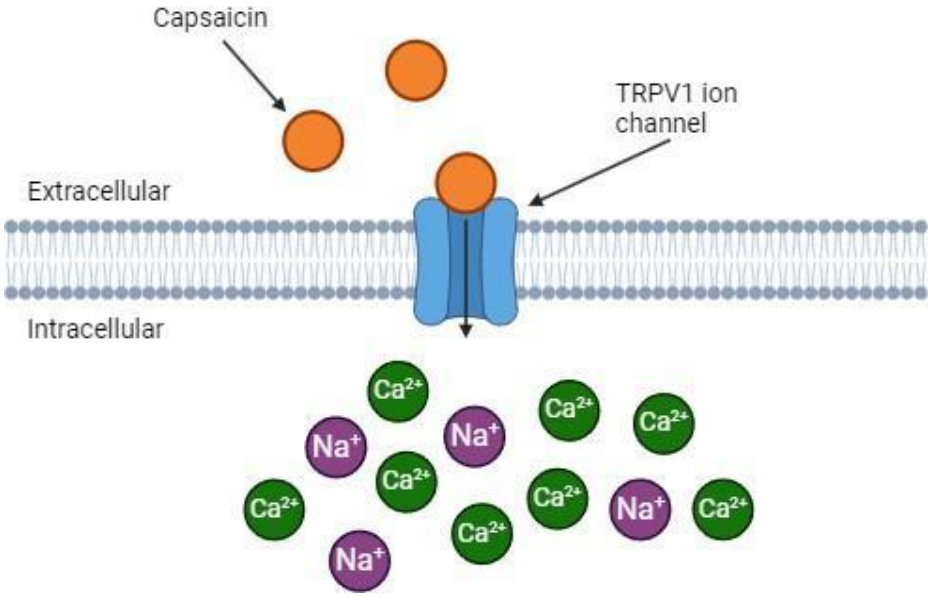

Figure 8. Capsaicin mechanism of action

Unlike other topical alternatives, patches are unique in their method of drug delivery as they can provide extended release of the drug in regulated concentrations to prevent overdose and unwanted prolonged effects. Neuropathic pain is a type of chronic pain. Therefore, capsaicin effectively attenuates pain for longer periods depending on several factors that are being researched in recent developments. The duration of the analgesic effect is affected by the concentration of capsaicin, capsaicin-induced calpain-mediated ablation of axonal terminals, axonal mitochondrial dysfunction, and microtubule disorganization[62]. Calpain is a protease activated by the influx of overbearing levels of calcium into the cell which cleaves cytoplasmic and nuclear substrates causing cells to end up undergoing apoptosis. While calpain enzymes are involved in processes such as cell division, differentiation, and migration, their apoptotic response allows for protection from other malignant cell lines including hepatocarcinoma, prostate cancer, human glioma, breast cancer cells, and human gastric cancer. Therefore, even in different contexts regardless of the causation of said neuropathic pain, capsaicin appears to be a versatile remedy.

A randomized clinical trial involving the application of NGX-4010, a high-concentration capsaicin patch, to treat painful HIV-associated neuropathy areas was conducive to a decrease in the average pain felt by participants (n=422)[63]. The study involved four groups: NGX-4010, 60

Minutes (60 min of high concentration capsaicin 640 mcg/cm^2), Control Group, 60 Minutes (60 min of low concentration capsaicin 3.2 mcg/cm^2), NGX-4010, 30 Minutes (30 min of high concentration capsaicin 650 mcg/cm^2), Control Group, 30 Minutes (30 min of low concentration capsaicin 3.2 mcg/cm^2). The change in mean for the pain score between weeks 2-12 of the study period on a scale from 0-10 (0 = no pain, 10 = worst pain) for the above groups listed were -32.8, -30.0, -26.2, and -19.1 respectively. The "NGX-4010, 60 Minutes" group exhibited the largest reduction in pain score. This suggests that a higher concentration of capsaicin and a longer duration of application is optimal.

Another common analgesia-induced patch used to treat neuropathic pain is through the local anesthetic lidocaine[64]. Frequently juxtaposed with capsaicin, both drugs are mediators for neuropathy, but should not be used interchangeably. Their mechanism of action, situational application, and analgesic effects differ. Lidocaine works to block nerve signals in the area of application by inhibiting the action potentials occurring between nerves through interference with sodium channels. It is mainly used in medical procedures that require localized analgesia, resulting in a numbing sensation in the area due to the blockage of transmission signals. However, both lidocaine and capsaicin are effective neuropathic pain relievers that produce anti-inflammatory effects, it is believed that lidocaine is more effective short term like in cases of dental procedures or minor abrasions while capsaicin is more effective long term involving treatment of allodynia and hyperalgesia.

A double-blinded, placebo-controlled, parallel-group study was conducted to observe the development of adverse effects in type 2 diabetics experiencing symptoms of peripheral neuropathy (pricking sensations, numbness, burning, and aching in feet) for more than 10 years. Only males ages 40-60 were chosen as participants for this study (n=273) to avoid possible hormonal issues as variables. Patients scored from 0-10 (0 = no pain, 10 = worst pain). The study groups are as follows: Group LL (5% lidocaine patch 700 mg lidocaine for 60 min), Group LP (placebo patch for 60 min), and Group LC (8% capsaicin patch 179 mg for 60 min). After 24 weeks, Group LC displayed significantly reduced pain scores compared to Group LP. The average pain scores for the groups are as follows: LL: 6.4 to 4.9, LP: 6.1 to 5.7, LC: 6.7 to 3.6.

Group average satisfaction scores (0 = poor, 4 = excellent) are as follows: LL: 2.1 to 3.2, LP: 2.2 to 2.5, LC: 2.0 to 4.2. Showing higher and improved scores than Group LL in both average pain score and satisfaction score, Group LC demonstrates a more potent analgesic effect.

5. Future Direction/Implications

The emergence of nanotechnology, external modalities, and passive treatments has changed the future of the pain management industry. With the status of pain alleviation not curing or fully treating the problem, these new developing treatments show promising outcomes. They have shown fewer side effects and complications because of their external and non-invasive nature. For the side effects, they also showed no addiction, respiratory depression, and irregular bowel movements that are common in the current treatments such as opioids.

In addition, the style of these procedures has been demonstrated to be more cost-effective when compared to surgical procedures and the repetitive prescriptions of ongoing pain medicine. Even with these advantages of the treatments, there still needs to be consideration that these are developing and still relatively new with more research needing to be done before widespread usage. Additionally, more research must be done to make sure that each method would address the root causes of pain. Despite these treatments still being developed, there would be ethical considerations to address during their development. Those ethical considerations include obtaining informed consent, ensuring patients understand both the benefits and risks, guaranteeing access to treatment without financial or insurance-related barriers, and addressing conflicts of interest among those promoting the treatments. These therapies have currently optimistic results and will change the future of pain treatment.

6. Conclusion

As the field of biotechnology continues to grow, the information gained here will help influence and promote numerous treatment modalities that will help address chronic pain in patients. These modalities would offer more options for the large population of individuals who suffer from pain. In addition, they would be able to treat chronic pain and relieve it greater

than the ongoing treatments. Nanotechnology can effectively work with opioids but enhance their safety profile with their controlled delivery and high specificity. The non-pharmaceutical and external treatments such as myofascial release, TENS, photobiomodulation, and the capsaicin patch are non-invasive and give little to no complications and chances of infections. Although these treatments require further research, they have shown positive outcomes with a good impact on the future of pain management. Furthermore, pain treatments will continue to advance and evolve, expanding the range of procedures available to patients, ultimately improving their wellbeing.

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