



# FOUNTAIN PLAZA PHARMACY

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## Topical Pain Creams for Management of Acute, Chronic, and Neuropathic Pain

Pain is one of the most common reasons people consult a physician. Recent advances in understanding the origin and progression of pain are allowing improved assessment and treatment, thus reducing unnecessary suffering and lost productivity, while improving overall quality of life.

One of the most exciting new concepts in pain management is the use of transdermal (topical) medications. Transdermal delivery allows a convenient, noninvasive, way to manage difficult types of pain. Side effects and drug interactions are minimized because, unlike oral or injected medications that require high blood levels to achieve effectiveness, topical creams are designed to provide high tissue concentrations without significant systemic absorption.

In the past, topical medications had relatively poor bioavailability, limiting their effectiveness. However, the development of a new generation of transdermal gels has changed this. These new specially formulated gels allow medications to readily penetrate the epidermis. Higher concentrations of active ingredients are targeted directly to the site of injury, greatly increasing a drug's effectiveness. Knowledge of the different type of pain receptors and their locations allows for the use of combinations of medication, which work synergistically, and at smaller individual doses to achieve optimum pain relief. Topically applied nonsteroidal anti-inflammatory drugs (NSAIDs), such as ketoprofen, increase the anti-inflammatory response and reduce swelling, thus helping to speed up wound healing. Because systemic absorption is low, gastrointestinal (GI) toxicity, common with NSAIDs, is rarely experienced. Topical application is especially advantageous to patients who cannot tolerate oral NSAID therapy.

Topical delivery has another advantage in that the drug absorption rate through the skin is slower and tissue levels remain higher for longer periods. The skin acts as a drug reservoir. The subsequent slow release of drug from the subcutaneous tissue allows for a longer duration of action than is achieved with oral administration.

Transdermal therapy is readily accepted in European countries where topically applied NSAIDs and other medications have been used for more than 15 years with great success. The primary reason why this therapy is less well known in the United States is because many of the drugs used in the formulations are no longer patent-protected. Drug companies are not interested in funding the research and development of transdermal delivery if they cannot get exclusive marketing rights for their products.

## **Potential Uses:**

Specially blended topical pain formulations, using a combination of medications to block multiple pain receptors, have been used successfully in the management of the following painful conditions:

- o Neuropathic pain
- o Burning feet syndrome, diabetic foot neuropathy
- o Chronic low back pain
- o Fibromyalgia Syndrome
- o Neck pain
- o Post Herpetic Neuralgia
- o Pain and inflammation of arthritis (hands, knees, joints) - rheumatoid arthritis and osteoarthritis
- o Trigeminal Neuralgia (TN or tic douloureux)
- o Pudendal Neuropathy and Pudendal Nerve Entrapment (PNE)
- o Sciatica pain
- o Muscle strains, tendon injuries
- o Plantar fasciitis
- o Herniated disks
- o Phantom limb pain following amputation
- o RSD - Reflex Sympathetic Dystrophy or CRPS - Complex Regional Pain Syndrome

## **What are Transdermal Gels?**

When many people think of a gel, the first thing that comes to mind is something similar to hairstyling gel. Those gels are usually water or alcohol-based and are very different from the gels that we use in our pain formulations.

We use a special product known as Pluronic Lecithin Organogel (**PLO**). Even though it is technically classified as a gel, PLO looks and feels more like a cream (from this point forward the term cream or gel will be used interchangeably).

PLO consists of two phases – an oil phase (lecithin isopropyl palmitate) and a water phase (pluronic gel). Combining the two phases creates tiny spherical units called micelles. Micelles permit the solubilization, dispersion, and transport of both fat-based (lipophilic) and water-based (hydrophilic) drugs across the skin membrane. Some of the unique characteristics of this delivery system include:

- o The water phase acts as a skin penetration enhancer.
- o The oil phase increases the drug's solubility and improves the absorption through the skin.
- o When combined in the appropriate ratios, the two phases work in harmony by acting as surface-active agents that temporarily disorganize the skin's structure and allow medications to penetrate into the tissues.
- o Studies using this special formulation have shown a ten-fold increase in the transport of drug through the skin when compared to water-only based delivery systems.

## **Advantages of transdermal delivery:**

- ⌚ **Provides high levels of active ingredient directly to the site of injury.** A study evaluating ketoprofen transdermal gel found that application to the knee joints of study patients resulted in tissue drug levels that were 100 times higher than blood levels drawn at the same time.  
Because multiple agents are targeted against a variety of pain receptors, these everyday agents, when applied as a transdermal gel, enable medical practitioners to lower the dose of more potent narcotics, as well as decrease the number of potential adverse effects of many of these agents.
- ⌚ **Reduces narcotic requirements.** Doctors know that drug tolerance is a significant problem with all opioid medications. Because of drug tolerance, narcotic doses can escalate over time. Many physicians are reluctant to continue prescribing large doses of narcotics for fear of misuse, abuse, or diversion. There is also a volume of literature suggesting that opioids, as single agent therapy, are not entirely effective in treating acute or chronic pain caused by nonmalignant conditions.  
Experience with transdermal delivery shows that, in the treatment of low back pain and neuropathic pain, patients require significantly lower doses of narcotic analgesics to control their pain. Patients are less sedated and their quality of life is greatly improved. Some experts are also suggesting that using a drug such as topical ketamine, an NMDA receptor antagonist, can actually help delay the development of opioid tolerance.
- ⌚ **Minimizes side effects.** Due to the unique properties of the transdermal gel base, blood concentrations are only about 5-10% of the levels achieved following oral or intramuscular (IM) administration. Lower blood levels significantly reduce the chances for development of side effects such as stomach upset and ulcers that can commonly occur with long-term use of NSAIDs. This is very advantageous since it is estimated that 30% of the total cost of treating arthritis in the US is due to treating the GI side effects of oral NSAIDs.  
Lower blood levels also decrease the possibility of drug interactions (e.g. Coumadin<sup>®</sup> with NSAIDs) and reduce the demands on the liver and kidneys for metabolism and excretion.

## **What is Acute Pain?**

Acute pain is defined by a recent onset and is usually transient in nature. Acute pain is self-limiting and performs a protective biological function by acting as a warning of on-going tissue damage. Acute pain frequently is associated with an inflammatory process. Examples include post-surgical pain, burns, bone fractures, and muscle strains. In most of these conditions, the pain subsides as the injury heals. Acute pain responds well to traditional pain medication (NSAIDs and opioids) when combined with other supportive measures such as rest and immobilization of the injured area.

## **What is Chronic Pain?**

Chronic pain is defined by persistent pain lasting at least 3 months or beyond.

Examples of chronic pain include neuropathic pain, diabetic neuropathy, postherpetic neuralgia, fibromyalgia pain, cancer pain, and arthritic pain.

Chronic pain serves no protective biological function. Rather than being the symptom of a disease process, chronic pain is itself a disease process. Chronic pain is unrelenting and not self-limiting. It can persist for years and even decades after the initial injury. Chronic pain may have multiple causes and factors and is more difficult to treat than acute pain. Chronic pain requires a multidisciplinary approach and customized treatment protocols. If chronic pain is inadequately treated, associated symptoms can include chronic anxiety, fear, depression, sleeplessness and impairment of social interaction. Chronic pain frequently goes beyond the patient to include family members and employment. The fear of pain can be more disabling than the pain itself. Many patients with chronic low back pain have such a fear of re-injury that it sometimes leads to a total avoidance of most forms of physical activity – including job duties – even though exercise and physical activity are usually part of the treatment process and are critical for preventing further physical deterioration.

## **What is Neuropathic Pain?**

Neuropathic pain is chronic pain caused by neural injury or neural dysfunction. Neuropathic pain is an extremely difficult type of pain to manage. The symptoms experienced by the patient with neuropathic pain differ from those experienced by patients with acute pain. Neuropathic pain usually fails to respond to standard analgesic interventions. Opioids may provide a degree of relief, but only at doses impractical for what may become lifelong therapy. People with neuropathic pain can experience anything from mild discomfort to excruciating torture. Typical features of neuropathic pain include shooting or stabbing (lancinating) pain, burning pain, hyperalgesia, and numbness. Many patients are unable to work, walk, or even sleep. For some patients something as straightforward as wearing clothes causes an unbearable burning due to clothing coming in contact with the skin – this type of pain, produced by a normally non-painful stimulus, is referred to as allodynia and is present in many patients with neuropathic pain.

Neuropathic pain can be possible whenever nerves are damaged, by trauma, by diseases such as diabetes, herpes zoster, or late-stage cancer, or by side effects to medication -- some AIDS drugs and chemotherapy agents can cause significant peripheral neuropathy. Neuropathic pain may also develop after amputation, including mastectomy. Unfortunately, some individuals experience pain without an obvious injury or suffer protracted pain that persists for months or years after the initial insult. This pain condition accounts for a large number of patients presenting to pain clinics with chronic, non-malignant pain. Rather than the nervous system functioning properly to sound an alarm regarding tissue injury, in neuropathic pain, the peripheral or central nervous systems are malfunctioning and become the cause of the pain.

## **Treatment of Pain:**

Two primary factors must be addressed to control pain effectively.

- o **Reduce the cause of the pain at the site of injury.** If you have a broken bone, torn ligament, or any other type of acute injury, the first thing that must be done is to correct or alleviate the cause of the injury and prevent further injury. With serious injuries, this might involve surgery to repair the problem. With less serious injuries, this might involve various degrees of immobilization, heat and/or ice packs, massage, and/or restricted use of the injured area.

Acute injuries are frequently associated with inflammation, which is the body's localized response to tissue, muscle, or bone damage. During inflammation, nociceptors (pain receptors in the body) become sensitized, discharge spontaneously, and produce ongoing pain. Physicians try to reduce the inflammation, swelling, and muscle spasms with medications such as NSAIDs, steroids, and muscle relaxants. Sometimes just reducing the inflammation and swelling is all that is needed to stop the pain perception.

- o **Reduce the transmission of pain impulses from the pain site to the brain.** The sensation of pain is the body's way of telling you that something is wrong. Your body has an extensive collection of nerve fibers that ultimately all connect to the spine. Pain is transmitted from the injury site through the nerve fibers to the spine. From the spine, pain signals are then transferred to the brain where the pain is perceived.

Blocking the transmission of pain impulses to the brain is one way that opioid narcotics work. Opioids attach to special opioid receptors located in the brain and spinal cord, and interfere and stop the transmission of pain messages to the brain. Opioids also work in the brain to alter our ability to recognize the sensation of pain. These drugs do not take the pain away, nor do they cause an injury to heal faster. If dosed high enough, narcotics can block even the most horrific pain, but often some "quality of life" is sacrificed. Large doses of narcotics cause increased sedation, drowsiness, lethargy, and depression. It is difficult to maintain a job or to have much of a family or social life when you are overly sedated on pain medication.

**How do Topical Pain Creams Work?** Depending on the ingredients in the cream, we can attack the cause of pain at the injury site, and/or block pain perception at the spinal cord level. Our creams contain multiple agents depending on the type of pain being treated. The drugs work in synergy and target a variety of pain receptors. We can use NSAIDs, such as ketoprofen, which targets inflammation in acute injury. We can also use drugs such as gabapentin and ketamine and apply them directly to the spinal segment of the involved dermatome – this works to block pain signals from reaching the brain.

Using the right combination of ingredients, we can help patients control their pain better and with less reliance on debilitating doses of narcotics.

## **What is a Dermatome?**

Refer to the map of the human dermatome in [Figure 1](#). The human body is composed of individual skin segments, or dermatomes. Each dermatome contains bundles of nerve fibers, which transmit sensory data such as touch, temperature, and pain to a particular vertebra on the spine, and from there to the brain. Returning nerve signals travel from the brain, down the spinal cord and then through the nerves in the dermatome to control functions such as muscle movements.

There are 30 unique spinal cord segments and corresponding dermatomes. The letter-number designations on the dermatome map show the relationship between the dermatome and its corresponding spinal segment. From top to bottom, the spinal vertebrae are classified as 'C' for cervical, 'T' for thoracic, 'L' for lumbar, and 'S' for sacral. Note: There are three dermatomes in the head and face area (designated by the letter 'V'), which are not directly connected to a spinal segment but are connected to the 5<sup>th</sup> cranial nerve (trigeminal nerve).

With an understanding of how nerves transmit and receive signals from the dermatome to the spine it is easy to see how certain diseases, such as shingles and some other neurological conditions, may affect just a certain area of the body. It also helps explain how spinal cord injuries can result in paralysis and loss of sensation to a particular area of the body while other areas are left unaffected.

## **Application Sites:**

### **For Acute or Localized Pain**

For acute pain, or localized neuropathic pain, apply some of the compound directly to the pain site. You can also apply some to the appropriate spinal segment, which corresponds to the dermatome involved. This will serve two functions. It will block the pain at the site where the pain seems to be originating (there are pain receptors located in the skin) and will block pain at the spinal level where pain impulses are fed to the brain. This is especially effective when there is an acute process going on. A recent injury that is still inflamed is a good example of this type of application.

### **For Regionalized or Neuropathic Pain**

This type of pain usually encompasses a larger area. It may not be practical to apply the cream to such a broad and possibly poorly defined area. This pain should be blocked at the spinal level where the pain impulses are transmitted to the brain. Apply the cream directly to the spinal segment of the corresponding dermatome.

For example, if your pain involves both legs, you should apply the cream to spinal segments L1-L5. Apply the creams to an area approximately 2"-3" wide x 3"-4" high. The cream will slowly work its way through the subcutaneous tissues to the correct site of action. Do not be too concerned about not knowing the exact spot to apply the creams. If you get the cream close to the spot, it will still be effective.

## **Application Instructions:**

- o Wash the application site with warm water and soap to remove skin oils. Cleaning the area with an alcohol swab is another effective way to remove skin oils and improve the penetrating properties of the gel.
- o Apply a small amount, usually 1gm (an amount about the size of medium pea).
- o Massage the cream into the skin until completely absorbed. You do not want any cream residue left on the skin. Patients with dry skin may find it helpful to wet their fingertips with a couple of drops of water and continue working the cream into the skin until it is fully absorbed.
- o Caregivers should wear gloves, finger cots, or wrap their finger with disposable plastic wrap to prevent them from absorbing the creams through their own skin.
- o Protect the application site from direct sun exposure.

## **Dosage:**

- o Typically, the creams are applied 3-4 times daily for the first few days to get the pain under control and then 2-3 times daily thereafter. The skin acts like a drug reservoir. The subsequent slow release of drug from the subcutaneous tissue helps explain why the creams may take 2-3 days to reach full effectiveness.
- o The key to success is to use the product faithfully. Since side effects and systemic absorption are minimal, the primary drawback to more frequent use is the extra cost. Adjustments can be made to the cream's ingredients to create the most effective product for the type of pain condition being treated. Patients should work closely with the prescriber to help develop the best formulation to treat their pain condition.

## **Storage:**

The creams should be stored at normal room temperature. The creams are stable for up to 3 months. If PLO cream is refrigerated for extended periods (1-2 weeks), the product may begin to show signs of separation into its component parts. Rarely, separation can also occur because of higher drug concentrations and/or the use of more than a few drug ingredients. For maximum stability, the final concentration of all ingredients should not exceed 20%. Cream separation is something that can be corrected by the addition of various emulsifying agents.

## **Are These Creams Available at Any Pharmacy?**

No. Only compounding pharmacies have the ingredients, equipment, and expertise necessary to formulate these products. Our compounding pharmacists have received special training in the preparation of customized dosage forms to meet a patient's specific needs. We purchase the active ingredients in bulk quantities so that we can pass the cost savings directly to our patients. We have patients all across the country that are benefiting from our customized products.

## **What are the Possible Side Effects?**

Transdermal delivery does not totally eliminate the risk of side effects, however, when applied to the skin, joints, or spinal segments, the pain creams are not absorbed significantly into the bloodstream and experience has shown that side effects are generally non-existent, even with repeated use. If side effects do occur, try using less product, or applying it less frequently. Patients usually find they can lower their dose of other pain medication once the creams start working. The most commonly reported side effects are a rash, irritation, or photosensitivity at the application site. These types of side effects occur with many topical preparations. There is always a possibility that a patient may be allergic to one or more of the cream's components. Patients allergic to egg whites may have an allergy to the lecithin component of the PLO gel. An accurate allergy history from all patients prior to starting therapy is important.

## **What are the Specific Ingredients Used in the Pain Creams?**

A variety of ingredients and concentrations can be incorporated into the pain cream formulations depending on the type of pain being treated. Because of the complex nature of pain, the use of multiple agents with complimentary modes of action is often key to the success of transdermal therapy. Some ingredients are better at relieving inflammation pain (ketoprofen, piroxicam). Other ingredients are more effective at relieving nerve pain (ketamine, gabapentin, clonidine, tetracaine, and amitriptyline). Some ingredients will relieve muscle spasms (baclofen, guaifenesin, cyclobenzaprine).

The correct cream formulation is something that can be determined by working closely with the patient, prescriber, and compounding pharmacist. The ultimate goal is to pick the combination of ingredients that result in the best therapeutic outcome.

Here is a list of the agents we use in our pain formulations (in alphabetical order). A summary of the agents used can be found in [Table 1](#).

**Acyclovir** – For patients with shingles or postherpetic pain, the addition of the antiviral drug acyclovir (in concentrations of 5%) can be very effective. Combine with gabapentin and ketamine for postherpetic pain.

**Amitriptyline** – Amitriptyline is a tricyclic antidepressant agent. It has been used extensively as an analgesic agent for management of neuropathic pain. Unfortunately, the higher oral doses needed to achieve an analgesic effect cause somnolence and dry mouth, thus limiting patient tolerance and compliance. Side effects are eliminated following topical administration. Amitriptyline is used topically in concentrations of 2-5%.

**Baclofen** – Baclofen is a GABA<sub>β</sub> receptor agonist. GABA receptor agonists primarily cause muscle relaxation. Baclofen is commercially available as an oral tablet and an intrathecal injection. Baclofen helps reduce painful muscle spasms and clonus in patients with multiple sclerosis and other musculoskeletal conditions. Baclofen is used topically in concentrations of 1-2%. Baclofen is effective but expensive.

**Clonidine** – Although the precise mechanism of action is unknown, it is believed that clonidine may decrease the site-specific local release of norepinephrine, an agent that stimulates sensitized nerve fibers to cause painful sensations. Clonidine is used orally to treat hypertension, but is also given by epidural or intrathecal injection to help control pain. It is not effective for pain when taken orally. Clonidine's topical effects were discovered when some patients experienced pain relief following the application of the clonidine-TTS patch. Unfortunately, the effects were very localized, thus limiting the usefulness of the patch. However, the ability to apply clonidine directly to the pain site or dermatome is a significant advantage of our cream formulations. Clonidine is used topically in concentrations of 0.1 – 0.2%.

**Cyclobenzaprine** – Cyclobenzaprine (trade name Flexeril<sup>®</sup>) is structurally similar to the tricyclic antidepressants (such as amitriptyline). It is prescribed orally to relieve muscle pain and stiffness caused by injuries such as sprains or strains. When incorporated into creams it is reported to be very effective in relieving muscle tightness in patients with Fibromyalgia Syndrome (FMS) and multiple sclerosis. Cyclobenzaprine is used in a concentration of 1-2%.

**Gabapentin** – Gabapentin (trade name Neurontin<sup>®</sup>) is an antiepileptic medication used to control seizures. There have long been recognized similarities with neuronal misfiring in epilepsy and neuropathic pain. Phenytoin, a commonly prescribed anticonvulsant medication, was shown to have analgesic effect in neuropathic pain in 1942. In neuropathic pain, injured nerve fibers may discharge spontaneously – usually at regular intervals – causing significant pain. Gabapentin is a glutamate antagonist. Glutamate is the chemical that stimulates the NMDA pain receptors (see ketamine section below). Blocking glutamate blocks pain transmission. When administered orally (dosage range of 2400-3600mg/day), Gabapentin has shown results in managing pain caused by diabetic neuropathy and postherpetic neuralgia. Topically, the concentrations used are around 5-6%. Gabapentin is very effective and is well tolerated. It should be considered as a mainstay ingredient for all neuropathic pain creams.

**Guaifenesin** – Oral guaifenesin is used as an expectorant to decrease viscosity of respiratory secretions. Topically, guaifenesin is an effective skeletal muscle relaxant. Concentrations used are 5-10%.

**Ketamine** – Ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist and is topically used in concentrations of 6%. When the pain receptors in the dermatomes start sending signals there is a release of glutamate, which in turn acts on the NMDA receptors in the spinal cord. Activation of NMDA receptors causes the spinal cord neurons to become even more sensitive and responsive to painful stimuli. Ketamine works on receptors in the both the periphery and in the spinal cord. There is also new evidence that blocking NMDA receptors with drugs such as ketamine decreases the development of tolerance to opioids such as morphine, hydrocodone (Vicodin<sup>®</sup>), and fentanyl (Duragesic<sup>®</sup>). Ketamine is another one of the core drugs used in our topical pain cream formulations.

**Ketoprofen** – Concentrations of 5-10% are commonly prescribed. Ketoprofen is a NSAID and provides excellent relief for acute inflammation and swelling resulting from soft-tissue and skeletal muscle injuries. It should be included as an ingredient whenever inflammation is suspected. Ketoprofen cream is particularly effective for treating arthritis inflammation in the back, hands, knees, or other joints. Ketoprofen cream is also effective for patients with gouty arthritis.

**Orphenadrine** – Orphenadrine is a muscle relaxant with NMDA antagonist activity. Topical concentrations used are 5-10%. It is reported to block pain transmission and cause muscle relaxant effects.

**Pentoxifylline** – Pentoxifylline is a Tumor Necrosis Factor antagonist (TNF-1 $\alpha$ ). Tumor necrosis factor is a substance produced primarily by monocytes and macrophages in response to inflammatory processes such as arthritis. Topical pentoxifylline reduces inflammation by inhibiting TNF at the cellular level. It is a useful ingredient whenever inflammation is present. Sciatica and neuropathic pain also respond well to pentoxifylline administration. Concentrations used are 5-10%.

**Piroxicam** – Piroxicam is a potent NSAID. Like other NSAIDs, it provides relief for acute inflammation and swelling resulting for soft-tissue and skeletal muscle injuries. Topical concentrations used on 0.5 - 1%. We frequently combine piroxicam and ketoprofen for patient's whose pain is primarily inflammatory in origin.

**Tetracaine & Lidocaine** – Both of these drugs are local anesthetics that have neuron membrane stabilizing effects. Lidocaine is currently available as a 5% transdermal patch (Lidoderm<sup>®</sup>) approved for management of postherpetic neuralgia. Tetracaine concentrations used in the pain formulations are 1-2%. Lidocaine concentrations used are 2-5%.

### **Other Considerations in the Management of Pain:**

**Magnesium Supplementation:** Magnesium plays a role in keeping glutamate away from the NMDA receptor. There are estimates that 50% of the population is deficient in magnesium. Supplementation should be considered.

**Free Radical Hyperexcitability Theory:** There is evidence that free radicals may cause neuronal hyperexcitability and exacerbate inflammation and swelling. Supplementation with antioxidants such as ascorbic acid (Vitamin C), Vitamin E and Alpha Lipoic Acid in therapeutic doses is reported to be beneficial in patients with neuropathic pain.

## A Special Note for Prescribers

To avoid cream separation problems, the maximum concentration of all active ingredients combined is **20%**. If you have any questions about a specific formulation for your patient, please consult with one of our pharmacists.

<b>Table 1. Summary of Agents Used in Topical Pain Preparations Drug Name</b>	<b>Mechanism of Action</b>	<b>Concentrations used Topically</b>	<b>Type of Pain</b>
<b>Acyclovir</b>	Anti-viral	5%	Shingles, active herpes, postherpetic pain
<b>Amitriptyline</b>	Exact mechanism of action unknown (possible neural membrane stabilization)	2-5%	Neuropathic pain, postherpetic pain
<b>Baclofen</b>	GABA <sub>β</sub> agonist, muscle relaxant, antispasmodic agent	1-2%	Neuropathic pain, multiple sclerosis, postherpetic pain
<b>Clonidine</b>	α-2 antagonist (blocks norepinephrine receptors)	0.1 – 0.2%	Acute or neuropathic pain
<b>Cyclobenzaprine</b>	Muscle relaxant, nerve membrane stabilizer (structural similar to tricyclic antidepressants)	1-2%	Neuromuscular pain (Multiple sclerosis, Fibromyalgia, muscle strains)
<b>Gabapentin</b>	Glutamate inhibition (NMDA receptor antagonism), neural membrane stabilization	5-6%	Neuropathic pain, postherpetic pain
<b>Guaifenesin</b>	Effective skeletal muscle relaxant when used topically	10%	Musculoskeletal pain, Multiple sclerosis, Fibromyalgia syndrome, sports injuries
<b>Ketamine</b>	NMDA antagonist	5-6%	Acute pain, neuropathic pain
<b>Ketoprofen</b>	NSAID – reduces inflammation	5-10%	Pain caused by inflammation
<b>Lidocaine</b>	Local anesthetic, nerve membrane stabilizer	2-5%	Neuropathic pain
<b>Orphenadrine</b>	NMDA antagonist/ muscle relaxant	5-10%	Acute pain, neuropathic pain, neuromuscular pain (MS, Fibromyalgia)
<b>Pentoxifylline</b>	Tumor Necrosis Factor antagonist (TNF-1α)	5-10%	Pain associated with an inflammatory process. Sciatica, low back pain, neuropathic pain
<b>Piroxicam</b>	NSAID – reduces inflammation	0.5 - 1%	Arthritis and Sports Injuries
<b>Tetracaine</b>	Local anesthetic, nerve membrane stabilizer	1-2%	Neuropathic pain