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Review

Current Pharmaceutical Compounding for Neuropathic Pain

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Abstract

An estimated 0.6-1.5% of the U.S. population is affected by neuropathic pain as reported by the American Academy of Pain Management. Currently, neuropathic pain management involves drug combination therapy. Compounding pharmacy plays a key role in meeting the demand for an increasing need for individualized and easily accessible drug preparations. To date, information about neuropathic pain drug compounding is presented as limited number of case studies. This review is to provide current information about compounded neuropathic pain drugs, their delivery system, and therapeutic effects, which is beneficial for compounding pharmacists and prescribers as they aim to improve existing therapy and formulas for neuropathic pain.

Introduction

Treatment of neuropathic pains is challenging. Current medical treatment of neuropathic pain seems inadequate with more than two thirds of patients having no suitable solution for their morbid disease and deteriorating quality of life [1]. As a result, healthcare providers have become increasingly interested in new ways to manage neuropathic pain and develop customized treatment plans for their patients. One of the problems is that neuropathic pain may be different from patient to patient, but the current medical treatment of neuropathic pain is mostly centered on the use of over-the-counter or prescribed medications, which are designed for overall use of all patients. In recent time, the treatment of neuropathic pain is to provide individualized regimens to meet unique and complex needs of patients.

Pharmaceutical compounding gives practitioners another latitude or option in managing patient maladies and, in many instances; compounded medications have been proven effective. They offer healthcare providers benefits such as customizable dosages and formulations, the ability to combine multiple drugs with various mechanisms of action, the likelihood of lower systemic absorption with minimization of side effects, and consequent improved adherence to treatment regimens. Scientific studies indicate that localized cutaneous neuropathic pain can be treated effectively and safely by topical medications [1]; however, only a few topical medications are indicated for neuropathic pain.

This paper reviews guidelines for neuropathic pain and the use of compounding for the management of neuropathic pain, emphasizing in their drug delivery systems, compounding technology, and therapeutic effects in the U.S.A.

Neuropathic Pain

Neuropathic pain is one of the most common reasons for seeking medical attention. Despite its prevalence, neuropathic pain is often under-recognized and inadequately treated. The prevalence of neuropathic pain typically rises with age and severity of the underlying condition. Based on specific causes, epidemiological estimates indicate a prevalence of 1% - 2%. However, the epidemiological surveys suggest that 6-8% of the general population report chronic pain with neuropathic characteristics [2]. Studies show that for every 1000 patients registered with a general practitioner, about 60-80 patients will have symptoms of chronic neuropathic pain. Half of these patients would require medication and regular support [3].

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory system" [4]. With this definition in mind, it would be appropriate to indicate that neuropathic pain can be caused by a number of diseases (e.g. diabetes, HIV infections, multiple sclerosis, herpes zoster), medical interventions (e.g. spinal surgery, cancer chemotherapy, amputation), and injuries (e.g. toxic exposures).Neuropathic pain is pain that is generated by nervous tissue itself. It is a disordered response to nerve injury of either the central nervous system or peripheral nervous system.

The difference between nociceptive pain, the commonest type of pain, and neuropathic pain is that nociceptive pain occurs as a result of tissue damage or disease in the presence of a functionally intact nervous system. However, in neuropathic pain, the nervous system itself is affected. Neuropathic pain is classified as a type of chronic pain. The differences are important for understanding the nature of the pain problem and especially for determining how to treat the pain.

Characteristics of neuropathic pain can be defined within the fol-

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lowing criteria, namely: spontaneous (stimulus independent) and stimulus evoked pains (elicited by mechanical, thermal or chemical stimulus). With stimulus independent pain, patients may complain of constant burning sensation, intermittent shooting, lancinating sensations, electric shock-like pain, dysesthesias (abnormal and unpleasant sensations), and paresthesia (abnormal, but not unpleasant sensations). However, with pain evoked by mechanical, thermal or chemical stimulus, patients may complain of having hyperalgesia (increased response to normally painful stimulus), mechanical allodynia (pain from non-painful stimuli) dynamic - brush evoked, static - pressure evoked and cold allodynia (pain evoked by cold stimulus) [5]. Common types of neuropathic pain are presented in Table 1.

The diagnosis of neuropathic pain is based on a medical history, review of systems, physical and neurological examination, and appropriate laboratory studies including blood and serologic tests, magnetic resonance imaging, and electro-physiologic studies. In some instances, nerve or skin biopsy is necessary to directly visualize nerve fibers. Physicians should also keep in mind that psychosocial factors are a major component of the experience of chronic pain and should be routinely addressed when patients are evaluated. In addition, psychological processes such as anxiety can influence the report of pain and in rare instances produce exaggerated responses [6].

Treatment Guidelines for Neuropathic Pain

Many guidelines have been published for the pharmacologic management of neuropathic pain [7]. These guidelines are fairly consistent and emphasize the importance of medication efficacy, patient comorbidities, potential side effects and drug interactions, abuse potential, and on cost. However, it should be noted that the effective treatment of patients suffering from neuropathic pain remains a clinical challenge despite the recent advances made in the identification of the mechanisms related to nervous system injury. Even though there are numerous treatment options available for relieving neuropathic pain, there is no consensus on the most appropriate treatment.

Most guidelines suggest the following medications as the first line

Table 1: Common types of neuropathic pain. [20]

Peripheral neuropathic pain	Acute and chronic inflammation demyelinating polyradiculoneuropathy
	Alcoholic polyneuropathy
	Chemotherapy-induced polyneuropathy
	Complex regional pain syndrome
	Entrapment neuropathies
	HIV sensory neuropathy
	Idiopathic sensory neuropathy
	Nerve compression or infiltration by tumor
	Nutritional deficiency-related neuropathies
	Painful diabetic neuropathy
	Phantom limb pain
	Postherpetic neuralgia
	Post-radiation plexopathy
	Radiculopathy
	Toxic exposure-related neuropathies
	Tic douloureux (trigeminal neuralgia)
	Posttraumatic neuralgias
Central neuropathic pain	Compressive myelopathy from spinal stenosis
	HIV myelopathy
	Multiple sclerosis-related pain
	Parkinson disease-related pain
	Postischemic myelopathy
	Postradiation myelopathy
	Poststroke pain
	Posttraumatic spinal cord injury pain
	Syringomyelia

treatment for most neuropathic pain excepttrigeminal neuralgia: gabapentin, pregabalin, tricyclic antidepressants (TCA), serotonin-norepinephrine reuptake inhibitors (SNRI) (duloxetine, venlafaxine) and topical treatments (capsaicin and lidocaine patch in the elderly). Tricyclic antidepressants are often the first drugs selected to alleviate neuropathic pain (first-line pharmacological treatment). Even though, they are very effective in reducing pain in several neuropathic pain disorders, treatment may be compromised (and outweighed) by their side effects. In patients with a history of cardiovascular disorders, glaucoma, and urine retention, pregabalin and gabapentin are emerging as the first-line treatment for neuropathic pain. In addition, these anti-epileptic drugs have a favorable safety profile with minimal concerns regarding drug interactions and showing no interference with hepatic enzymes [8]. Tramadol, tramadol/acetaminophen and strong opioids may be used as the second line of treatment. With regard to human immunodeficiency virus (HIV)-associated polyneuropathy, lamotrigine (in patients receiving antiretroviral treatment), or smoking cannabis, capsaicin patches are indicated as the first line of defense. The following drugs are suggested as first line treatment for trigeminal neuralgia: oxcarbazepine and carbamazepine. However, patients with intolerable side effects of first-line treatment can opt for lamotrigine or surgery [9].

Sequential and combination treatment with medications have been used in many neuropathic pain cases. The current understanding of the pathophysiologic mechanisms of neuropathic pain is consistent with the existence of multiple pain mechanisms, each of which may respond differently to medications with different mechanisms of action. Therefore, it is empirically and theoretically appropriate to recommend to patients who do not respond to one of these medications to be treated with another one. It is also common for patients to have a partial response to these medications, and combination treatment should be considered when this occurs. Among the pitfalls of combination therapy include an increased risk of adverse effects as the number of medications is increased and difficulty identifying which of several medications is responsible for the adverse effects.

Current State of Compounding Pharmacies

Long before manufacturing of drugs, compounding was the only source of medicine. At that time, nearly all prescriptions were compounded. However, with the introduction of penicillin in the 1920s and the advent of mass drug manufacturing in the 1950s and '60s, compounding of medications rapidly declined. The pharmacist's role as a preparer of medications quickly changed to that of a dispenser of manufactured dosage forms, and most pharmacists no longer were trained to compound medications. Nevertheless,compounding is still an integral part of today pharmacy. It now accounts for approximately 1% of the drugs prescribed medications [10].

Compounding is described in Chapter 795 of the United States Pharmacopeia (USP) as "the preparation, mixing, assembling, altering, packaging, or labeling of a drug, drug-delivery device, or device in accordance with a licensed practitioner's prescription, medication order, or initiative" [11]. Although compounded medications may have unique formulations, they are prepared under the guidance of the USP, often through the combination of active pharmaceutical ingredients (APIs) utilized in FDA-approved drugs. The FDA traditionally regulates drug manufacturers, but states regulate pharmacies. However, it is appropriate to indicate that three government agencies regulate compounding pharmacies. These are:

- The state boards of pharmacy ensure that pharmacies follow state regulations for pharmacy practice.
- The FDA regulates "the integrity of the drugs" and the active pharmaceutical ingredients from which they are made.
- The Drug Enforcement Administration regulates compounding pharmacies' handling of controlled substances.

The demand for custom made prescription medications continues to grow because manufactures cannot fulfill the needs of the individual patient. More and more physicians are seeing the benefit of compounded products and adding them to their daily prescription protocols. The upsurge in pharmaceutical compounding may also be attributed to pharmacies stepping in on a local basis to fulfill the chronic drug shortages issues facing the country.

There a lot of compounding pharmacies that practice compounding. According to the International Academy of Compounding Pharmacists (IACP), there are around 56,000 community-based pharmacies in the U.S. About half of them directly serve local patients and doctors. And that some 7,500 compounding pharmacies specialize in what the IACP calls advanced compounding services like neuropathic pain treatment.

Compounding for Neuropathic Pain

The role of compounded medications in the treatment of neuropathic pain over the past decades have begun to increase as modern technology, innovative techniques, and research have allowed more pharmacists to customize medications to meet specific patient needs. Alarge number of drugs has been formulated and compounded by pharmacists to treat neuropathic pain. A significant portion of these compounded preparations includes topical/transdermal dosage forms such as creams, gels, pastes, ointments, etc. While the efficacy and doses of these drugs in systemic dosage forms have been widely established, little is known about the permeation and efficacy of these compounds from topical compounded preparations.

It is currently estimated that one percent of all prescriptions are compounded daily by pharmacists working closely with physicians and their patients. Pharmaceutical compounding helps to addresses some deficiencies that could affect the treatment of the illnesses. Among these include:

- Providing unique medication strengths: A medicine may be available only in one or two strengths which might not appropriate for the patient. Compounding provides a dosage that can meet the physician and patient's needs. With the help of compounders, there is no need to take too much medicine which could cause

adverse effects or too little which may sub-therapeutic or not be effective. For instance, topical and transdermal creams and gels can be formulated to provide high local concentrations at the site of application, for trigger point application, or in a base that will allow systemic absorption.

- Providing unique dosage forms: Medicines often are available only in tablets or capsules. The "one-size-fits-all" nature of many mass-produced medications meant that some patients' needs were not being met. Certain individuals with swallowing difficulties may need a liquid, suppository, or other dosage forms. Through compounding, several varieties of dosage form, including capsules, topical and vaginal creams, gels, oral and topical liquids, lozenges, troches, rapid dissolving tablets, mini troches, suppositories, and injectable can be made.
- Providing unavailable medications: Prescription compounding helps to solve many medication challenges including provision of an equivalent substitute medication when there is a drug shortage, back-order, or discontinuation. If the production of a drug is stopped due to limited demand, compounders can compound that drug for the patients if they have FDA approved active pharmaceutical ingredients.
- Flavoring bad tasting medicine: Some individuals will not take a medicine because of bad taste. Compounders can prepare dosage forms in several flavors that may be preferred by the patient.
- Preventing allergies: Commercial medicines may contain flavors, preservatives, dyes, and fillers. A patient maybe allergic to any one of these ingredients. To avoid these unpleasant or life-threatening reactions, compounders can prepare medicines that are free of materials to which a patient is known to be allergic.
- Improving adherence: The approach that many physicians used to provide the patient with the most effective, long-term pain relief from neuropathic pain is poly-pharmacological in nature. This approach often combines a series of oral medications targeting different mechanisms of pain relief. As a result, patients may have to administer multiple pills at different times of day, which can become taxing and confusing for some patients. This contributes to lower patient adherence to treatment plans. Putting different ingredients together help address this problem.

Type of Delivery System used in Compounded Medication for Neuropathic Pain

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound into the body to achieve its desired therapeutic effect as well as safety. Drug delivery is a concept that is heavily integrated with dosage form and route of administration. The term delivery system has several definitions in healthcare and may include any of the following:

- Device used to deliver the drug (e.g., teaspoon, syringe, nebulizer, IV fluid, infusion pump).
- Design feature of the dose form that affects the delivery of the drug, such as the coating on some capsules that resists breakdown by the gastric fluids in the stomach so that the capsule will release medication, instead, into the intestines
- Means for transporting a drug to it's site of action within the body

The drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Most common routes of administration include the preferred non-invasive peroral (through the mouth), topical (skin), transmucosal (nasal, buccal/sublingual, vaginal, ocular and rectal) and inhalation route. Many medications such as peptide and protein, antibody, vaccine and gene based drugs, in general may not be delivered using these routes because they might be susceptible to enzymatic degradation or cannot be absorbed into the systemic circulation efficiently due to molecular size and charge issues to be therapeutically effective. For this reason, many protein and peptide drugs have to be delivered by injection or a nanoneedle array. For example, many immunizations are based on the delivery of protein drugs and are often done by injection [12]. It should be noted that a greater percentage of the compounding are topical and transdermal formulations, hence much of the emphasis in this presentation would be on them. Common delivery systems for neuropathic pain treatment are extensively covered in Section 7.

Topical and Transdermal Formulations

Over the past decade, compounding pharmacists have made great strides in their ability to formulate a wide variety of medications into cream and gel bases that actively transport the medication through the skin directly to the site of action. Instead of dealing with oral absorption complexities, transdermals offer almost complete delivery without many of the side effects associated with the medication when it is taken by mouth. Of course, gastric disturbances are eliminated when the medicine is applied to the skin. In addition, smaller amounts of active ingredient are used, which results in a much lower potential for systemic side effects [13].

Drug products topically administered via the skin fall into two general categories, those applied for local action and those for systemic effects. Topical dermatological product is designed to deliver drug into the skin in treating a disorder. Local actions include those at or on the surface of the skin, those that exert their actions on the stratum corneum, and those that modulate the function of the epidermis and/or the dermis. Common products in the former category include: creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. Creams, ointments, and gels generally are referred to as semisolid dosage forms. The most common drug products applied to the skin for systemic effects are referred to as self-adhering transdermal drug delivery systems (TDS) or transdermal patches.

There are two main pathways by which drugs can cross the skin and reach the systemic circulation. The more direct route is known as the transcellular pathway, while the other route is intercellular in nature. With transcellular pathway, the, drugs cross the skin by directly passing through both the phospholipids membranes and the cytoplasm of the dead keratinocytes that constitute the stratum

corneum. The second pathway (intercellular route) which is more common passes through the skin via the small spaces between the cells of the skin, making the route more tortuous. Although the thickness of the stratum corneum is only about 20 μm, the actual diffusional path of most molecules crossing the skin is on the order of 400 μm. A third pathway to breach the stratum corneum layer is via tiny microchannel created by a medical micro-needling device. This approach is efficient in enhancing skin penetration ability for lipophilic as well as hydrophilic compounds. Devices and formulations for transdermal administered substances include transdermal patch and gel [13]. It should however be noted that the choice of delivery system depends on many factors. Among these factors include:

- Active ingredient to be delivered
- Amount of active ingredient to be delivered
- Means or route that ingredient is to be delivered
- To what sites
- At what rate
- Over what period of time
- For what purpose

Table 2 presents some examples of topical and transdermal formulations for neuropathic pain. In Section 7 more of these are also presented.

Compounding Bases and Permeation Enhancers

Transdermal pain compounds are typically prepared by using either a single or combination of multiple active pharmaceutical ingredients (APIs) in a specially designed compounding base with permeation enhancers. The first widely recognized compounded transdermal base was pluronic lecithin organogel (PLO), known as the first generation, which is an oil and aqueous emulsion introduced as a drug delivery vehicle. It has polymeric surfactant that enhances drug micelle formation shown to enhance the skin permeation of many drugs. The lecithin in it increases fluidity of stratum corneum, leads to exfoliation of stratum corneum and low grade inflammation with chronic use. PLO separates at cold temperatures and therefore do not refrigerate or send through mail during cold months [14].

Lipoderm and Vanpan, second generation permeation enhancers, are more advanced versions. They have shown improvements in consistency and stability. Lipoderm has been shown to successfully deliver four pain medications, including ketamine hydrochloride (HCl), gabapentin, clonidine HCl, and baclofen, simultaneously into human skin. Lipoderm is the proprietary formula (PCCA) containing lecithin. Vanpan is also a proprietary formula (PCCA); however this is used for more lipophilic drugs [15].

Other permeation enhancers include oleic acid, propylene glycol, ethanol, glycol ether/isopropanol, and DMSO. These permeation enhancers might cause irritating. However, lower-dose combinations of enhancers have been used to decrease irritation. Permeation enhancers employ these mechanisms to cross the stratum corneum:

- Change in lipid fluidity in the stratum corneum
- Solubilization of lipids between corneocytes
- Generation of pores on the surface of corneocytes
- Actual exfoliation of the stratum corneum

In addition to the above-mentioned enhancers, there are other enhancers that have started to gain prominence. These are sonophoresis/phonophoresis, and iontophoresis.

Sonophoresis is the use of ultrasound to drive molecules of topically applied medication to produce therapeutic concentrations at selected sites through the skin. The medication preparations are applied to the skin and allow to absorb for a period of time after which ultrasound is applied. phonophoresis has been suggested by early studies to enhance the absorption of analgesics and anti-inflammatory agents. In a randomized study (n = 60) comparing the effectiveness of ibuprofen phonophoresis with conventional ultrasound therapy in patients with knee osteoarthritis, it has been shown to speed the onset of action of EMLA cream (lidocaine/prilocaine) in humans, reducing the time needed for local analgesia from 60 minutes to only 5 minutes [16].

Iontophoresis offers substantial benefits for the transdermal of neuropathic medications, and can be valuable in addition to existing treatment modalities. Iontophoresis introduces the ionizable drugs through intact skin by the administration of continuous, direct electrical current into the tissue. Iontophoresis is a clinically effective, painless and safe mode of delivery ionized neuropathic drugs into the tissues. Iontophoresis, in conjunction with other conservative therapies and interventions, has been shown to effectively manage painful symptoms associated with superficial tissue

Table 2: Examples of some topical and transdermal formulations for neuropathic pain

Delivery System	Treatment
Topical ketamine gel [21]	Hyperalgesia (an exaggerated sensation after a painful stimulus) and reduction of allodynia (a painful sensation elicited by a non-painful stimulus)
Ketamine ointment [22]	Regional pain syndrome
Topical amitriptyline and ketamine ointment [23]	Neuropathic pain syndromes
Tetrahydrocannabinol/ cannabidiol oromucosal spray [24]	Peripheral neuropathic pain
Intra-nasal ketamine [25]	General neuropathic Pain
Capsaicin gel [26]	Painful diabetic neuropathy

structures in a wide variety of patients [17].

In general, the common enhancers used by most compounding pharmacies are pluronic organogel (PLO), lipoderms, and propylene glycol, while sonophoresis and iontophoresis are done from some specialized compounding pharmacies. With these enhancers, compounded transdermal and topical medications can effectively reduce neuropathic pain symptoms while offering a decreased risk of adverse effects commonly associated with oral pain medication, and they may help decrease the risk of drug abuse and addiction. Hence, compounded transdermal and topical preparations for pain management can provide healthcare providers with individualized and potentially more effective options for the treatment of both acute and chronic pain-related conditions.

Therapeutic Effects of Compounded Medications for Neuropathic Pain

Majority of compounded medications for neuropathic pain are topical agents. Topical agents have the potential to deliver drugs locally without systemic toxicity. They are often considered for the treatment of localized neuropathic

pain when oral therapies have failed or have been stopped due to side effects. Some of the drugs that have typically used in compounding formulations for the treatment of neuropathic pain were presented in table 3. A variety of ingredients and concentrations can be incorporated into the neuropathic pain cream formulations depending on the type of pain being treated. Because of the complex nature of neuropathic pain, the use of multiple agents with complimentary modes of action is often a key to the success of transdermal therapy. The efficacy and safety of these formulas used in the treatment of neuropathic pain has been well demonstrated in randomized controlled trials.

Compounded preparations containing a combination, rather than a single API, are often used to treat neuropathic pain. The multimodal approach to pain management, which involves using combinations of analgesics, has successfully been used in various applications to more efficiently provide analgesia. Most of the current pain medications on the market target the μ-opioid, COX, serotonin, or norepinephrine receptors on the ascending and/or descending pathways. When these pathways are utilized at the same time, the analgesic effect can often be reached at a lower dose, partially allowing the side effect profile of multi-modal therapies to be lower than that of an individual medications therapy. Because of its complexity, neuropathic pain is generally treated by block the various physiologic pathways with various mechanisms. Among these pathways are: [18, 19]

- NMDA antagonist
- μ-receptor agonist
- Calcium channel blocker
- Alpha-2 Agonist
- AMPA antagonist
- GABA agonist
- NERI

Therefore, it is not uncommon to have 3-4 active ingredients in each formulation (Table 4). When compounding topical preparations containing multiple APIs, it is important to undertake two verification checks, namely the APIs compatibility and biocompatibility. With APIs compatibility, it is essential to check whether there are no significant interactions exist between the various APIs (chemical incompatibilities). One should also verify that there are no significant interactions between the APIand the vehicle

Table 3: Common medications used in compounding formulations for neuropathic pain

Medication	Classification	Concentration
Lidocaine [27]	Anesthetic nerve pain	2 – 10%
Ketoprofen [28]	Non-steroid anti-inflammatory drug (NSAID)	5-10%
Gabapentin [29]	Glutamate Antagonist	6 – 10%
Ketamine [30, 31]	NMDA Antagonist	5 – 10%
Guaifenesin [32]	Skeletal Muscle Relaxer	10%
Amitriptyline [33, 34]	Antidepressant/Sympatholytic	2 – 5%
Bupivacaine [31]	Anesthetic-Nerve Pain	0.5 -0.75%
Clonidine [35]	Alpha-2 Agonist	0.1 – 0.2%
Dextromethorphan [36]	NMDA / CA Channel blocker	5 – 10%
Carbamazepine [37]	NMDA / Sodium Channel Blocker	2 – 5%
Morphine [29]	MU Agonist	5 – 30%
Nifedipine [38]	L-Type Calcium Blocker	2– 16%
Orphenadrine [39]	NMDA / L Ca+ Channel Blocker	5–10%
Tetracaine [40]	Anesthetic-Nerve Block	2–10%
Baclofen [28]	GABA β agonist, muscle relaxant, antispasmodic Agent	1-2%
Piroxicam [41]	NSAID	0.5 - 1%

Table 4: Examples of combinations used in neuropathic pain management [19, 42-45]

Treatment	Formulas
Sensory Neuropathy "Tingling" Sensation	Gabapentin 6%, loperamide 10% & lidocaine 2% , amitriptyline 2-5% + Clonidine 0.1 –0.2% + Ketamine 5% + Baclofen 2% or clonidine 0.1%
Chemotherapy-induced peripheral neuropathy	Baclofen 0.76%, amitriptyline 3%, and ketamine, 1.5% in PLO
Provoked vestibulodynia	Amitriptyline 2%, baclofen 2% in cream base
Radiation skin reaction	Amitriptyline 2%, ketamine 1%, and lidocaine 5% in PLO
Neuropathic pain syndromes:	Amitriptyline 2% and ketamine 1% in cream
Acute herpetic neuralgia and PHN	Aspirin 2.5%-7.5% dissolved/suspended in diethyl ether
Chronic human neuropathic pain	Doxepin 3.3% and capsaicin 0.025% in cream
Knee Pain	- Diclofenac 5-10% + lidocaine 5% + DMSO 10-20% - Ketorolac 8% + Tetracaine 5% + CMO 4% + DMSO 20%
Sciatica Pain	Gabapentin 6%, Diclofenac 4%, Lidocaine 2%, DMSO 5%
Raynaud's Disease	Nifedipine 6% (2-10%) + Pentoxifylline 10% (5 –15%) + Sildenafil 4% (1 –5%)
Pain for radiation Burns	Ketamine 5%, gabapentin 6%, morphine 0.5%, lidocaine 1%
Shingles	Ketamine 10%, bupivacaine 0.5% Ketamine 4%, morphine sulfate 4% (good for allodynia) Hydromorphone 1 –5%, lidocaine 1 –5% Lidocaine 4%, tetracaine 4% A foam could also be utilized Ketamine 2% + morphine sulfate 2%

(chemical/physical incompatibilities) and between the API and the biotransforming enzymes in the skin. The efficacy of these compounded drugs could decrease if there are significant interactions between the various components of the compounded medication [19]. The possibilities of interactions between the various APIs are higher with combination therapy than monotherapy. Pain with multiple pathophysiology mechanisms fair can be treated better with combination therapy. Most of the side effects are skin related such as skin rash.

Conclusion

Pharmacy compounding continues to deliver a vital health need to patients that are unable to be treated with FDA-approved medications. Many patients have benefited tremendously from the services provided medication compounders. The benefits of well-tailored compounds are a huge benefit for patients. The biggest advantage of compounded medications is their customizability where it is impossible for drug companies to have every strength, dosage form, or flavoring available for each individual. The ability to produce individualized therapy versus one-size fits all is crucial for many patients with neuropathic pain. It is important for a practitioner to be able to formulate a unique combination of medications and to rely on a compounding pharmacy to make it. The trend in health care is changing towards individualization of drug therapy. It is envisaged that in the future, pharmacotherapy might be more specific and physicians may be working collaboratively with compounding pharmacists to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.

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Reference

1. Baron R, Binder A,Wasner G (2010) Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 9(8): 807-819.
2. Smith BH, Torrance N (2012) Epidemiology of neuropathic pain and its impact on quality of life. Curr Pain Headache Rep 16(3):191-198.
3. Mc Dermott AM, Toelle TR, Rowbotham DJ, Schaefer CP, Dukes EM (2006) The burden of neuropathic pain: results from a cross-sectional survey. Eur J Pain 10(2):127-135.
4. Jensen T.S, Baron R, Haanpaa M, Kalso E, Loeser JD, et al.(2011) A new definition of neuropathic pain. Pain. 152(10): 2204-2205.
5. Freynhagen R, MI Bennett (2009) Diagnosis and management of neuropathic pain. BMJ 12: 339:3002.
6. Dworkin R.H, Backonja M, Rowbotham MC, Allen RR, Argoff CR, et al. (2003) Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 60(11): 1524-1534.
7. O'Connor, RH Dworkin, Joseph Audette, Ralf Baron, Dr Med (2009) Treatment of neuropathic pain: an overview of recent guidelines. Am J Med 122(10 Suppl): 22-32.

8. Vranken J.H (2009) Mechanisms and treatment of neuropathic pain. Cent Nerv Syst Agents Med Chem. 9(1): 71-78.

9. AttalN, Cruccu G, Baron R, Haanpaa M, Hansson P (2010) EFNS guidelines on the pharmacological treatment of neuropathic pain: revision. Eur J Neurol 17(9): 1113-1188.

10. Andrea Branvold, Maria Carvalho (2014) Pain management therapy: the benefits of compounded transdermal pain medication. J Gen Practice 2:188.

11. United States Pharmacopeia (2014) Chapter 795 in Pharmaceutical compounding-nonsterile preparations, United States Pharmacopeial Convention: Rockville.

12. Wang N.X, HAvon Recum (2011) Affinity-based drug delivery. Macromol Biosci 11(3): 321-332.

13. Morganti P, Ruocco E, Wolf R, Ruocco V(2001) Percutaneous absorption and delivery systems.Clinics in dermatology 19(4): 489-501.

14. Jones M (2003) The history of pluronic lecithin organogel. International journal of pharmaceutical compounding **7**.

15. Branvold AC, Maria Carvalho (2014) Pain management therapy: the benefits of compounded transdermal pain medication J Gen Practice 2(6):188.

16. Michlovitz SL (2005)Is there a role for ultrasound and electrical stimulation following injury to tendon and nerve? Journal of hand therapy : official journal of the American Society of Hand Therapists 18(2): 292-296.

17. Kozanoglu E, Basaran S, Guzel R, Guler-Uysal F (2003) Short term efficacy of ibuprofen phonophoresis versus continuous ultrasound therapy in knee osteoarthritis. Swiss medical weekly 133(23-24): 333-338.

18. Sawynok J (2014) Topical analgesics for neuropathic pain: preclinical exploration, clinical validation future development. European journal of pain 18(4): 465-481.

19. Zur E (2014) Topical treatment of neuropathic pain using compounded medications. The Clinical journal of pain 30(1): 73-91.

20. DworkinR.H, Backonja M, Rowbotham MC, Allen RR, Argoff CR, et al. (2003) Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Archives of neurology 60(11): 1524-1534.

21. Finch PM, L Knudsen, P D Drummond (2009) Reduction of allodynia in patients with complex regional pain syndrome: A double-blind placebo-controlled trial of topical ketamine. Pain 146(1-2): 18-25.

22. Ushida T, Tani T, Kanbara T, Zinchuk VS, Kawasaki M, et al.(2002)Analgesic effects of ketamine ointment in patients with complex regional pain syndrome type 1. Regional anesthesia and pain medicine 27(5): 524-528.

23. Lynch M E, Clark AJ, Sawynok J, Sullivan MJ (2005) Topical amitriptyline and ketamine in neuropathic pain syndromes: an open-label study. The journal of pain : official journal of the American Pain Society 6(10): 644-649.

24. Zettl Uk, Paulus Rommer, Petra Hipp, Robert Patejdl (2016) Evidence for the efficacy and effectiveness of THC-CBD oromucosal spray in symptom management of patients with spasticity due to multiple sclerosis. Therapeutic advances in neurological disorders 9(1): 9-30.

25. HugeV, Lauchart M, Magerl W, Schelling G, Beyer A, et al. (2010)Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. European journal of pain 14(4): 387-394.

26. Kulkantrakorn K, Lorsuwansiri C, Meesawatsom P (2013) 0.025% capsaicin gel for the treatment of painful diabetic neuropathy: a randomized, double-blind, crossover, placebo-controlled trial. Pain practice : the official journal of World Institute of Pain 13(6): 497-503.

27. Moulin DE, Boulanger A, Clark AJ, Clarke H, Dao T, et al.(2007) Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. Pain research & management 12(1): 13-21.

28. Allen L (2010) Baclofen 5%, gabapentin 5%, ketoprofen 10%, and lidocaine 5% in pluronic lecithin organogel. International journal of pharmaceutical compounding 14(6): 515-517.

29. Gilron I , Balley JM, Tu D, HoldenRR, Weaver DF, et al.(2005) Morphine, gabapentin, or their combination for neuropathic pain. The New England journal of medicine 352(13): 1324-1334.

30. Mahoney JM, VardaxisV, Moore JL, Hall AM, Haffner KE, et al.(2012) Topical ketamine cream in the treatment of painful diabetic neuropathy: a randomized, placebo-controlled, double-blind initial study. Journal of the American Podiatric Medical Association 102(3): 178-183.

31. Uzaraga I, Gerbis B, Holwerda E, Gillis D, Wai E (2012) Topical amitriptyline, ketamine, and lidocaine in neuropathic pain caused by radiationskin reaction: a pilot study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 20(7): 1515-1524.

32. Allen L (2000) Cyclobenzaprine 1% and guaifenesin 10% in Speed gel. International journal of pharmaceutical compounding.

33. Lynch ME, Clark AJ, Sawynok J, Sullivan MJ (2005) Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial. Anesthesiology 103(1): 140-146.

34. Lynch ME, AJ Clark, J Sawynok (2003) A pilot study examining topical amitriptyline, ketamine, and a combination of both in the treatment of neuropathic pain. The Clinical journal of pain 19(5): 323-328.

35. Campbell CM, Kipnes MS, Stouch BC, Brady KL, Kelly M, et al. (2012) Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy. Pain 153(9): 1815-1823.

36. Allen L (2011) Amitriptyline 4%, dextromethorphan hydrobromide 20%, and tramadol hydrochloride 5% in pluronic lecithin organogel Gel. International journal of pharmaceutical compounding 15(3): 242-251.

37. Allen L (2008) Carbamazepine topical preparations.

38. Allen L (2011) Nifedipine 160 mg/mL in pluronic lecithin organogel. International journal of pharmaceutical compounding 36(12): 39-40.

39. Winter L, Post A (1979) Analgesic combinations with orphenadrine in oral post-surgical pain. The Journal of international medical research 7(3): 240-246.

40. Holmes MV, Dawe RS, Ferquson J, Ibbotson SH (2004) A randomized, double-blind, placebo-controlled study of the efficacy of tetracaine gel (Ametop) for pain relief during topical photodynamic therapy. The British journal of dermatology 150(2): 337-340.

41. Van Haselen R, Fisher PA (2000) A randomized controlled trial comparing topical piroxicam gel with a homeopathic gel in osteoarthritis of the knee. Reumatology 39(7): 714-729.

42. Jones M (2000) Chronic neuropathic pain: pharmacological interventions in the new millenium - A theory of efficacy. International journal of pharmaceutical compounding 6(1): 4-6.

43. Quan D, Wellish M,Gilden DH (2003) Topical ketamine treatment of postherpetic neuralgia. Neurology 60(8): 1391-1392.

44. McCleane G (2000) Topical application of doxepin hydrochloride, capsaicin and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. British journal of clinical pharmacology 49(6): 574-579.

45. Lehman JS, Sciallis GF (2008) Effective use of topical amitriptyline hydrochloride 2.5% and ketamine hydrochloride 0.5% for analgesia in refractory proctodynia. Journal of drugs in dermatology 7(9): 887-889.