PAIN MANAGEMENT

The Importance of Individualized Therapy

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"Pain is one of the most common reasons people consult a physician, yet it frequently is inadequately treated, leading to enormous social cost in the form of lost productivity, needless suffering, and excessive healthcare expenditures."

American Academy of Pain Medicine and American Pain Society. *The use of opioids for the treatment of chronic pain [consensus statement].*

Chronic pain afflicts approximately 10-20% of the adult population. Advances in research and development have greatly enhanced our ability to treat both acute and chronic pain disorders. However, while the number of treatment options—including antidepressants, anticonvulsants, opioids, nonopioid analgesics, local anesthetics, and alpha-adrenergic agents—for such conditions as polyneuropathy, postherpetic neuralgia, low back pain, soft tissue injuries, and arthritic conditions has expanded, many patients - particularly those with persistent pain - continue to experience inadequate pain relief and/or intolerable adverse effects.

Pain control is essential because, even when the underlying disease process is stable, uncontrolled pain prevents patients from working productively, enjoying recreation, or taking pleasure in their usual roles in the family and society. Chronic pain may have a myriad of causes and perpetuating factors, and therefore can be much more difficult to manage than acute pain, requiring a multidisciplinary approach and customized treatment protocols to meet the specific needs of each patient.

Assessment

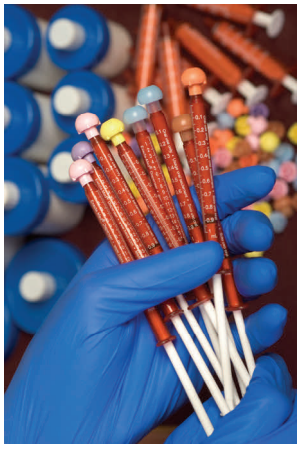
"Pain can be managed. Physicians must determine the severity and frequency of their patients' pain experience to prescribe the most appropriate and effective pain management regimen. ***Pain treatment needs to be individualized.***"[3]

The goal of the initial assessment of pain is to characterize the pain by location, intensity, and aggravating and relieving factors. Frequently, a 10-point Numeric Pain Intensity Scale or Visual Analog Scale is used to facilitate communication between the patient and health care professionals, and to monitor the adequacy of therapy. Regular follow-up should occur and routine recording of pain intensity along with other vital signs is recommended.

Treatment

By combining various agents which utilize different mechanisms to alter the sensation of pain, physicians have found that smaller concentrations of each medication can be used. Optimal treatment may involve not only the use of traditional analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, but may also include medications that possess pain-relieving properties, including some antidepressants, anticonvulsants, antiarrhythmics, anesthetics, antiviral agents, and NMDA antagonists. Adjuvant drugs - including antihistamines and corticosteroids - are valuable during all phases of pain management to enhance pain relief, treat concurrent symptoms, and counteract the side effects.

As we learn more about the biochemical and pathophysiologic mechanisms of pain, our knowledge enables us to develop targeted strategies for specific conditions. ***"Combination therapy is frequently the only effective approach for managing the complex array of chemical mediators and other contributors to the individual pain experience. As topical formulations are developed, they provide hope for more effective drug combinations, with fewer systemic adverse drug effects and drug-drug interactions."***



Topical agents, used alone or in combination with other therapies, are proving to be both safe and effective in reducing pain and improving function in patients with a variety of neuropathic and non-neuropathic pain states. Research indicates that topical analgesics create an efficacious option for adjuvant drug therapy, with minimal risk of significant systemic absorption and drug-drug interactions. For example, topical administration of NSAIDs offers the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse effects, such as peptic ulcer disease and GI hemorrhage. Topically applied NSAIDs have a superior safety profile to oral formulations: GI adverse drug reactions are rare with topically applied NSAIDs, compared with a 15% incidence reported for oral NSAIDs.

Transdermal medications are also a very useful option when patients are unable to take medication orally, and this route of administration can often eliminate the need for injectable therapy. Transdermal administration avoids first pass hepatic metabolism, and is an excellent option in patients with fluctuating hepatic function.

The International Association for the Study of Pain defines a dermatome as "the sensory segmental supply to the skin and subcutaneous tissue." Dermatome maps can be helpful in determining the most effective site of application for transdermal pain therapy.

Pain Myths and Facts

The following information was abstracted and quoted with permission from referenced lecture notes of Alan Spanos, M.D., MA. Dr. Spanos, a graduate of Oxford University, is a Pain Specialist at Blue Ridge Clinical Associates, Chapel Hill, NC.

Basic textbook paradigm portrays pain as:
-the experience attending sudden tissue damage, causing involuntary withdrawal of the damaged body part, with severity proportional to the extent of tissue damage, beginning as excruciating but reducing as tissue heals, and disappearing when healing is complete.

But in fact:
-tissue damage often causes no immediate pain; its severity bears no relation to the extent of tissue damage; it may build up rather than decrease during healing; and it may persist indefinitely after all tissue healing is over.

"The classical image is of pain as a specific sensation, recorded by specialized nerve receptors in the tissues and transmitted intact to the brain, where it is somehow registered in consciousness and then reacted to. Nothing could be further from the truth. The nerve impulses that trigger pain arise out of very complex processes in the extraneural tissues. Here, and at every step up through the nerves, spinal cord, brainstem and brain, the afferent flow is subject to both amplifying and suppression factors in an extraordinarily complex network, so that the final input to the brain is the product of very extensive 'reworking.' Pain is therefore a highly 'constructed' experience. The hierarchy of amplification and suppression serves to allow pain, and responses to it, to be molded by past experience and future expectation. It also results in substantial differences among individuals in their pain physiologies, which is reflected in the richly varied responses to analgesics from one individual to another."

Clinical Advances in Pain Management: Targeted Peripheral Analgesics Transdermal and Topical Therapy for Acute and Chronic Pain

The following information was presented at the 22nd Annual Scientific Meeting of the American Pain Society: 50 million Americans have chronic pain. Advances in research and development have greatly enhanced the ability to treat both acute and chronic pain disorders. However, while the number of treatment options—including antidepressants, anticonvulsants, opioids, nonopioid analgesics, local anesthetics, and alpha-adrenergic agents—for such conditions as polyneuropathy, postherpetic neuralgia, low back pain, soft tissue injuries, and arthritic conditions has expanded, many patients, particularly those with persistent pain, continue to experience inadequate pain relief and/or intolerable adverse effects. ***Topical agents, used alone or in combination with other therapies, are proving to be both safe and effective in reducing pain and improving function in patients with a variety of neuropathic and nonneuropathic pain states.***

Jana Sawynok, Ph.D., professor of pharmacology at Dalhousie University, Nova Scotia, stated that currently, ***topical administration of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, capsaicin, local anesthetics, and alpha-adrenergic agonists is being used to treat a variety of clinical conditions***. Scientific evidence indicates that topical analgesics create an efficacious option for adjuvant drug therapy, with minimal risk of significant systemic absorption and drug-drug interactions.

Dr. Sawynok noted that NSAIDs act peripherally to reduce the production of prostaglandins that sensitize nerve endings at the site of injury, generating analgesic effects. A newer strategy has been the development of topical formulations of NSAIDs to minimize systemic absorption and consequent adverse drug effects. One study reported the efficacy of NSAIDs in musculoskeletal and soft-tissue injuries as well as rheumatic diseases. These reports suggest clear evidence that topical NSAIDs are effective analgesics and may be administered in various dosage forms, including a gel or spray, to treat soft-tissue injuries.
Advanced Studies in Medicine, Johns Hopkins University, Volume 3 (7A), July 2003

What Determines the Extent of Absorption of Transdermally Administered Medications?

- Area of application
- Skin characteristics (i.e. thickness and hydration)
- Molecular weight of the drug
- Use of chemical penetration enhancers
- Drug solubility (lipid or water)
- Stability of formulation
- Vehicle base selection

The optimal transdermal formulation is highly individualized.

The consistency and characteristics of the selected base are of paramount importance. Options include pluronic lecithin organogel (PLO), vanishing-penetrating base, USP DMSO, and numerous patented formulations such as Lipoderm®. Proper preparation of transdermal medications requires the use of chemicals and equipment that are not available in most pharmacies.

Our compounding professionals can compound topical or transdermal preparations that contain a combination of medications to individualize therapy and meet the specific needs of each patient.

Oral versus Topical NSAIDs in Rheumatic Diseases

NSAIDs are among the most commonly prescribed drugs worldwide and are responsible for approximately one-quarter of all adverse drug reaction reports. NSAIDs are widely prescribed for patients with rheumatic disease-a population at increased risk for serious gastrointestinal (GI) complications. Topical administration of NSAIDs offers the advantage of local, enhanced drug delivery to affected tissues with a reduced incidence of systemic adverse effects, such as peptic ulcer disease and GI hemorrhage. NSAIDs administered topically penetrate slowly and in small quantities into the systemic circulation; bioavailability and maximal plasma NSAID concentration after topical application are generally less than 5 and 15%, respectively, compared with equivalent oral administration. Product formulation may have a dramatic impact, not only on absorption rates but also on penetration depth. Compared with oral administration, topical application leads to relatively high NSAID concentrations in the dermis. Concentrations achieved in the muscle tissue below the site of application are variable, but are at least equivalent to that obtained with oral administration. NSAIDs applied topically do reach the synovial fluid, but the extent and mechanism (topical penetration versus distribution via the systemic circulation) remain to be determined. In addition, marked interindividual variability was noted in all studies; percutaneous absorption may be strongly influenced by individual skin properties. Overall efficacy rates attributable to topical NSAIDs in patients with rheumatic disorders ranged from 18 to 92% of treated patients. Topically applied NSAIDs have a superior safety profile to oral formulations. Adverse effects secondary to topical NSAID application occur in approximately 10 to 15% of patients and are primarily cutaneous (rash and pruritus at site of application). GI adverse drug reactions are rare with topically applied NSAIDs, compared with a 15% incidence reported for oral NSAIDs.

Drugs. 2000 Sep;60(3):555-74

Topical Ibuprofen Gel for Acute Soft Tissue Injury: Efficacy and Absorption

The efficacy of a novel, proprietary topical formulation of ibuprofen 5% gel (Ibugel, Dermal Laboratories Ltd, UK) and ibuprofen 400 mg tablets (1200 mg daily) was compared in a double-blind, parallel group study in patients with acute soft tissue injuries. Patients received either active gel plus placebo tablets (n=50) or active tablets plus placebo gel (n=50) for at least 7 days. The gel was applied or one 400 mg ibuprofen tablet was taken three times daily. The two treatments showed similar efficacy. There were no significant differences between the groups for either the primary efficacy endpoint or for other efficacy measures including swelling and the times to clinically significant relief from pain at rest or on movement. In summary, the study concluded that ibuprofen gel shows similar efficacy to oral ibuprofen 400 mg and may offer improved tolerability.

In a separate study, the efficacy of ibuprofen 5% gel was evaluated in a placebo-controlled study in patients with soft tissue injuries. Patients received either ibuprofen gel (n=40) or placebo gel (n=41) for a maximum of seven days. Pain and interference with physical activity were assessed daily using visual analogue scales. Clinically meaningful reductions in pain were achieved significantly faster in patients using ibuprofen gel. By day 7, 75% of patients in the active gel group had a clinically meaningful reduction of pain compared with 39% of patients who received placebo. Also, by day 7, 79% of patients in the active gel group had a clinically meaningful reduction in interference with physical activity, compared with 44% of patients who received placebo.

A comparison of six different topical preparations all containing ibuprofen 5% showed that the composition of the vehicle can have a significant impact on the percutaneous penetration of the active medication.

Int J Clin Pract. 2002 Mar;56(2):102-6
J Clin Pharm Ther. 2002 Dec;27(6):409-17
Skin Pharmacol Appl Skin Physiol. 2003 May-Jun;16(3):137-42

Looking for an alternative to COX-2 inhibitors? Topical NSAIDs have a safety profile which is superior to oral formulations, and offer the advantage of local, enhanced delivery to painful sites with a reduced incidence of systemic adverse effects. We can compound topical preparations that contain a combination of medications to meet the specific needs of each patient.

Review of Topically Applied NSAIDs

Moore et al. of the University of Oxford, England performed a quantitative systematic review of randomized controlled trials of topical non-steroidal anti-inflammatory drugs compared to placebo or oral non-steroidals. The result: 86 trials involving 10,160 patients concluded that topical NSAIDs are effective in relieving pain in acute and chronic conditions. None showed significant benefit of oral over topical preparations. "Topical non-steroidal anti-inflammatory drugs have a lower incidence of gastrointestinal adverse effects than the same drugs when they are taken orally. The low incidence of systemic adverse effects for topical NSAIDs probably results from the much lower plasma concentration from similar doses applied topically to those administered orally. Topical application of ibuprofen resulted in measurable tissue concentrations in deep tissue compartments, more than enough to inhibit inflammatory enzymes."

British Medical Journal Vol 319: Jan 31, 1998; 331-338

Efficacy and Safety of Topical Diclofenac Solution for Treatment of Primary Osteoarthritis

A randomized, double-blind, double-dummy equivalence trial compared the safety and efficacy of a topical diclofenac solution versus oral diclofenac in relieving the symptoms of primary osteoarthritis (OA) of the knee. A total of 622 men and women with radiological evidence of primary knee OA and mild to severe symptoms were randomly assigned to treatment with a topical diclofenac solution plus placebo oral capsules, or placebo topical solution plus oral diclofenac (50 mg) capsules. Patients applied 50 drops of study solution and took 1 study capsule 3 times daily for 12 weeks. Safety analyses of patients applying topical diclofenac solution revealed some minor skin irritation at the application site--mostly skin dryness in 83/311 (27%) patients--but a significantly reduced incidence, relative to oral diclofenac, of total and severe gastrointestinal (GI) adverse events, including dyspepsia, abdominal pain, diarrhea, and nausea. The number of patients developing abnormal liver function tests (including clinically significant elevation), hemoglobin, and creatinine clearance was significantly higher in the oral diclofenac group. The researchers concluded that application of this topical diclofenac solution to the knee of patients with OA produced relief of symptoms equivalent to oral diclofenac, with minor local skin irritation, but significantly reduced incidence of diclofenac-related GI complaints and abnormal laboratory values.

Based on the premise that a topical NSAID formulation may provide symptom relief with fewer adverse effects than the same medication administered orally, a topical diclofenac sodium solution-containing the absorption enhancer dimethyl sulfoxide-was evaluated for the relief of the symptoms of primary OA of the knee. A total of 326 patients with abnormal radiographic findings and flare of pain and were randomized to receive 40 drops of topically-applied diclofenac solution or a vehicle-control solution, 4 times daily, for 12 weeks. Researchers evaluated pain and physical function and stiffness and pain on walking, at baseline and after final application, and assessed safety by evaluation of adverse events, vital signs, and irritation at the application site. Topical diclofenac solution was significantly more effective than the vehicle-control solution for all outcome measures. There was no significant difference between groups in NSAID-related gastrointestinal tract complaints or in dropouts due to study-related adverse effects. Topical diclofenac was found to be effective in the treatment of the symptoms of primary OA of the knee, with only minor local irritation and no significant systemic adverse events.

A topical diclofenac 1.5% solution has been approved in Canada, the United Kingdom, Italy, Austria, Finland, Luxembourg, Greece, Portugal, Iceland and the Caribbean. The product is under FDA review in the United States.

J Rheumatol. 2004 Oct;31(10):2002-12
Arch Intern Med. 2004 Oct 11;164(18):2017-23

Percutaneous Absorption of Ketoprofen

"A topical formulation of ketoprofen has been developed for the temporary relief of minor aches and pains of muscle and joints and to minimize gastrointestinal effects after oral administration... The percutaneous absorption of drugs from topical application is known to be influenced by differences in skin structure at various regions of the body." This study in compared the absorption from a 3% gel applied topically to the back, arm and knee. "The systemic concentrations of ketoprofen have also been found to be 100 fold lower compared to tissue concentrations below the application site in patients undergoing knee joint surgery. Topically applied ketoprofen thus provides high local concentration below the site of application but lower systemic exposure."

Pharmaceutical Research 13(1): 168-172

Benefits of Topically-Applied NSAIDs: Alternatives to Problem-Causing Oral Agents

The bioavailability of a single, topically applied, 200-mg dose of ketoprofen (delivered in a ketoprofen 20% gel) relative to a single 50-mg oral dose in healthy volunteers was studied in an open-label crossover study. The subjects were randomized to receive an oral 50-mg ketoprofen capsule or a single topical dose of ketoprofen 20% in a poloxamer-lecithin organogel (PLO). Blood samples were collected at intervals up to 10 hours after administration, and plasma ketoprofen concentrations were determined by high-performance liquid chromatography with ultraviolet or mass spectrometry detection. The median oral maximum plasma concentration (Cmax) exceeded the topical Cmax by nearly 200-fold (4.15 versus 0.021 microg/mL). The authors concluded that the relative bioavailability of ketoprofen was low and highly variable when the drug was administered as a single dose in a PLO-based ketoprofen 20% gel. This confirms previous reports that topical administration of NSAIDs produces high tissue concentrations beneath the site of administration, but low plasma levels, and therefore provides symptom relief with fewer adverse effects than the same medication administered orally.

Am J Health Syst Pharm. 2004 Dec 1;61(23):2541-4

Topical NSAIDs for Breast Pain

More than 70% of women complain of breast pain at some time during their lives. There are many protocols that treat mastalgia with great success. Unfortunately, most of these treatments have significant side effects that occur at unacceptably high rates.

A prospective, randomized, blinded, placebo-controlled study was performed to evaluate the effects of topical NSAIDs on cyclic and noncyclic mastalgia. A total of 108 patients were randomly assigned to receive either topical NSAIDs (50 mg diclofenac in topical gel) or placebo every 8 hours. Severity of pain was measured before, during, and after 6 months of treatment. The authors concluded that topical application of NSAIDs was effective in both cyclic and noncyclic mastalgia with minimal side effects.

The authors felt that topical NSAID therapy was preferable to oral administration because topical therapy minimized the incidence of side effects, was easy for patients to use, and reduced the "time and effort" required of medical staff.

A previous prospective study of the effectiveness of the topical NSAID gels was carried out in 26 women with severe breast pain. The results showed a satisfactory relief of pain in 81% of the women, including two women with severe scar pain after lumpectomy and radiotherapy. Relief of severe pain was rapid and no side effects were reported.

These factors compare favorably with established recommended treatments (i.e., danazol, bromocriptine, tamoxifen) which usually involve months of continuous treatment, tailoring of drug dosages and a significant incidence of intolerable side effects. Topical NSAID application is an effective, safe, acceptable and easily administered treatment for severe cyclical and non-cyclical breast pain.

J Am Coll Surg 2003 Apr;196(4):525-30
J R Coll Surg Edinb 1998 Jun;43(3):158-9

Local NSAID Therapy for Episiotomy Pain

To determine if diclofenac suppositories produce effective and lasting analgesia following perineal injury, a randomized, double-blind, placebo-controlled trial was conducted involving 100 women who sustained second degree tear or episiotomy during spontaneous vaginal delivery at term. Suppositories containing 100 mg diclofenac or placebo were administered at the time of repair and approximately 12 hours later. The mean pain score was significantly reduced in the diclofenac group at 24, 48 and 72 hours after delivery compared with the control group. In addition, less supplementary analgesia was required (eight women only at 72 hours compared with 15 in the control group) and this was limited to acetaminophen or topical treatments to the perineum. The researchers concluded that rectal diclofenac provides effective analgesia after perineal repair and its effect appears to be maintained into the second and third postpartum days.

A previous double-blind, randomized placebo-controlled study assessed the efficacy of indomethacin suppositories as a post-episiotomy analgesic. Thirty patients received two 100 mg indomethacin suppositories, and 30 patients received placebo within 15 minutes of an episiotomy repair. Subjective symptoms of pain were evaluated 15, 30, 60 and 90 minutes post-repair. None of the patients who received indomethacin complained of post-episiotomy pain; whereas the control patients manifested varying degrees of pain.

Br J Obstet Gynaecol 1998 Jun;105(6):627-31
Int J Gynaecol Obstet 1988 Feb;26(1):57-60
Int J Gynaecol Obstet 2002 Aug;78(2):159-61

Neuropathic Pain

includes a variety of conditions such as diabetic neuropathy, post herpetic neuralgia, post mastectomy pain, phantom limb pain, reflex sympathetic dystrophy (RSD or Complex Regional Pain Syndrome), and pain caused by blunt trauma or crushing injuries. Symptoms of neuropathic pain may not be evident for weeks to months after the injury. The likelihood of effective management worsens as the symptom duration increases; therefore, prompt evaluation and treatment are vital.

Neuropathic pain continues to be one of the most challenging forms of chronic pain to successfully treat. Although many different therapeutic options are available, their utilization is limited due to a high incidence of drug-drug interactions and other contraindications. Many of these problems may be minimized by using topical preparations. Multiple ingredients with complementary modes of action have been found to be effective. Compounded medications using special bases that enhance penetration at the site of pain have proven to be more efficacious than the use of simple creams, gels, and ointments.

NMDA receptors are primarily responsible for the majority of cases of neuropathic pain. By using NMDA receptor antagonists along with other agents, pain control can be significantly improved. NMDA antagonists such as ketamine are often used first line followed by additives such as sodium channel blockers, alpha-2 agonists, or substance P blockers. Because receptors for these medications have been found in local tissues, compounded topical preparations have shown positive outcomes in the management of chronic pain. Therapy usually starts with three medications in low dosages compounded into a suitable base and applied at eight hour intervals. Because side effects are rare, dosage increases may occur daily or every other day until pain is controlled. In order to achieve maximum results, the patient, practitioner, and pharmacist must work together closely, so that each formulation can be prepared to meet the unique needs of a specific patient.

The following medications have been compounded as topical formulations, according to the *International Journal of Pharmaceutical Compounding*:

Class of Drug	Medication
NMDA antagonist	Ketamine, Amantadine, Dextromethorphan, Orphenadrine, Haloperidol
Glutamate antagonist	Gabapentin
AMPA-Na+ channel blocker	Gabapentin, Carbamazepine, Valproic acid, Phenytoin
Alpha-2 agonists	Clonidine, Tizanidine
NE reuptake inhibitors	Tricyclic antidepressants
GABA*b* agonists	Baclofen
Non-NMDA Ca++ channel blockers	Nifedipine

Alpha-Adrenoceptor Agonists

Clonidine has been used successfully to treat patients with chronic pain conditions. The efficacy of local clonidine in sympathetically maintained pain may result from presynaptic inhibition of noradrenaline release from sympathetic nerves, as well as actions directly on primary afferent nerve terminals. Acting systemically, transdermal clonidine relieved symptoms of neuropathic pain in patients with diabetic neuropathy. ***Applied as an extemporaneously compounded cream for local effects, clonidine provides relief from orofacial neuralgia-like pain.***

As we learn more about the biochemical and pathophysiologic mechanisms of pain, our knowledge enables us to develop targeted strategies for specific conditions. An appropriate plan for pain management can be developed based on whether the pain is inflammatory or neurogenic in origin. ***"Combination therapy is frequently the only effective approach for managing the complex array of chemical mediators and other contributors to the individual pain experience. As topical formulations are developed, they provide hope for more effective drug combinations, with fewer systemic adverse drug effects and drug-drug interactions."***

Alpha Adrenoceptors Increased in Hyperalgesic Skin

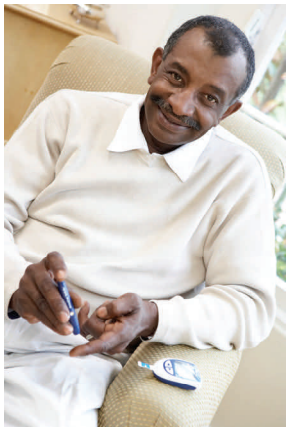
Evidence of an adrenergic component of cutaneous hyperalgesia in painful peripheral neuropathy has prompted speculation that an increased density or sensitivity of peripheral alpha-adrenoceptors contributes to sensory abnormalities and chronic neuropathic pain in conditions such as reflex sympathetic dystrophy. Drummond et al. identified alpha 1-adrenoceptors in the epidermis and

dermal papillae of normal individuals, and in the hyperalgesic and pain-free skin of patients with RSD. The mean density of alpha 1-adrenoceptors was significantly greater in the hyperalgesic skin of RSD patients than in the skin of normal individuals.

Alpha 2-adrenergic agonists may relieve pain in sympathetically maintained pain (SMP) syndromes (such as RSD) by spinal, peripheral, and central nervous system actions. A study at Wake Forest University Medical Center examined analgesic efficacy and side effects of epidurally administered clonidine in patients with severe, refractory RSD. Twenty-six patients with severe chronic pain consistent with RSD were studied in a randomized, blinded, placebo-controlled design. Cervical or lumbar epidural catheters were inserted and patients received epidural injections of clonidine or placebo. Pain, sedation, blood pressure, and heart rate were monitored. Clonidine, but not placebo, caused extensive pain relief, sedation, and decreased blood pressure and heart rate after bolus epidural injection. Sedation and hypotension may limit bolus epidural clonidine administration, and the role for chronic epidural infusion of clonidine has not yet been established. *However, transdermal clonidine has been demonstrated to produce analgesia in the area surrounding its application site in patients with SMP, without the risks associated with epidural injection.*

Clin Sci (Colch) 1996 Jul;91(1):73-7
Anesthesiology 1993 Dec;79(6):1163-9

Transdermal Clonidine for Diabetic Peripheral Neuropathy



A formal clinical trial of transdermal clonidine using a two-stage “enriched enrollment” design was conducted by the Neurobiology and Anesthesiology Branch of the National Institutes of Health. “Post-hoc analysis of many variables suggested that patients who described their pain as sharp and shooting may have a greater likelihood of responding to clonidine.”

Pain 1995 Mar;60(3):267-274

Topical clonidine gel has been investigated as an innovative treatment for peripheral neuropathic pain, including widespread and frequently debilitating conditions where current treatments are often ineffective. In initial clinical trials, topical clonidine gel was associated with minimal side effects and was found effective where other treatments had failed.

While clonidine is an alpha2-adrenergic receptor agonist widely prescribed in oral form or as a transdermal patch for the treatment of hypertension, it has also been shown to produce a localized concentration-dependent analgesia. Because its effect is concentration-dependent, however, the compound does not provide analgesia at the site of pain when administered orally. Moreover, when delivered via transdemal patch, clonidine produces analgesia in only a narrow band with poor pain relief in areas not covered by the patch. In addition, the systemic concentrations of clonidine produced by the transdermal patch may result in systemic side effects, including dry mouth, drowsiness, fatigue, headache, lethargy and sedation, insomnia, dizziness, impotence, dry throat, constipation, nausea and change in taste.

Schwartz *et al.* studied the safety and analgesic effect of topical clonidine gel for the treatment of pain in 10 patients with chronic diabetic neuropathy. Patients applied clonidine gel to each foot/leg twice daily for 2 weeks, and then gradually increased the dosing frequency to 4 times daily until the end of the 6-week study. Patients were evaluated at enrollment and at 2, 4, and 6 weeks, rating their pain on an 11-point pain scale ranging from 0 (no pain) to 10 ("pain as bad as it could be.") At the end of the study, all patients reported some pain relief, with 3 patients claiming complete relief and 7 moderate relief. Adverse events were mild, suggesting minimal systemic absorption of the drug.

http://www.medscape.com/viewarticle/420350 (accessed 10/08)

Topical Clonidine for Orofacial Neuropathic Pain

“An open-label trial of clonidine, an alpha 2-adrenergic agonist, was prescribed for patients with a clinical diagnosis of oral neuropathic pain or neuralgia involving the oral cavity. Clonidine (0.2 mg/g) was prepared in a cream base and applied four times daily to the site of pain. Seventeen patients were assessed: 10 were diagnosed with neuropathic pain, and 7 with neuralgia. Two of the 17 patients had complaints overlapping both neuropathic and neuralgic pain. In the patients with neuropathic pain, an overall mean reduction in severity of burning of 36% (on a 10-point visual analogue scale) was reported. Half of these patients reported clinical improvement; however, no patients reported complete resolution of symptoms. Of the patients with characteristics of neuralgia, 57% improved; and in those who reported improvement, a mean reduction of approximately 54% was reported. In the 4 patients with neuralgia who responded, a 94% reduction in pain was reported, with complete resolution of pain in 2 patients. This

open-label clinical trial suggests that topical clonidine may be effective in the management of some patients with oral neuralgia-like pain, but may have a more limited effect in those patients with oral neuropathic pain. Besides type of pain, no other variables predicted which of the patients would achieve pain reduction with topical clonidine. Although confirmation of clinical efficacy requires double-blind clinical studies, this initial trial suggests that further study is warranted."

J Orofac Pain 1997 Fall;11(4):346-52

Mexilitene for Diabetic Neuropathy

Diabetic Peripheral Neuropathy (DPN) affects up to 50% of diabetic patients, and may result from either hyperglycemia or insulin deficiency. Although analgesics may offer some relief, they often fail to adequately control the pain. Antidepressants, particularly tricyclics, and anticonvulsants have been shown to be effective for DPN. However, side effects may be bothersome. Success with intravenous lidocaine prompted research with mexilitene, since it is orally active. A multicenter, randomized, double-blind, controlled trial of one hundred patients showed that mexilitene had a significant effect on sensory pain, such as burning. (*Diabetes Care* 1992;15:1550-55) Another study by Oskarsson et al. evaluated daytime and nighttime pain at three dosage levels and found mexilitene to be effective in relieving nighttime pain and improving sleep disturbances. (*Diabetes Care* 1997;20:1594-97) The most commonly reported side effects were gastrointestinal disturbances.

Topical Aspirin for Relief of Pain due to Herpes Zoster and Postherpetic Neuralgia

"Topical applications of analgesic and neuroleptic agents [to treat HZ and PHN] have recently been reported with greater frequency. Their efficacy has varied greatly." This study of 42 consecutive patients found "all patients initially were substantially relieved of pain and reported that it began to diminish within 1 to 5 minutes" after application of the topical aspirin. Maximum relief was achieved in 20 to 30 minutes and typically lasted 2 to 4 hours (occasionally up to 8 to 10 hours). When pain again became distressing, patients repeated the application (three to four times daily). Most patients promptly reduced or discontinued their use of other analgesics. Those with PHN continued use of the topical aspirin formulation for several weeks to more than a year, as their pain gradually diminished. "The locus of pain origin and analgesia induced by topical aspirin is most likely at cutaneous free nerve ending pain receptors. The mechanism responsible for the analgesic properties of aspirin is probably not the same as that responsible for its anti-inflammatory properties."

Arch Neurol 1993;50:1046-1053

Bareggi et al compared the efficacy and skin and plasma levels of a topical aspirin/diethyl ether mixture versus oral aspirin in acute herpes zoster and postherpetic neuralgia. Nineteen patients, 11 with AHN and 8 with PHN were given, on different days, a single 500-mg oral dose of ASA or a topical dose (750 mg) of (ADE) daubed onto the painful skin. The analgesic effect was assessed by means of a visual analogue scale (VAS). After ADE application, the analgesic effect was very rapid and VAS scores were lower than at baseline. Pain significantly decreased by 82.6% after topical and 15.4% after oral ASA. After ADE, 95% of the patients had excellent or good pain relief, but after oral administration 79% of the patients had a *poor* response. Skin concentrations of ASA, but not of SA, after ADE were about 80 to 100 fold those after oral administration. Plasma levels of ADE were undetectable or very low. The researchers concluded that the analgesic effect of ASA (in AHN and PHN) can be obtained only after topical administration, because by this route the skin levels of ASA are much higher than after oral administration. The mechanism is exclusively local; there are no active drugs in plasma after topical administration.

In a double-blind, crossover, placebo-controlled study, DeBenedittis and Lorenzetti compared ADE with two other NSAID (indomethacin and diclofenac) drug/ether mixtures. Comparative treatment results showed that only aspirin was significantly superior to placebo. Good-to-excellent results were achieved by 87% of AHN patients and by 82% of PHN patients treated with the ADE mixture.

Aspirin in chloroform solution has been shown to be a simple and effective adjuvant in the management of chronic neurogenic pain.

Eur J Clin Pharmacol 1998 May;54(3):231-5
Pain 1996 Apr;65(1):45-51
Arch Phys Med Rehabil 1997 Apr;78(4):437-9

Topical Gabapentin for Pain of Peripheral Origin

"Gabapentin has been shown to have antihyperalgesic properties and the site of drug action is reported to be the central nervous system." The goal of a study at the University of Texas was to determine whether gabapentin also has a peripheral site of action. Rats received intraplantar injections of gabapentin which significantly reduced formalin-induced nociceptive behaviors. The antihyperalgesic effect of gabapentin was not due to a systemic or local anesthetic effect. "Although the mechanism of action of GP has yet to be elucidated, these results indicate that GP has a peripheral site of action and thus may offer a novel therapeutic agent for topical or local treatment of pain of peripheral origin."

Pain 1998 May;76(1-2):201-7

Topical Tricyclic Antidepressants for Neuropathic Pain

Phillips and Al-Muhairi of Boston University School of Medicine, recently reported the case of a 66-year-old woman who presented with severe burning sensations in both soles of her feet, which worsened at night and disturbed her sleep. The patient has insulin-dependent diabetes. Skin on both feet was hypersensitive to touch and pressure, peripheral pulses were intact, and capillary refilling time was normal. The patient was diagnosed as having diabetic neuropathy. The soles of her feet were treated with topical doxepin twice daily for four weeks. The patient responded dramatically with loss of the severe burning sensation and no side effects.

Tricyclic antidepressants (TCAs) are important drugs in the treatment of painful neuropathy. Their analgesic effect is independent of their antidepressant activity and generally occurs at low doses with onset of pain relief in one to two weeks. For example, the analgesic effect of topically applied doxepin hydrochloride in chronic human neuropathic pain has been described in a randomized, double-blind, placebo-controlled study of 200 adult patients. Fewer side effects were reported compared with oral administration (the most prominent being a transient somnolence). Minimal percutaneous absorption of topical doxepin occurred with plasma levels of topical doxepin ranging from 0 to 47ng/mL compared to 30 to 150ng/mL reported for orally administered doxepin. Contact sensitization and dermatitis has been reported. Rational use of doxepin cream will minimize side effects. Thin films of doxepin cream should be applied to no more than 10 percent of body surface area, and under no circumstances should occlusive dressings be used.

Other studies have shown that topically applied amitriptyline is effective as an analgesic in humans.

Wounds 2003;15(8):272-276
Br J Clin Pharmacol 2000;49:574-9
Pain Clin 2000;12(1):47-50.
Reg Anesth Pain Med 2003 Jul-Aug;28(4):289-93
http://www.medscape.com/viewarticle/431465 Accessed 10/08.

Neuropathy Foot Cream

The following testimonial appeared in the December 1999 issue of *Neuropathy News*, a patient newsletter.

"My local [compounding pharmacist] has created a cream to help alleviate the pain of foot neuropathy. It reduces the burning and sharp, needle-like pain. All you need is a very thin coat. The directions call for using it four times a day, but I find it particularly helpful at night. [The formulation contains] 2% amitriptyline and 2% baclofen in a transdermal gel.

"Compounding pharmacists have the unique training and ability to create medications that address the individual needs of patients. One of the most helpful products they use are transdermal gels that allow for the passage of medication directly through the tissue into the area of pain. Many of the medications typically prescribed for neuropathy patients such as amitriptyline, lidocaine, mexilitene, ketamine and [gabapentin] can cause significant side effects when taken orally. Transdermal gel minimizes systemic side effects and maximizes local pain relief. Compounding pharmacists have many resources that offer relief from neuropathic pain."

In *Diabetes Interviews*, January 2000, Neil A. Burrell, DPM, CDE, of Beaumont, Texas, wrote "We have a very high success rate using amitriptyline and baclofen mixed in a gel component. This compound is applied to the feet three times per day, and offers immediate relief... [For] recalcitrant neuropathic pain, many times we use a combination of tramadol, gabapentin and amitriptyline."

Alpha Lipoic Acid for Diabetic Neuropathy

Alpha Lipoic Acid (also known as thiotic acid, a natural cofactor in dehydrogenase complexes) is an antioxidant nutrient which is currently used in Europe to treat and prevent complications associated with diabetes, including neuropathy (painful peripheral nerve degeneration), cataracts and macular degeneration. Additionally, researchers have found that ALA can actually reverse neuropathy, aid in glucose utilization, and in some cases, help diabetics reduce their reliance on insulin. In two multicenter, randomized, double-blind, placebo-controlled trials, researchers in Germany have reported that treatment with ALA using a well-tolerated oral dose of 800 mg/day for 4 months may improve cardiac autonomic dysfunction (CAD) in patients with Type 2 diabetes (NIDDM).

Lidocaine 8% Intranasal Spray for Trigeminal Neuralgia

Trigeminal neuralgia is a recurrent severe shooting neuropathic pain which can be triggered by light stimuli such as touch, chewing, talking and brushing the teeth. An attack of trigeminal neuralgia lasts only seconds to a few minutes, but multiple excruciating attacks may occur in a single day. Treatment continues to be a major therapeutic challenge. Trigeminal nerve block by injection is often accompanied by excruciating pain originating from punctured nerve fibers, possibly resulting in paresthesia. Many patients thus prefer to avoid such injections.

The second division of the trigeminal nerve passes through the sphenopalatine ganglion (SPG), which is located posterior to the middle turbinate and is covered by a mucous membrane. Anatomically, the location of the SPG makes it accessible for topical application of anesthetics. As an alternative to using drops or applying a solution using a cotton swab, Kania *et al.* tested the effect of lidocaine 8% applied as a metered-dose spray (two sprays, each 0.1 ml). In a randomized, double-blind, placebo-controlled, crossover study, 25 patients with second-division trigeminal neuralgia were randomized to receive two sprays of either lidocaine 8% or saline placebo. All patients had received previous treatment with carbamazepine, but 11 patients had to discontinue carbamazepine because of side effects.

Ninety percent of the patients treated with intranasal lidocaine 8% spray reported a significant reduction of pain intensity using a VAS scale. This rate is comparable with that reported for oral carbamazepine. The onset of effect with intranasal lidocaine, however, appeared within 30 minutes or less, while oral carbamazepine did not have any effect for at least 48 hours. The effect of lidocaine treatment persisted for 4.3 hours (range 0.5-24 hours). After using lidocaine spray, patients should be cautioned to check their gag reflex before eating or drinking.

Compared to other current therapies for trigeminal neuralgia, intranasal lidocaine spray has some advantages:

1. Rapid pain relief. Patients can eat, drink, talk and wash their faces shortly after application.
2. Non-oral therapy. Patients often cannot take oral medications because the pain intensity is aggravated upon mouth opening.
3. Portable device. The patient can carry a metered-dose spray bottle and use it whenever pain appears.
4. No serious adverse reactions. All reported side effects were limited to local irritation; burning, stinging or numbness of the nose and eye, and bitter taste and numbness of the throat. No patients had difficulty speaking or swallowing.

A criticism of the study is that only single episodes were treated.

CONCLUSION: Intranasal lidocaine 8% administered by a metered-dose spray produced prompt but temporary analgesia without serious adverse reactions in patients with second-division trigeminal neuralgia.

Br J Anaesth. 2007 Feb;98(2):275

NMDA Receptor Antagonists for Neuropathic Pain

Recently discovered *N*-methyl-d-aspartate (NMDA) receptors prompt nerve cells to be hypersensitive to pain. “Neuropathic pain associated with hyperalgesia and allodynia is often persistent, and results in significant suffering and impaired quality of life. Recent evidence indicates that NMDA receptor antagonists can block pain transmission in dorsal horn spinal neurons and reduce nociception... Amantadine is an agent available for long-term use in humans, and has recently been shown to be an NMDA receptor antagonist... Several animal studies with NMDA receptor antagonists have shown long-term prophylactic and therapeutic effects which last far beyond the drug presence in body tissues.” This report presents the cases of three patients in whom acute administration of amantadine (200 mg IV) resulted in complete resolution of chronic neuropathic pain and its associated hyperalgesia and allodynia. Elliot *et al.* of Cornell University Medical College showed that the NMDA receptor antagonist dextromethorphan can modulate morphine-mediated analgesic tolerance. Ketamine is an NMDA antagonist which may be useful in the treatment of postherpetic neuralgia.

In neuropathic pain, several types of central effects are indicated in the pathological activation of the central nociceptive neurons. One mechanism is represented by central sensitization, which refers to abnormal hyperexcitability of central nociceptive neurons dependent on the activation of the N-methyl-D-aspartate (NMDA) glutamtergic receptors on the membrane of spinal dorsal horn neurons. This is caused by massive release of excitatory amino acids, glutamate and aspartate, making the NMDA receptor another potential target for the control of neuropathic pain. Therefore, the rationale for using dextromethorphan in neuropathic pain is that DM is an antagonist of the NMDA receptor. Antagonists of glutamate are thought to be neuroprotective. Additionally, dextromethorphan is a sigma receptor agonist, suppressing the release of excitatory neurotransmitters. Thus, appropriately elevated blood levels of dextromethorphan are a potential therapeutic solution to a common and painful symptom complex. The usefulness of dextromethorphan in treating neuropathic pain is suggested by the results of controlled and uncontrolled clinical studies reported in scientific literature. A significant commercial advantage of the product will be that neuropathic pain patients, such as those who suffer from diabetic neuropathy, will be able to avoid products that contain narcotics.

Pain 1998: 74; 337-339
Pain 1994: 59; 361-368
Clin J of Pain 1994 Vol 10:240-242

Topical Ketamine to Treat Postherpetic Neuralgia

The most common complication of herpes zoster (shingles) is postherpetic neuralgia (PHN), a severe, deep, burning, or jabbing pain that persists for months and often years after resolution of zoster rash. Although gabapentin and topical lidocaine are approved for management of PHN, better symptomatic therapies are needed. Ketamine hydrochloride is an NMDA receptor antagonist that has been used to treat neuropathic pain in patients with various conditions, including PHN. Previously, a pilot study indicated that topical application of ketamine, in gel concentrations ranging from 10 mg/ml to 150 mg/ml and single doses ranging from 10 to 700 mg, effectively relieved sympathetically maintained pain.

Quan *et al.* of University of Colorado Health Sciences Center, Denver, examined the effectiveness of topical ketamine in 23 patients with PHN. 13 men and 10 women with PHN applied a thin film of topical ketamine gel (5 mg/ml) two or three times daily over the skin where pain was severe. The mean duration of PHN was 31.8 months (range, 1–132 months). Medical records were reviewed retrospectively to determine the effect of ketamine on PHN. Of the 16 PHN patients treated with topical ketamine alone or in addition to a stable pre-existing medication regimen, 5 reported a reduction in pain from severe to moderate and 5 reported a reduction from severe to mild. Of the seven patients who started ketamine and other new medications (Aspercreme®, Flexall®, capsaicin, famciclovir, or sertraline) simultaneously, two reported improvement in pain from severe to moderate and three reported improvement from severe to mild. Overall, 15 of 23 (65%) patients reported significant pain reduction. There was no significant difference between the proportion of patients who improved in the group that received only ketamine compared with the group that received ketamine with other new medications. Although length of the follow-up period varied, patients usually noticed a favorable or unfavorable response within days. Patients who did not improve with ketamine had a longer mean duration of PHN than those who did improve (45 vs 25 months), although the ranges for the two groups were similar (1–129 vs 1–132 months). The only reported side effect was minor skin irritation.

In other randomized, placebo-controlled trials, gabapentin, amitriptyline, nortriptyline, opioids, topical lidocaine, and capsaicin have helped PHN patients, but pain persists for many patients. Quan *et al.* found that topical ketamine reduced pain for PHN patients with no systemic side effects, indicating negligible or no generalized absorption. Our results were obtained by retrospective analysis of clinical records. The evaluation of the effectiveness of topical ketamine was based on patients' reports of pain relief using a simple three-level pain-rating scale. This data indicates that further trials with topical ketamine are warranted.

Neurology 2003;60:1391-1392
Int J Pharm Compounding 1998; 2: 122–127

Topical Ketamine for Neuropathic Pain

A study was conducted to determine if topical application of ketamine in a pluronic lecithin organogel to a pathological site would provide pain relief without producing the side effects of intravenous and intramuscular ketamine administration. In an open clinical pilot study of five referral patients diagnosed with sympathetically maintained pain who were unresponsive to

conventional modalities, a single dose of topical ketamine was administered to upper and lower extremities. The result was significant pain reduction (65% - 100%) relative to pretreatment, with pain intensity measured using a validated numeric analogue scale (NAS). "Initial response was within 20 seconds to three minutes, with NAS rating 15 minutes postapplication. No reported side effect occurred on patient follow-up at 24 and 48 hours."

Int'l J Pharm Comp Vol. 2 No. 2 March/April 1998 pp. 122-127

Topical Ketamine for Treatment of Mucositis Pain

Ketamine oral rinse provided effective palliation of intractable mucositis pain in a 32-year-old woman with squamous carcinoma of the tongue undergoing radiation therapy. Pain at rest and with eating was decreased by ketamine, allowing for a tapering of her opiate dose. No side effects of ketamine were reported. Treatment benefits most likely resulted from ketamine's inhibition of peripheral N-methyl D-aspartate (NMDA) receptors, though other mechanisms of action may have been contributory. Slatkin and Rhiner (Department of Supportive Care, Pain and Palliative Medicine, City of Hope National Medical Center, Duarte, California) believe that further evaluation of topical ketamine in the treatment of mucositis-related pain, and, potentially, other causes of inflammatory oral pain, are warranted.

Pain Med. 2003 Sep;4(3):298-303

Topical Medications for Chronic Pain Patients

Stephen P. Hersh, M.D., F.A.P.A.

Director, Medical Illness Counseling Center; Clinical Professor, G.W.U. School of Medicine; Member, American Pain Society

At the December meetings of the World Foundation for Pain Relief and Research, I learned that an increasing number of physicians who specialize in the treatment of various chronic pain conditions find it helpful to work with compounding pharmacists. Such pharmacists give the treating physicians increased freedom to work creatively with their patients towards symptom relief combined with improved function. Creative mixtures of well-understood, FDA-approved medicines (documented effectiveness and known toxicities) are possible. This freedom for creative therapeutics is especially important for chronic pain, no matter what its source, since no single modality provides total relief for these conditions.

Over the past year, I have been very pleased to observe decreased suffering in a series of patients with two very different, complex disorders: a) patients with fibromyalgia; b) patients with sympathetically maintained pain syndromes (RSD) that were associated in time with trauma from accidents or surgery. Using FDA-approved medications in lotions or creams prepared for transdermal absorption decreased symptoms with resultant improved functioning in the home and community. These medications are added to - not instead of - other therapeutic agents and interventions. (Transdermal creams and lotions have the additional psycho-social value of allowing the patient as well as a patient's loved one to participate in the treatment process by massaging the lotion or cream into the affected areas.) Fibromyalgia patients, particularly those with trigger points involving the trapezius and sterno-cleido-mastoid muscles, appear to be significantly helped by combination of lidocaine with ketoprofen, or lidocaine, ketoprofen, and cyclobenzaprine. Gentle massage 2-3 times each day combined with acupressure over trigger points using these lotions clearly adds to the patients' sense of well-being. RSD patients have found a decrescendo of their pain (i.e. movement from an 8-9 on a 10 point scale down to a 5-6) using gabapentin/clonidine creams applied to the affected area 2 to 3 times each day. Effectiveness with both lotions and creams in these different conditions seems to occur cumulatively over 4 to 10 days.

Instant relief has not been my goal nor has it been my experience. Obviously my comments are anecdotal. The data are my observations and the patients' reports. Despite the absence of a double blind study, I encourage physicians treating chronic pain patients to consider the modality of compounded topical medications. Unless a patient is allergic to one of the compounds in the topical medication, these are interventions that, unlike many in the treatment of chronic pain, truly do no harm.

Topical Formulation to Relieve Neuropathic Pain

Patient: 55 y.o. male with liver dysfunction and unremitting knee pain secondary to accident seven years prior. Patient had used long-acting morphine orally with limited success. Doses of morphine were escalating when the compounding pharmacist suggested a topical (transdermally absorbed) preparation to the physician.

Compounded Medication: Amitriptyline 2.5%, baclofen 1%, clonidine 0.2%, and ketamine 2% were prepared as a pluronic lecithin organogel (PLO) and 30 grams were dispensed with the instructions to apply 1 cc topically along pain path, every eight hours. By using this transdermal formulation, the patient was able to discontinue the morphine in two days. He has been able to control all pain using the compounded medication only.

Advantages of Compounded Medication: The medications in this transdermal formulation are known to relieve neuropathic pain when administered orally, but oral use has been associated with many potential side effects. Ketamine is an antagonist of *N*-methyl-d-aspartate (NMDA) receptors, which prompt nerve cells to be hypersensitive to pain. Several animal studies with NMDA receptor antagonists have shown long-term prophylactic and therapeutic effects which last far beyond the drug's presence in body tissues. *Pain* 74: 1998; 337-339

Since this patient had liver dysfunction, transdermal administration offered the additional advantage of bypassing first-pass liver metabolism, and the need for frequent dosage changes which are often required by patients with compromised liver function.

Note: This transdermal formulation has been prescribed for ten other patients and has been successful in nine cases.

References:

Joyce Cook, R.Ph.
G. Nemanishen, M.D., Mission, British Columbia

Excellent Outcomes using Medications in Topical Gel for Neuropathic Pain

Maureen A. Carling, R.N.

Patient #1: This 75 year old terminally ill patient had lung cancer with metastases to chest wall, spine, and pelvis. He also had severe gout affecting both feet.

Assessment revealed pain in the posterior-lateral aspect of both sides of the chest wall, with pain shooting down into the pelvis and inward to the spine; pain in the left sacroiliac joint and pain in both great toes, which extended up into the arches. His pain was severe and uncontrolled, and was described variously as: "Intermittent ache; occasional burning, shooting, stabbing; worse on movement." This suggests neuropathic and bone pain.

He was taking Oxycontin® 20 mg every 8 hours with OxyIR® 5 mg for breakthrough pain. The OxyIR® did not relieve the pain and at times made him confused. He was also taking Indocin® 25 mg every 8 hours for the gout.

The fact that he was alert taking Oxycontin® 20 mg every 8 hours suggested that he did have some soft tissue pain, which is usually fully opioid responsive.

The Oxycontin® was adjusted to 30 mg q 12 hours with OxyIR® 5 mg, 1 - 2 capsules for breakthrough pain and the patient was taught to discriminate between opioid responsive and opioid resistant pain. The Indocin® was discontinued.

A compounding pharmacist made up: Clonidine 0.2%, Amitriptyline 3 - 5%, Guaifenesin 2 - 3%, and Ketoprofen 5 - 10% in a PLO gel. This was applied as a thin film over the sites of pain and then the dermatomes were traced around to the back and the sites marked. An amount the size of a green pea was applied at spinal level. The gel was applied 2 - 3 times daily.

He was given Depakote® orally starting at a dose of 250 mg q HS, increasing by 250 mg q HS every four nights until pain free to a maximum of 1500 mg q HS. As the neuropathic pain came under control, his soft tissue pain also decreased, necessitating the reduction of the Oxycontin® dosage by 10 mg on two occasions.

He died completely pain free on Oxycontin® 10 mg q 12 hours, Depakote® 250 mg q HS and the twice daily application of the topical gel.

Transdermal Gels Compounded for Pain Management

Symptoms	Formulation
Inflammation	Ketoprofen 10% Ketoprofen 10%, Lidocaine 4%

Comment: Topically applied NSAIDs are effective in treating acute and chronic pain due to inflammation. Faster onset compared with oral administration of an NSAID and little/no gastrointestinal upset. Lidocaine, an APA receptor antagonist, provides additional pain relief via action at peripheral receptors.
Sig: BID-QID to affected area [Usual starting dose is 1 cc]

Neuropathy Ketoprofen 5%; Amitriptyline 2%; Carbamazepine 2%

Comment: Applied topically to painful area of neuropathy. An alternative when patient cannot tolerate side effects or is refractory to oral pain meds.
Sig: BID-QID to affected area [Usual starting dose is 1 cc]

Neuropathy Gabapentin 6%, Clonidine 0.2%

Comment: Peripheral receptors causing pain have responded to this combination.
Sig: BID-QID to affected area [Usual starting dose is 1 cc]

Plantar fasciitis &
Achilles tendonitis Ketoprofen 5%; Ketamine 5%; Amitriptyline 2%; Carbamazepine 2%)

Comment: Presence of ketamine 5% in this formulation provides excellent results in two conditions which are hard to treat. Ketamine is a potent NMDA receptor antagonist. Typical psychomimetic ketamine side effects have not been reported with transdermal application.
Sig: Apply to painful area BID-QID [Usual starting dose is 0.5 cc]

The above information also appeared in table format in an article entitled "Podiatry and Pharmacy: Working Together" in *Drug Topics* June 18, 2001, pp. 43-56

Transdermal Lidocaine & Ketoprofen for Pain Management

by Babak Arvanaghi, M.D., Pain Management Clinic, Suburban Hospital, Bethesda, MD

"I have used Lidocaine 10%/Ketoprofen 20% in many pain syndromes including diabetic polyneuropathy, post-herpetic neuralgia, and osteoarthritis of the hands, toes, knees, and shoulder.

"Conventional therapies include the use of NSAIDs with their significant side effect profile (especially in the elderly) and trials of neuropathic medications for the neuropathic pain syndromes, again with their own side effects.

"The lidocaine/ketoprofen preparation has been used in dozens of patients. Side effects have been essentially non-existent, and a significant number of patients have had good results to the point that **a trial of topical medication has become one of my standard approaches in the treatment of patients suffering from chronic pain**."

Note:
The preparation that Dr. Arvanaghi uses is a lotion titrated to proper pH for transdermal absorption**.** It is typically dispensed in a quantity of 30 grams, and is applied three to four times daily to the affected area.

The strength of the lotion can be titrated to achieve the desired response in each patient. Depending upon the symptomatology, a number of other medications may be included in the preparation, including cyclobenzaprine (for muscle relaxant) or guaifenesin (for spasms).

The lotion is well-absorbed through the skin, leaving no greasy film or residue. This preparation can *not* simply be compounded by placing the required ingredients in a base such as white petrolatum or Unibase™. This transdermal lotion contains a number of ingredients not found in most pharmacies, which together with significant physical agitation, increases micelle formation to optimize the therapeutic benefit. (Micelles are spaghetti-like structures that produce a macroscopic viscosity, increasing the transdermal penetration.) Appropriate mixing requires the use of an ointment mill or other homogenization process which we use in our compounding laboratory.

Analgesic Gel for Brachial Plexus Tumors

Dr. Charles Shoemaker, Newport, RI

A 60 year old female with brachial plexus tumors presented with severe shoulder pain and neuropathic pain. She had taken various opioids with very limited success. After consulting with the compounding pharmacist, I prescribed a transdermal PLO gel (pluronic lecithin organogel) containing ketamine 10%, gabapentin 6%, and ketoprofen 10%. Prior to application, her numerical pain assessment score was 7 - 8 while resting. The numerical assessment of pain was reduced to 0 within 15 - 20 minutes of applying the analgesic gel, and pain relief lasted six hours before reapplication was necessary.

The medication was dispensed in a 12 gm needleless syringe with instructions to gently rub a 1 gm dose into trigger points every 6 - 8 hours. No changes in dosing were necessary, and the medication has been refilled four times. This compounded medication was very convenient and "user friendly". The patient did not experience any systemic side effects or adverse effects of any kind.

Treatment of Intractable Pain with Topical Large-Dose Capsaicin

Robbins et al of UCSF Dept. of Anesthesia administered capsaicin at doses of 5%-10% to individuals with Reflex Sympathetic Dystrophy (Complex Regional Pain Syndrome) and neuropathic pain, who were poorly controlled by conventional pharmacologic interventions. Previous limitations to trials with larger-dose, topical concentrations of capsaicin included intense burning sensations experienced after application. To enable patients to tolerate the high concentrations, the researchers first performed regional anesthesia. Of 10 patients, 9 obtained substantial analgesia that lasted 1-18 weeks. Analgesia lasted from < 1 wk (1 patient) to more than 50 wks (1 patient). Patients received one to eight treatments. With one exception, patients receiving more than one treatment obtained additional relief with subsequent treatment. IMPLICATIONS: Pain from sensory neuropathies, associated with many diseases, can produce greater disability than the primary disease processes themselves. Currently available therapies are limited. However, the intermittent application of large-dose topical capsaicin may provide significant pain relief, decrease chronic analgesic dependence, and decrease aggregate health care expenditures. NOTE: High dose capsaisin (5-10%) therapy should be limited to refractory cases which are not responsive to lower doses or other therapy.

Topical capsaicin is known to be a safe and effective pain management adjunct for rheumatoid arthritis, osteoarthritis, neuralgias, and diabetic neuropathy. To determine the effectiveness of capsaicin for painful cutaneous disorders and neural dysfunction, Hautkappe et al. of Dept of Anesthesia and Critical Care, Univ. of Chicago, analyzed data from 33 reports on the efficacy of capsaicin. They concluded that capsaicin is effective for psoriasis, pruritus, and cluster headache; it is often helpful for the itching and pain of postmastectomy pain syndrome, oral mucositis, cutaneous allergy, loin pain/hematuria syndrome, neck pain, amputation stump pain, and skin tumor; and it may be beneficial for neural dysfunction.

Anesth Analg 1998 Mar;86(3):579-83
Clin J Pain 1998 Jun;14(2):97-106

Reflex Sympathetic Dystrophy

Reflex Sympathetic Dystrophy (RSD), also known as Complex Regional Pain Syndrome, is a complicated pain problem, characterized by severe pain and progressive physical changes that persist long after the original injury (may have been as severe as a bullet wound or as simple as a sprained ankle) has healed. RSD can also occur after routine surgery. Victims of RSD usually describe the pain as burning or shooting with extreme sensitivity to touch. Even an article of clothing rubbing the affected area may cause severe, extraordinary discomfort. RSD usually occurs in an extremity, but can occur almost anywhere, including the chest, breast or abdomen.

RSD develops slowly, in stages, over several months or years. Initially, the area may appear swollen and feel warm to touch due to inflammation as well as spasms of the surrounding blood vessels. Later, the blood supply to the area diminishes and the area becomes cool to touch. The skin becomes shiny and waxy and there is a loss of hair and skin tone. Pain increases and there can be weakening of the underlying bone. Finally, there is wasting of the affected muscles and disabling pain. Left untreated, the area can develop contractures from disuse which can become permanent. Bone scans and thermography are sometimes used in diagnosing RSD.

Due to the complicated and progressive nature of this potentially devastating pain syndrome, treatment must be aggressive and must focus on rehabilitation as well as pain management. Nerve blocks have been used to break the pain cycle and prevent

progression of symptoms. Narcotic medications will decrease the pain of RSD but do not impact the underlying problem. In the early stages, it is preferable to use pain medicines that are also anti-inflammatories. Steroids may be prescribed short term to relieve symptoms and arrest their progression. Anti-depressants are used to inhibit pain pathways. Anti-convulsants and anesthetic agents may also be helpful.

Calcitonin for RSD and Phantom Limb Pain

Salmon calcitonin (especially intranasal) provides an interesting analgesic effect in a series of painful conditions including reflex sympathetic dystrophy syndrome (RSD; RSDS), adhesive capsulitis, ankylosing spondylitis, rheumatoid arthritis, vertebral crush fractures and metastasis, phantom limb pain, etc. By comparison with the injectable, the intranasal route seems particularly interesting because of less undesirable effects, and a more rapid and probably more powerful analgesia. The development of RSD is a common complication after surgery. Exacerbation or recurrence of RSD is a major concern after a second intervention at the site of previous surgery. It is unclear whether the risk of recurrent RSD can be reduced by using appropriate precautions. In a case series of consecutive patients with a history of RSD after surgery who were reoperated at the site of a previous surgery, Marx et al. examined whether recurrences of RSD can be avoided by using a standardized protocol involving perioperative calcitonin prophylaxis. None of the patients experienced a recurrence of RSD. The researchers concluded that the recurrence of RSD after surgery in patients requiring operative intervention at the site of former dystrophy appears to be unlikely with careful perioperative management.

In addition to sympathetic influences, several other pathophysiological mechanisms may underlie the development and/or perpetuation of RSD, including neurogenic inflammation with the release of neuropeptides by primary nociceptive afferents and sympathetic efferents. Neuromediators, particularly substance P, calcitonin gene-related peptide, and neuropeptide Y, may play a pivotal role in the genesis of pain in RSD. They induce an inflammatory response (cutaneous erythema and edema) and lower the pain threshold.

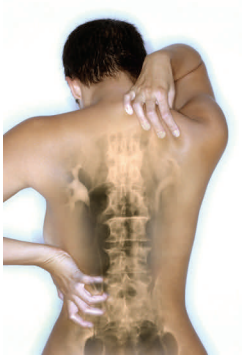
Due to the complicated and progressive nature of this potentially devastating pain syndrome, treatment must be aggressive. Nerve blocks have been used to break the pain cycle and prevent progression of symptoms. In the early stages, it is preferable to use analgesics that are also anti-inflammatories. Steroids may be prescribed short-term to relieve symptoms and arrest their progression. Anti-depressants are used to inhibit pain pathways. Anti-convulsants and anesthetic agents may also be helpful.

Phantom limb pain (PLP) is also a challenging disorder that is often difficult to treat. Like all other types of pain, PLP is a tremendous source of morbidity and should be treated aggressively. Though evidence is very limited, one or two doses of intravenous salmon calcitonin 200 IU may be an effective treatment. The minor adverse effects reported in the literature would seem to indicate the relative safety of this regimen; however, clinicians should be aware of the rare but severe hypersensitivity reactions that can occur with salmon calcitonin. Intranasal calcitonin appears to be similar in efficacy to the parenteral formulation, at least in pain associated with vertebral crush fractures. Long-term studies using intranasal calcitonin for relief of PLP are warranted given the ease of administration of this dosage form.

Bone. 2002 May;30(5 Suppl):84S-86S
Clin Rheumatol. 2001;20(2):114-8
Joint Bone Spine. 2003 Feb;70(1):12-7
Ann Pharmacother. 1999 Apr;33(4):499-501

Opioids

The effects of opioids on pain transmission within the dorsal horn of the spinal cord and at the brain stem have been well documented. Although these are centrally based mechanisms, more recent evidence reports that opioid receptors also are present on the peripheral terminals of thinly myelinated and unmyelinated cutaneous sensory fibers. Peripheral actions of opioids appear early after the induction of inflammation but are not prominent in normal tissue.



Preclinical studies suggest opioids may produce benefits when applied topically to somatic sites. In a clinical setting, the analgesic effect of opioids has also been reported when applied to painful ulcers and skin lesions. One report shows efficacy in relieving pain associated with burns. Systemic use of opioids has caused adverse effects; therefore, the topical application of opioids, with fewer systemic effects, has potential as an alternative option.

Opioid Responsive vs. Opioid Resistant Pain

At a recent international Professional Compounding Centers of America seminar, Maureen Carling, R.N., discussed "Symptom Management in the Terminally Ill." She used an algorithm to demonstrate how the patient's description and duration of pain can determine the type of pain that is being experienced and if that pain will be responsive to opioids, thereby helping a practitioner to initiate the most appropriate therapy.

Type of Pain	*Responsiveness to Opioids*
visceral	usually responsive
soft tissue	usually responsive
bone	semi-responsive
nerve compression	semi-responsive
pleuritic	semi-responsive
colic	resistant
muscle spasm	resistant
nerve destructive or deafferentation	resistant

Ultra Low Dose Naloxone May Improve Analgesia for Patients Receiving Opioids

Recent preclinical and clinical studies conducted by Crain and Shen of the Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, and others have demonstrated that cotreatments with extremely low doses of opioid receptor antagonists, e.g. naloxone (NLX), nalmephene, and naltrexone (NTX), can markedly enhance the efficacy and specificity of morphine and related opioid analgesics, and simultaneously attenuate opioid tolerance, dependence, and other aversive side-effects such as nausea, vomiting, and pruritus. *In vitro* and *in vivo* studies provide cellular mechanisms that can readily account for the unexpected enhancement of morphine's analgesic potency in recent clinical studies. The striking consistency of these multidisciplinary studies on nociceptive neurons in culture, behavioral assays on mice, and clinical trials indicates that clinical treatment of pain can be significantly improved by administering morphine or other conventional opioid analgesics together with extremely low doses of an excitatory opioid receptor antagonist. In a double-blinded clinical trial involving 120 post-surgical pain patients, patient visual-analog assessments at 24 hours indicated that the groups cotreated with nalmephene plus morphine reported significantly lower scores of pain severity and higher scores for pain relief. Low-dose NTX is a particularly attractive agent for cotreatment with morphine or other opioid agonists in chronic pain patients because of its well-established effectiveness as an opioid receptor antagonist with a long duration of action (approx. 24 hours) and no significant toxicity.

Doses of morphine far below those currently required for clinical treatment of pain may become effective when coadministered with appropriately low doses of opioid antagonists, although "these results are unexpected and 'paradoxical' when viewed from the standpoint of traditional opioid pharmacology concepts... A major uncertainty lies in the possibility that low doses of opioid antagonists may not only enhance morphine's analgesic potency but might also increase morphine's depressant effects on the respiratory system", but this concern has not yet been realized in clinical trials.

Pain 2000 Feb;84(2-3):121-31

Hydrocodone *without* Acetaminophen

by Alan Spanos, M.D., M.A.
Pain Specialist, Director of Blue Ridge Clinical Associates, Raleigh, NC

A 35 year old woman with two small children has chronic back and leg pain after 3 lumbar surgeries for sciatica. She recently fell, causing a contusion around the sciatic nerve in the buttock, with dramatic worsening of her leg pain and neurologic deficits. Nerve conduction studies confirmed a peripheral nerve injury that should slowly resolve over a number of months, but meanwhile she was housebound because of the pain. A TENS unit, nonsteroidals and tricyclics did not help. She was agreeable to using opioids. She understood she would become physically dependent on them, but that she will be able to taper off them gradually when the nerve heals.

Several opioids were tried, but they all either made her too drowsy, or caused a rash. The exception was Lorcet® (hydrocodone with acetaminophen). This did not make her sleepy or give her a rash, and it did help the pain somewhat. The drawback was the acetaminophen in the preparation. To avoid liver damage from this, I prescribed only 6 tablets daily, and this left her without pain relief for much of the day. There is no proprietary hydrocodone preparation that does not include acetaminophen.

The compounding pharmacist had a simple answer - capsules of pure hydrocodone without acetaminophen. Each capsule contains 40 mg. hydrocodone: four times the dose in the strongest Lorcet® tablet. Now the patient takes one capsule, 4 times daily. Her pain relief lasts through the day, and the only side effect is mild constipation, which is helped by a stool softener. She can do housework, go shopping and take care of her family again; and I don't worry about her liver any more.

Topical Opioids in Palliative Care

This case report was excerpted from an article by Krajnik et al published in Pain 80 (1999) 121-125.

"Patient A was a 89-year-old blind man with a short history of acute lymphocytic leukemia who refused chemotherapy. Seven years previously, a bronchial carcinoma had been resected at lobectomy. He was admitted to the hospital due to rapid deterioration, increasing dyspnea and pain below the left knee and on the right foot. A presumed bacterial infection was treated with i.v. antibiotics without benefit. He deteriorated further and was transferred to the Hospice for terminal care. On examination a 3 x 7 cm painful and inflamed subcutaneous upper tibial infiltrate was found. The skin was red but intact and the knee joint appeared normal. At rest he reported the pain to be 4/10 and at touch 8/10 on the numerical analog scale (NAS). Two milliliters of morphine gel 0.08% (1.6 mg) was applied under occlusion to the painful area. The pain decreased to 0/10 at rest and 2/10 on touch, although the 'touch' could not be standardized. Analgesia lasted for 7 hours. Following this observation 2 ml of morphine gel was applied under occlusion three times a day. Similar treatment was applied to the right foot. At both sites the tender infiltrate disappeared within 1 week of therapy. The skin was not anaesthetized but was painless on touch. No symptoms of morphine toxicity were observed. After 7 days the pain rating decreased further to 0/10. Frequency of applications was decreased to twice daily and later discontinued. The pain did not recur. The patient died free of pain 15 days after admission."

Discussion: The type of base used is critical to the success of this therapy, and can significantly affect the extent of transdermal absorption. The low pH of necrotic wounds limits the use of local anesthetic agents for treating severe pain from skin and mucous membrane disease. Morphine (pKa 9.8) is very stable at low tissue pH and therefore may be suitable for the treatment of local wound pain.

Transdermal Opioids for Systemic Pain Management

"For a topical medication to be successful, it must reach the target site and have efficacy at that site... There is a direct relationship between the medication's molecular size and skin penetration." The following case study, documented by Mark Turris, RN, MSN, of the Vancouver (British Columbia) Home Hospice Program, describes the use of topical (transdermal) opioids for systemic pain control in a patient for whom the conventional routes of analgesic administration were not an option.

Patient was a 90 y.o. male with head and neck cancer diagnosed six months previously, who presented with uncontrolled pain in his mouth secondary to the cancer. Initially, his pain had been controlled with an oral opioid, but to reduce his need to swallow, his analgesic was changed to a fentanyl patch with liquid oral hydromorphone used for breakthrough pain (BT). Over several weeks, his ability to swallow decreased, pain increased, and the dose of fentanyl was titrated upwards. He then began refusing oral medications, and also refused injections and suppositories. The pharmacist and hospice team discussed possible options including adapting hydromorphone for a topical application. The pharmacist suggested the use of Lipoderm® cream base to "help drive the drug through the skin into the bloodstream." Based on prior experience with topical opioids and the low dosage for the BT (2 mg), the decision was made to use the equivalent oral dose topically and monitor the patient closely for pain control and possible side effects. Hydromorphone 2 mg/0.2 ml cream was compounded and dispensed in a topical syringe, with directions to apply 0.2 ml to healthy skin and gently rub in every hour as needed. (Nurses were instructed to wear gloves when applying the medication.) The cream was used twice the first day for BT doses. "Within 15 minutes of application, good effect was indicated by reduced restlessness." During the following weeks, doses of fentanyl patch and hydromorphone for BT were titrated upward to maintain pain control until the patient died peacefully.

J Pain Symptom Manage. 2008 Jul;36(1):e13-4.

Morphine Topical Gel to Relieve Pain and Inflammation of Cutaneous Ulcers and Oral Lesions

A number of studies have reported the analgesic effect of morphine when applied topically to painful skin ulcers. Morphine may exert a local action, as opioid receptors have been demonstrated on peripheral nerve terminals. Morphine sulfate 10 mg in Intrasite gel was applied topically to skin ulcers of hospice inpatients. The topical morphine was not absorbed in the majority of patients, suggesting any analgesic effect was mediated locally rather than systemically. However, in ulcers with a large surface area, systemic absorption may occur.

A compounded 0.1% morphine gel was applied several times daily to inflammatory mucosal lesions (oral, anogenital and one cutaneous ulcer). All patients experienced a significant reduction in pain with the use of topical morphine gel and no side effects were seen.

Topically applied opioids have provided effective analgesia without adverse effects, including tolerance, in adult patients with painful inflammatory conditions. The use of topical morphine gel is reported in two children with epidermolysis bullosa, where acute inflammatory pain is a major symptom and where effective analgesia is a significant clinical problem. The gel provided rapid reduction in pain scores without any reported adverse effects or tolerance. A topical route of analgesia might be extremely beneficial for children with other painful skin lesions, including burns or post-surgical wounds, and further studies are now required.

J Pain Symptom Manage. 2004 May;27(5):434-9
Schmerz 2004 Nov 26
Arch Dis Child. 2004 Jul;89(7):679-81

Chemoradiotherapy-Induced Esophagitis Pain Relieved by Topical Morphine

Concurrent chemoradiotherapy causes esophageal toxicity in almost 90% of patients. Systemic analgesics and the usual topical treatments such as antacids, viscous lidocaine, and aluminum hydroxide-magnesium carbonate provide limited benefit. Although peripheral opioid receptors are not detectable in normal tissue, they appear in inflamed tissue and the analgesic effect of peripheral opioids in an experimental model increases linearly with the duration of inflammation. Moreover, the number of peripheral sensory-nerve terminals is increased in inflamed tissues. Experimental and clinical studies suggest that opioid analgesia in patients with painful inflammatory tissues might be enhanced with topical application. Clinical trials suggest that topical morphine is effective in relieving mucositis-associated pain following concomitant chemoradiotherapy in head and neck carcinoma. Gairard-Dory et al reported three cases in which topical morphine successfully relieved the pain of esophagitis. All patients had been treated previously with oral morphine which had provided no relief from esophagitis pain. Patients swallowed from 2 to 10 mL of 0.1% morphine viscous gel three times a day, 5 to 60 minutes before eating. The gel covered esophageal surfaces and produced topical anesthesia as it was swallowed. Benefit continued to increase over several days of use. In prior studies, relief of oral mucositis pain was obtained by a topical 0.1% morphine solution. The major advantages of topical morphine administration are simplicity, low incidence of side effects, and low cost.

J Pain Symptom Management 30;2 (Aug 2005); 107-9

Loperamide Used Topically for Pain

Preclinical and clinical evidence indicates that locally administered opioid agonists produce an antihyperalgesic effect through peripheral opioid receptors in inflamed tissue. Loperamide, a mu opioid agonist often used as an anti-diarrheal, does not cross the blood-brain barrier and therefore lacks central effects after systemic administration. The authors defined the effects of topical loperamide on a thermal injury-induced hyperalgesia.

METHODS: In halothane-anesthetized rats, thermal injury was induced by placing the plantar surface of a hindpaw on a hot plate (52.0+/-1 degrees C) for 45 seconds. Loperamide was prepared in a cream emulsion (0.5%, 1.7%, and 5.0%). The drug was applied as follows: before or after injury on the injured paw, on a normal paw, and after injury on the injured paw of morphine-tolerant rats. Paw withdrawal latency to a radiant heat source was measured to determine the nociceptive threshold. A pharmacokinetic study was performed.

RESULTS: Thermal injury yielded a significant thermal hyperalgesia. Loperamide, but not the vehicle, posttreatment on the injured paw resulted in a dose-dependent antihyperalgesic effect, which was reversible with naloxone. Treatment with loperamide on the normal paw produced short-lasting hypoalgesia, but the effect was not reversible with naloxone. Pretreatment with loperamide was effective at 1 and 2 hours, but not 4 hours. A rightward shift of the dose-response curve was observed in rats made tolerant to

systemic morphine with subcutaneous morphine pellets. No rats with drug treatment displayed any evident behavior changes (e.g., loss of corneal or pinna reflexes or change in ambulation). Drug activity in the tissue revealed an elimination half life of 2.3 hours and negligible concentration in the blood.

CONCLUSIONS: **Loperamide, a peripherally acting mu opioid agonist, applied topically at the site of inflammation possesses a significant antihyperalgesic action without any systemic side effects.**

Anesthesiology 1999 Jan;90(1):225-34

Migraine Therapy

Fixed Combination of Indomethacin, Prochlorperazine, and Caffeine versus Sumatriptan in Acute Treatment of Multiple Migraine Attacks

A fixed combination of indomethacin, prochlorperazine, and caffeine is the most commonly used drug for the acute treatment of migraine in Italy. No studies have been published comparing the efficacy of this combination with sumatriptan, the most widely prescribed of the triptans. To compare the efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine suppositories with sumatriptan suppositories in the treatment of 2 consecutive migraine attacks of moderate or severe intensity, DiMonda et al. conducted a multicenter, randomized, crossover study. One hundred twelve patients with migraine with or without aura according to the diagnostic criteria of the International Headache Society were randomized to treat 2 migraine attacks with a fixed combination of indomethacin, prochlorperazine, and caffeine and 2 migraine attacks with sumatriptan. Both drugs were rectally administered in a single dose for each attack. Patients were asked to take study medication as soon as possible at the onset of a headache.

Of the 112 patients, 88 were compliant to the protocol. ***More attacks became pain-free at 2 hours postdose (primary end point) on the combination than on sumatriptan (49% versus 34%)***. The ***combination was statistically superior to sumatriptan in the time to a pain-free response*** (a higher percentage of attacks became pain-free from 0.5 hours postdose to 5 hours postdose), in alleviation of nausea, and in a sustained pain-free response (pain-free at 2 hours postdose with no use of rescue medication or relapses within 48 hours). Moreover, a significant consistent response was achieved for the combination compared with sumatriptan across (higher percentage of patients pain-free at 2 hours postdose in the first, second, third, and fourth treated attack) and within patients (pain-free in 2 of 2 treated attacks in 35% of patients taking the combination and 20% of patients on sumatriptan). Both drugs were well-tolerated.

This study, analyzed according to the more recent guidelines for controlled trials in migraine, showed that a fixed combination of indomethacin, prochlorperazine, and caffeine is significantly more effective than sumatriptan in the acute treatment of migraine attacks.

Headache 2003 Sep;43(8):835-44

Gabapentin for Migraine Prophylaxis

At seven participating centers, 143 patients with migraine were randomized in a 2:1 ratio and received either gabapentin (n = 98) or matching placebo (n = 45). The majority of these patients were white (92.0%) and women (82.8%), with a mean age of approximately 39.4 years and a history of migraine episodes for a mean of about 21 years. At the end of the 12-week treatment phase, the median 4-week migraine rate was 2.7 for the gabapentin-treated patients maintained on a stable dose of 2400 mg/day and 3.5 for the placebo-treated patients, compared with 4.2 and 4.1, respectively, during the baseline period. Additionally, 26 (46.4%) of 56 patients receiving a stable dose of 2400 mg/day gabapentin and 5 (16.1%) of 31 patients receiving placebo showed at least a 50% reduction in the 4-week migraine rate. The average number of days per 4 weeks with migraine was also statistically significant and favored gabapentin. Researchers at Houston Headache Clinic concluded that gabapentin is an effective prophylactic agent for patients with migraine. In addition, gabapentin appears generally well tolerated with mild to moderate somnolence and dizziness.

Headache 2001 Feb;41(2):119-28

"Although the mechanism of action of gabapentin has yet to be elucidated, [results of a study conducted at Marine Biomedical Institute, University of Texas Medical Branch] indicate that **gabapentin has a peripheral site of action and thus may offer a novel therapeutic agent for topical or local treatment of pain of peripheral origin**."

Pain 1998 May;76(1-2):201-7

Piroxicam Triturates for Migraine

A study in *Headache* (1993;33:296-300) evaluated the efficacy of a Fast Dissolving Dosage Form of piroxicam 40mg as a single sublingual dose in the acute treatment of migraine without aura. Medication (or placebo) was taken within 2 hours from the beginning of a migraine attack. In the piroxicam group of 20 patients, "a significant reduction in pain intensity was observed after only 15 minutes. After an hour, headache disappeared in 15 patients, became mild in 4 and remained unchanged in only one subject. Associated symptoms also quickly disappeared after piroxicam FDDF administration and headache recurred in only two patients within the 24 hour period. Sublingual administration of piroxicam was well tolerated." Two subjects complained of oral discomfort, described as mild and transient.

Intranasal Lidocaine for Migraine

In a prospective, randomized, double-blind, placebo-controlled trial, Maizels et al evaluated the effectiveness of intranasal lidocaine for treatment of acute migraine headache. 81 patients (67 women and 14 men; median age, 42 years) with a chief complaint of headache who fulfilled criteria of the International Headache Society for migraine participated. Patients were excluded if headache had lasted more than 3 days or if the frequency of severe headache was more than once per week. Patients were randomized in a 2:1 ratio to receive a 4% solution of intranasal lidocaine or saline placebo, respectively. The primary outcome measure was at least 50% reduction of headache within 15 minutes after treatment. Secondary measures include reduction in nausea and photophobia, use of rescue medication, relapse of headache, and change in headache disability scores. Of 53 patients who received intranasal lidocaine, 29 (55%) had at least a 50% reduction of headache compared with 6 (21%) of 28 controls. Nausea and photophobia were significantly reduced. Rescue medication for headache relief was needed in 28% patients in the lidocaine group vs 71% of controls. Among those with initial relief of headache, relapse of headache occurred in 10 of 24 in the lidocaine group vs 5 of 6 in the control group, usually within the first hour after treatment. The authors concluded that intranasal lidocaine provides rapid relief of headache in approximately 55% of ambulatory patients with migraine. Relapse of headache is common and occurs early after treatment.

In a separate noncontrolled study, 23 migraine headache patients were treated with intranasal instillation of 0.4 mL of a 4% lidocaine solution during attacks of varying intensities. Migraine attacks were aborted in 12 of 23 patients, of which 8 were completely relieved within 5 minutes. In no case did an aborted attack return to more than a dull level within 24 hours. Unilateral attacks were significantly more treatment-responsive when compared to bilateral attacks. Nausea, associate with migraine attacks in 6 of 12 responders, was similarly aborted by lidocaine in 5 of 6 patients. Other side effects included mild nasal and eye burning of short duration (seconds), and oropharyngeal numbness of approximately 20 minutes' duration.

Headache 1995 Feb;35(2):79-82
JAMA 1996 Jul 24-31;276(4):319-21

Riboflavin for Migraine Headache

The brain of migraineurs is characterized between attacks by a reduction of mitochondrial phosphorylation potential. Riboflavin, which has the potential of increasing mitochondrial energy efficiency, was found to be effective for migraine prophylaxis in an open pilot study. Forty-nine patients suffering from migraine (45 without aura, 4 with aura) were treated with 400 mg of riboflavin as a single oral dose for at least 3 months. Mean global improvement after therapy was 68.2%. This prompted a multicenter, double-blind, randomized, parallel group, placebo-controlled trial. Improvement was most pronounced during the last month of treatment, with decreases in attack frequency, number of headache days, and severity. There were no drug related side effects with the possible exception of diarrhea in one patient. Although the effect of riboflavin is moderate, it may be considered as a first line prophylactic agent in certain people with migraines because of its favorable efficacy/side effect profile and its reasonable cost.

Cephalalgia 1994 Oct:14(5):317
Neurology March 1997; 48:A86-A87

Lysine Acetylsalicylate (LAS) and Metoclopramide (MTC) Oral Combination Compared to Oral Sumatriptan for Treatment of Migraine Attacks

At the University of Copenhagen, Department of Neurology, in two double-blind, randomized, clinical trials, oral lysine acetylsalicylate 1620 mg (equivalent to 900 mg aspirin) combined with metoclopramide 10 mg (LAS+MTC) was compared with placebo and oral sumatriptan 100 mg. In both trials, the LAS + MTC combination was superior to placebo with therapeutic gains of 30% and 31% for the first treated attack, the same range as those found for 100 mg oral sumatriptan. LAS+MTC combination was quite comparable to 100 mg sumatriptan, with success rates for the first attack of 57% and 53%, respectively.

During migraine attacks, aspirin absorption is delayed, presumably due to gastric stasis. A combination of aspirin with metoclopramide, which returns the absorption of aspirin to normal during migraine attacks, has been recommended to combat nausea and vomiting. LAS+MTC is significantly more effective in the treatment of nausea than sumatriptan, and is better tolerated (adverse effects in 18% and 28%, respectively).

Lancet 1995; 346: 923-926
Funct Neurol 2000;15 Suppl 3:196-201

Topical Anesthetic Gels and Sprays

It is essential that topical anesthetics be dispensed by a licensed practitioner according to state law, together with clear written instructions for use that have been prepared by a licensed healthcare professional. Application of topical anesthetics in excessive doses, or to extensive body surface area, or use under occlusion, can result in absorption of toxic amounts of drug.

The efficacy of any compounded medication is influenced by the technique and equipment used in preparing the formulation, the purity and quality of the ingredients, choice of vehicle (base), and proper use of additives such as penetration enhancers.

Lidocaine Adrenaline Tetracaine Gel for Topical Anesthesia in Linear Scalp and Facial Lacerations

According to Ernst et al., the "search continues for a topical anesthetic that affords painless, safe application, does not contain narcotics or controlled substances, and has a maximum safety with complete anesthesia." A randomized, prospective, double-blinded clinical trial in an inner-city Emergency Department with an Emergency Medicine residency program compared topical LAT gel (4% lidocaine, 1:2000 adrenaline, 0.5% tetracaine) to topical TAC gel (0.5% tetracaine, 1:2000 adrenaline, 11.8% cocaine) for analgesic efficacy, side effects, and costs in 95 adults as well as 95 children aged 5 to 17 years with linear lacerations of the face or scalp. Gels were applied into and around the wound edges using a cotton-tipped applicator. Care was taken not to apply gels too near mucous membranes. Onset of anesthesia was 10 to 30 minutes. Physicians and patients/parents separately rated the overall pain of suturing using a modified multidimensional scale designed specifically for children, or a standard visual analog scale for adult patients. According to patients/parents, no difference could be detected in percent of sutures causing pain in the LAT versus TAC group. Physicians also found LAT statistically the same as TAC in effectiveness. Follow-up of over 90% of patients revealed no reported complications for either medication. The authors concluded that LAT gel worked as well as TAC gel for topical anesthesia in facial and scalp lacerations. Considering the advantages of using a noncontrolled substance, avoidance of potential serious side effects associated with cocaine administration, and substantially less expense with LAT, LAT gel appears to be better suited than TAC gel for topical anesthesia in laceration repair.

Pediatrics 1995 Feb;95(2):255-8
Am J Emerg Med 1995 Mar;13(2):151-4

Clinical experience has shown that adrenaline in the gel helps to stop bleeding secondary to injury, and application of the gel makes it much easier to cleanse the wound. LAT can also be compounded as a spray.

Topical Piroxicam vs. EMLA Cream to Relieve Pain and Inflammation After Laser Hair Removal

Fifty female volunteers were enrolled in a prospective, randomized, double-blind, clinical study over a 6-month period to compare the efficacy of piroxicam 0.5% gel and EMLA cream on pain control and subsequent inflammation in neodymium:yttrium-aluminum-garnet (Nd:YAG) 1,064 nm laser hair removal. Patients were randomly assigned to receive topical piroxicam (group P) or

EMLA cream (group E). Topical analgesics were applied to the treatment sites for 60 minutes. The pain scores and side effects were recorded using a visual analog scale (VAS) before the hair removal, during the hair removal, at the end of the hair removal, and 1 hour, 2 hours and 24 hours after the hair removal. Patients' characteristics and the treatment settings of the Nd:YAG 1,064 nm laser were similar in the two groups. The pain scores (VAS) were similar, and satisfaction was high in both groups after the hair removal. The number of blanching and erythema episodes were significantly higher in group E than in group P. Inflammatory side effects were less frequent in group P than in group E after the procedure. This study showed that topical piroxicam and EMLA provided adequate and similar pain relief after Nd:YAG 1,064 nm laser hair removal in female volunteers. Topical piroxicam was associated with fewer inflammatory side effects than was EMLA cream, because of its anti-inflammatory effect after the procedure.

Lasers Med Sci. 2008 Aug 21. [Epub ahead of print]

Topical Triple-Anesthetic Gel—compared with other topical anesthetics

A study evaluated the clinical efficacy of a triple-anesthetic gel containing benzocaine, lidocaine, and tetracaine ("BLT"), and compared it with three other topical anesthetics for induction of local anesthesia prior to treatment with a 532-nm KTP laser. Some patients were also treated with an 810-nm diode laser to standardize responses to different wavelengths. The other anesthetics included a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% cream, with and without occlusion; a lidocaine 5% cream; and a lidocaine 4% microemulsion gel; versus a control. At all intervals (15, 30, 45, and 60 minutes after application), pain scores were significantly lower with the BLT gel than with the 3 other topical anesthetics. All topical anesthetics were superior to the control at all intervals. BLT gel worked the fastest and produced no adverse side effects. The researchers concluded that BLT gel which is properly formulated and contains penetration enhancers can provide effective cutaneous anesthesia as early as 15 minutes after application without occlusion, reaching a maximum effect 30 minutes after application.

The rapid proliferation of laser and cosmetic procedures has made adequate analgesia essential for patient comfort and tolerability of optimal settings which are necessary for maximal results. It is impractical and inefficient for patients to occupy treatment rooms for an hour or longer waiting for their topical anesthetic to take effect. Additionally, a topical anesthetic that has a faster onset of action may result in less systemic absorption and a higher safety profile. Convenience of application without need for occlusion is another important consideration.

Thirty patients were enrolled in this study which was conducted at a clinic in California, and the BLT gel was compounded at a private pharmacy. The pluronic lecithin organogel base contained dimethyl sulfoxide to help increase penetration into the skin. BLT gel should be stored at room temperature and only be applied to intact skin, with or without occlusion, for 10 to 30 minutes. BLT gel is contraindicated in patients with allergies to PABA, hair dyes, and sulfonamides. The authors report that they have used BLT gel to treat thousands of patients over the past 3 years, with no allergic reactions or signs of systemic toxicity.

Cosmetic Dermatology 2003 Apr;16(4):35-7

Lidocaine - Tetracaine Spray

Submitted by Michelle Orr, R.N.

Case # 1

83 y.o. Caucasian male with Cerebro-Vascular Accident (stroke) and Peripheral Vascular Disease.

Each day, this confused patient would attempt to push the nurse away due to pain caused by a dressing change for a stasis ulcer on his left heel. The dressing change protocol involved debridement of loose eschar, silver nitrate to hypergranulated areas, application of Silvadene®, and dry gauze.

After consultation, Lidocaine - Tetracaine Spray was prescribed with directions to spray the ulcerated area prior to each dressing change. Once this therapy was initiated, the fighting stopped, and the patient presented with only occasional grimaces.

Case # 2
76 y.o. Caucasian male with liver cancer and edema. Enlarged scrotum was excoriated and weeping.

Lidocaine - Tetracaine Spray was prescribed with directions to spray the affected area every four hours as needed and prior to treatments. His pain decreased, which was comforting to the patient and allowed him to rest. The analgesia also enabled the therapist to use elevation and ice packs three times daily to decrease edema without pain. The analgesia produced by the Lidocaine - Tetracaine Spray usually lasted about 30 to 45 minutes. As the patient was able to tolerate treatments, healing was more rapid.

Tranilast Transdermally for Treatment of Keloid and Hypertrophic Scars and Relief of Pain and Itching

Shigeki et al of the Department of Orthopedic Surgery, Hiroshima University School of Medicine, Japan, evaluated the feasibility of transdermal delivery of tranilast [N-(3,4-dimethoxycinnamoyl) anthranilic acid], an inhibitor of collagen synthesis, for the treatment of keloid and hypertrophic scars in hairless rats and humans. Tranilast was effectively delivered transdermally (using iontophoresis) into the restricted skin tissues of hairless rats and the affected parts of four patients with hypertrophic scars with no skin damage. In four other patients, tranilast given iontophoretically for a period of 30 minutes a week reduced the patients' complaints of pain and itching after only one or two treatments. Murakami et al studied the transdermal delivery of tranilast using an ethanol solution containing oleic acid and propylene glycol as penetration enhancers. Results of these two studies indicate that transdermal delivery of tranilast using a properly compounded vehicle is a useful treatment for keloid and hypertrophic scars, particularly for relieving pain and itching, and is more beneficial than tranilast given orally.
Tranilast:

- inhibits chemical mediators by macrophages and inflammatory cells (membrane stabilizing)
- inhibits migration and proliferation of smooth muscle cells
- has an anti-inflammatory effect
- restores cytokine-induced nitric oxide production

Scand J Plast Reconstr Surg Hand Surg 1997 Jun;31(2):151-8
J Pharm Pharmacol 1998;50: 49-54
http://www.mayo.edu/cme-rst/dec2000/07-Tilbury/tsld008.htm

Pediatric Pain Management

Golianu *et al* of the Department of Anesthesia, Stanford University Medical Center, note that the past decade has brought about an explosion of knowledge about the physiology of nociception and many new techniques for pain relief, new analgesic drugs, and new applications of old analgesic drugs. These techniques include methods of opioid administration by ***transdermal and transmucosal absorption*** and the use of neuraxial analgesia for the management of pain in children. Interest in the use of regional anesthesia in children has been rekindled, and ***analgesic properties of many agents not typically considered analgesics, such as clonidine and ketamine***, have been recognized. Perhaps the greatest advance has been the paradigm shift in the recognition that pain not only exists in infants and children but also is a significant cause of morbidity and even mortality. Given the unprecedented interest in pain management in adults and children, physicians can now utilize ***new methods of drug delivery*** and receptor-specific drugs that provide analgesia without the untoward side effects of existing analgesics.
Pediatr Clin North Am 2000 Jun;47(3):559-87

Ketoprofen for Heel Pain: Treatment of "Sever Disease" in Children

Sever disease is the most common cause of heel pain in pre-pubertal children. This inflammatory condition is a result of minor repetitive trauma and typically occurs during a growth spurt or at the beginning of a new sport season. A case report described the use of topical ketoprofen 10% gel to relieve pain and inflammation in an 8-year-old girl with Sever disease. In addition, physical therapy intervention consisted of 6 visits over a 3-week period with traditional interventions (including rest, discontinuation of

activities that aggravate the condition, hot and cold packs, heel lifts, calf stretching, and strengthening). The patient experienced improvement in pain rating, the Lower Extremity Functional Scale, strength, and range of motion. She was able to return to activities after 18 days of intervention, which was 30 days less than in cases that did not include the use of ketoprofen gel. Topical use of ketoprofen reduces the risk of gastrointestinal side effects that occurs when it is taken orally.

Phys Ther. 2006 Mar;86(3):424-33

Acetaminophen with Codeine: Oral vs. Rectal Administration in Postoperative Pediatric Patients

Owczarzak and Haddad of the Department of OTO/HNS at Columbia- New York Presbyterian Hospital examined whether acetaminophen with codeine administered per rectum is an effective alternative for pain control compared with oral administration after an adenotonsillectomy. In a prospective, randomized control study, 75 children aged 1 to 5 years were assigned randomly to receive either rectal or oral postoperative pain medication. A journal with eight questions was kept for 10 days after the operation, and an overall survey of five questions was filled out at the first postoperative visit. Equivalent postoperative pain control was achieved with suppositories and oral medication, with few side effects and good tolerance. Total number of doses given per day were similar. Furthermore, many parents preferred the suppositories to oral medication in maintaining postoperative pain control because of ease of administration. If given the choice for future surgeries, many parents would switch or consider switching from oral pain medication to suppositories.

Laryngoscope 2006 Aug;116(8):1485-8

Miscellaneous

Dextromethorphan Single Agent Preparations

Most commercially-available dextromethorphan preparations have drawbacks to use for pain management. Dextromethorphan is frequently combined in cough/cold preparations with various antihistamines, decongestants, expectorants, or analgesics. Decongestants may raise concerns for hypertensive patients, and antihistamines may cause problems for those with BPH or glaucoma. Liquid “cough syrups” often contain sugar and/or alcohol, and have an unpleasant taste.

Our compounding pharmacy can prepare a dosage form containing dextromethorphan as the only active ingredient, in the most appropriate dose and dosage form for each patient - including capsules or a pleasantly-flavored liquid.

Diphenhydramine for Pain

Clinical and animal data suggest that antihistamines may have efficacy in the management of pain. While many mechanisms of action have been proposed for the analgesic action of antihistamines, the exact mechanism is unknown. Controlled clinical trials in different pain models have demonstrated that antihistamines have direct and adjuvant analgesic activity. Researchers (Pain and Palliative Care Service, Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York) report three patients with advanced cancer pain refractory to adjuvants and oral, intravenous, and epidural opioids, who achieved sustained pain relief after the repeated administration of diphenhydramine. ***Diphenhydramine may be useful in the treatment of neuropathic and nociceptive pain that has failed to respond to treatment with opioids and adjuvant analgesics.*** The authors suggest a starting dose of 25 mg diphenhydramine every 6 to 8 hours, with titration to effect.

J Pain Symptom Manage 2001 Aug;22(2):699-703

Treatment for Vulvodynia

Vulvodynia has been redefined by the International Society for the Study of Vulvovaginal Disease as "vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder". The pain can be generalized or localized; and provoked or unprovoked, or both. Treatments include general vulvar care; topical, oral, and injectable medications; biofeedback and physical therapy; low-oxalate diet and calcium citrate supplementation; acupuncture, hypnotherapy, and surgery. "No one treatment is clearly the best for an individual patient."

Long-term use of overnight topical lidocaine may minimize feedback amplification of pain and may allow for healing. In one report, patients applied a copious amount of 5% lidocaine ointment to the affected area at bedtime and placed a cotton ball generously coated with the 5% lidocaine ointment on the vestibule to assure overnight contact with the area. After a mean of 7 weeks, 76% were able to have intercourse after therapy as compared with 36% at baseline. There was a significant decrease in pain with sexual activity. However, it is important to use caution in using excessive amounts of lidocaine, because reports of lidocaine toxicity exist. For some patients with localized pain and vaginismus (painful, involuntary spasms of the vagina), a combination of topical amitriptyline 2% and baclofen 2% in a water washable base has been useful for point tenderness. Topical nitroglycerin has been reported temporarily to improve vulvar pain and dyspareunia; however, headache was a limiting side effect. Topical therapies not shown to benefit vulvodynia include topical corticosteroids, topical testosterone, and topical antifungal medications. Choosing the proper vehicle for these medications is as important as choosing the proper medications or combinations. In general, creams contain more preservatives and stabilizers and often produce burning on application, whereas ointments are usually better tolerated. "A compounding pharmacy is used to formulate these topical medications... **It is important to have a close relationship with a compounding pharmacist who can help to determine the proper combination of ingredients**."

Benzocaine may produce allergic contact dermatitis and should be avoided. Diphenhydramine is present in many topical anesthetic and anti-itch preparations, but it is also a common sensitizer that should be avoided.

A 47% complete response to oral tricyclic antidepressants for the treatment of vulvodynia (both generalized and localized) was reported in 33 women attending a vulvar pain clinic. Amitriptyline is often used as a first line agent, started at an oral dose of 5 mg to 25 mg nightly and increased by 10 to 25 mg weekly, generally not to exceed 150 mg daily.[1]

Gabapentin appears to be very effective in the treatment of unprovoked generalized vulvodynia, and has a very low side effect profile.[2] Lori Boardman, MD, ScM, associate professor in the Department of Obstetrics and Gynecology at Women and Infants' Hospital of Rhode Island, Brown Medical School, notes that sedation and dizziness associated with oral gabapentin can limit its clinical applicability. "Topical therapy can circumvent these side effects for at least two reasons. First, the topical route of delivery reduces systemic absorption of the medication, and second, the amount of active drug in topical preparations is significantly less than that administered orally. Although there is little data on using topicals with vulvar pain patients, studies of topical preparations in the treatment of other forms of chronic neuropathic pain suggest beneficial outcomes with minimal side effects." Dr. Boardman is the director of the Colposcopy and Vulvar Clinics, where patients with both generalized and localized vulvodynia have responded favorably to 2% gabapentin cream (applied three times daily) prepared by local compounding pharmacists.[3] In 2005, Johns Hopkins' Bayview General Clinic Research Center funded a protocol by Anne Burke, M.D. entitled "A Pilot Study of 6% Topical Gabapentin Cream for Vestibulodynia."[4] When using a topical preparation to treat vulvodynia, it may be appropriate to try a "test dose" of a base to determine tolerance.

Call our compounding professionals to discuss individualized treatments and non-irritating topical preparations.

[1] Journal of Lower Genital Tract Disease 2005;9(1):40–51
[2] J Reprod Med 2007 Feb;52(2):103-6
[3] National Vulvodynia Association News, Winter 2005
[4] Bayview GCRC Newsletter, Summer 2005

Topical Gabapentin: Well-Tolerated Pain Relief for Vulvodynia

In 2002 and again in 2006, the National Institutes of Health characterized vulvodynia (defined as chronic, unexplained vulvar pain or discomfort, characterized by burning, stinging, irritation, or rawness) as a poorly understood and underresearched focal pain syndrome for which optimal treatment remained unclear. Nearly 14 million U.S. women may at some point in their lives experience the symptoms of chronic vulvar burning and pain, and a localized form of vulvodynia involving the vulvar vestibule is thought to be the leading cause of dyspareunia in premenopausal women. Treatment recommendations range from topical

therapies to oral medications, physical therapy and biofeedback, and surgical excision, although the latter is reserved for women with localized pain only. Although many of these modalities demonstrate efficacy, many are also associated with adverse effects, require numerous visits to physicians, or are invasive. For example, topical nitroglycerin, topical lidocaine, and topical capsaicin have all demonstrated promise as treatments for localized vulvodynia. However, adverse effects, including headaches with topical nitroglycerin and local irritation with topical capsaicin, have limited the use of these medications.

Oral gabapentin has been used to successfully manage neuropathic pain syndromes (including vulvodynia). Topical therapy should largely circumvent adverse effects associated with oral gabapentin for at least two reasons: the amount of active drug in topical preparations is significantly less than that administered orally, and second, the topical route of delivery reduces systemic absorption of the medication. Transdermal 6% gabapentin (60 mg/mL) applied as described below would result in a total daily exposure of approximately 100 mg of active drug, well below the therapeutic ranges necessary with oral administration and equivalent to the recommended maximal dosages for patients with marked renal impairment. Because evidence suggests a peripheral process in the development of vulvodynia, Boardman *et al.* of the Department of Obstetrics and Gynecology, Women and Infants' Hospital of Rhode Island, Providence, proposed that if gabapentin cream was efficacious and well-tolerated, it could be a useful addition to current treatment options.

To evaluate the clinical efficacy and tolerability of topical gabapentin in the treatment of women with vulvodynia, between January 2001 and December 2006, 51 women with vulvodynia (19 with generalized vulvodynia, 32 with localized) were treated with 2% to 6% gabapentin. Local compounding pharmacists prepared gabapentin cream by dissolving gabapentin powder in ethoxy diglycol, levigating the mixture into Lipoderm™ (an enhanced base which facilitates tissue penetration), and placing the final product in plastic tubes for dispensing. Creams were dispensed as 2%, 4%, or 6%; the initial choice of dose was determined by the physician. In general, postmenopausal women were initially started on one of the two lower doses secondary to concerns over irritation; if, however, the therapeutic effect was suboptimal and the product tolerated, a higher dose was then prescribed. Patients were instructed to apply a small amount of cream (approximately 0.5 mL, equivalent to the size of a pea) three times daily.

After a minimum of 8 weeks of therapy, the mean pain score among the 35 evaluable women was significantly reduced from 7.26 to 2.49 (mean change -4.77). Overall, 28 of 35 (80%) demonstrated at least a 50% improvement in pain scores. Among patients with localized vulvodynia, sexual function improved in 17 of 20 with evaluable results (6 of 9 reinstituted vaginal intercourse, whereas all 11 patients experiencing decreased frequency of intercourse reported increased frequency after treatment). Discontinuations occurred in 7 of 50 (14%) treated (3 for irritation and 1 for urinary complaints), after which the adverse effects resolved. Common adverse effects of oral gabapentin, including dizziness, somnolence, and peripheral edema, were not reported by any of the 50 patients studied. The conclusion: “Topical gabapentin seems to be well-tolerated and associated with significant pain relief in women with vulvodynia.”

Obstet Gynecol. 2008 Sep;112(3):579-85

Case Report of Treatment-Resistant Vulvodynia

Abstract

Vulvodynia is a painful vulvar medical condition with many proposed etiologies and treatments. We describe two compounded pharmaceutical treatments of an elderly female with treatment-resistant vulvodynia. The first treatment consisted of 4% cromolyn sodium, 2% Lidocaine USP, 4% Amitriptyline HCl USP, 0.025% Atropine Sulfate USP, and 2% Ketoconazole USP in a polyethylene glycol base. It merely increased the patient’s discomfort. The second treatment consisted of Atropine Sulfate USP, Ketoconazole USP and Biotin USP as a combination in a cocoa butter base. It resulted in the full remission of the vulvodynia.

Background

Vulvodynia literally means "vulvar pain." Therefore, vulvodynia is a symptom, not a disease. One that indicates a variety of unpleasant chronic vulvar sensations, including burning, rawness, soreness, irritation, sensitivity, a creeping sensation and sometimes dyspareunia.[1] Classical primary “vulvodynia” is *without* objective physical findings to explain the symptoms. A satisfactory understanding of prevalence, pathogenesis, natural history, and management of this distressing condition continues to be elusive. Prevalence studies suggest one in six women may experience vulvodynia, although such a figure reflects clinic, patient or author reporting bias. Symptoms are as likely to be found in non-white as in white women. Although infection is often blamed, evidence for its role or that of inflammation is minimal. Immunohistochemistry has shown altered density of nerve endings and estrogen receptors. There may be overlap with other pain syndromes.

Several reviews have examined the many therapies available. Pharmacological alteration of nerve conduction (tricyclic antidepressants, gabapentin, local anesthetics), biofeedback and sometimes surgery are helpful, but not always. Therefore, a pressing need exists for case-control studies of potential causes of vulvodynia and for randomized trials of interventions.[2,3]

With this background, we present a case report on the successful treatment of a treatment-resistant seventy-four year old woman with vulvodynia. On her intake she was clearly in discomfort sitting in her chair. She reported a six year history of "severe vulvodynia" diagnosed by four gynecologists and three primary care physicians who prescribed various treatments that were "not helpful."

Her treatments included:

- Hormone replacement therapy--estradiol and Premarin®
- Vaginal lubrication to decrease inflammation associated with intercourse
- Antibiotics for a bacterial infection
- Multiple antifungal creams
- Counseling to avoid irritants—she was given a list of substances to avoid, e.g., propylene glycol found in many lubricants, certain cosmetics and shampoos
- Prednisone—to reduce a possible autoimmune inflammatory response
- An oxalate reduced diet—to reduce any small irritating crystals
- An anti-allergy diet
- Pelvic muscle biofeedback
- Low dose amitriptyline

Methods

With these unsuccessful preliminary treatments, and an unknown etiology, we considered a vaginal suppository with multiple ingredients with different therapeutic mechanisms. All precursor agents were United States Pharmacopeia pharmaceutical grade quality.

Her first suppository included 4% cromolyn sodium, 2% Lidocaine USP, 4% Amitriptyline HCl USP, 0.025% Atropine Sulfate USP, and 2% Ketoconazole USP in a polyethylene glycol base. The patient used the first suppository and immediately experienced a worsening of her vaginal pain, and was directed to discontinue treatment. It was determined that she had incorrectly reported that she had "no allergies," and actually had an allergy to lidocaine. It was hypothesized this *might* have been the source of her discomfort.

Another final option was proposed. It contained a combination of Atropine Sulfate USP 0.25mg, Ketoconazole USP 100mg, and Biotin USP 100mg in a cocoa butter base. These components were selected since vulvodynia etiologies include hyperirritability of pelvic floor muscles, chronic yeast infections, human papillomavirus, neuropathic dysfunction and nutritional deficiencies. Therefore, we considered a suppository which might address these various possible etiologies in a localized delivery treatment.

The use of low-dose local atropine was intended to decrease any possible hyperirritability of pelvic floor muscles, which could lead to painful spasms. The genital tract is lined with involuntary smooth muscle which have muscarinic receptors. Atropine, an antispasmodic, can block these muscarinic receptors and therefore, atropine may be effective in reducing the pain of vulvodynia.[4-10] Ketoconazole is an azole antifungal that has demonstrated anti-inflammatory activity.[11, 12] Biotin is a water-soluble B vitamin that has been shown to improve neurologic symptoms in patients. The results of clinical studies have provided evidence that marginal biotin deficiency is more common than was previously thought.[13] Even oral supplementation in healthy elderly patients, eating well, and taking a single multivitamin, still showed 39% had essential nutrient deficiencies, including deficiencies of biotin.[14] In addition, 1 in every 123 individuals may have biotinidase deficiency, so some women with chronic vaginal candidiasis, possibly causing treatment resistant vulvodynia, *might* respond to biotin administration.[15] Cocoa butter was chosen as the base to minimize chemical insult and for its soothing properties.

Results

The patient was instructed to use one suppository vaginally in the morning and evening. After twelve days of treatment, she returned for a consultation. She experienced a dramatic elimination of her vaginal pains and discomfort. Specifically, when asked about the effects of the treatment, she explained "it was no longer a problem." She began to talk about other goals with her family. Twice she was asked again about her pain and the vulvodynia. She explained that her "pain was entirely gone," and that she was "very pleased that finally" she had "a treatment that worked." In contrast to previous visits, she smiled and appeared comfortable as she sat, conversed and moved around the room, in complete contrast to her intake session.

Conclusion

The atropine sulfate, ketoconazole and biotin formula was successful for this elderly woman. However, it would be inappropriate, due to the complexity and uncertainty of this disorder's etiology, to assume that this treatment would be successful in most vulvodynia patients. We do believe a sub-group would benefit, but have no scientific grounds to propose a percentage that might

find this treatment useful.

Nevertheless, any suggestion that this patient had a spontaneous resolution during the week she initiated treatment does not seem compelling. We believe this compounded suppository was the agent of pain relief for three reasons. She had *six years* of continuous suffering, her pain promptly ended with treatment and lasted over ten months, and the treatment is consistent with some of the proposed causes of vulvodynia.

This case demonstrates that compounding is not merely an integral component of the profession of pharmacy, but it is also a useful tool for physicians in obtaining treatment options. Sample options include combination medications and transdermal medications in which oral routes are not functional or optimal due to nausea, diarrhea or iatrogenic irritation of the intestinal lining. Compounders also make an unappealing liquid medication more palatable or convert tablets into liquid delivery systems.[16] *They also are routinely involved in creating precise hormone replacement preparations.*

Pharmaceutical compounding involves additional accredited training or a fellowship, just as subspecialties or certifications in medicine require additional training. The compounding of individualized pharmaceutical agents falls under the authority of the individual state boards of pharmacy, and not the U.S. Food and Drug Administration, since compounding is not considered manufacturing.[17] *Further, professional compounders adhere to strict compounding regulations, and use base medications meeting United States Pharmacopeia pharmaceutical quality standards.*

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References

1 Fischer G. Management of vulvar pain. *Dermatol Ther*. 2004;17:134-49.
2 Lotery HE, McClure N, Galask RP**.** Vulvodynia. *Lancet*. 2004;363:1058-60.
3 Smart OC, MacLean AB. Vulvodynia. *Curr Opin Obstet Gynecol*. 2003;15:497-500.
4 Miyamae K, Yoshida M, Murakami S, Iwashita H, Ohtani M, Masunaga K, Ueda S. Pharmacological effects of darifenacin on human isolated urinary bladder. *Pharmacology*. 2003;69:205-11.
5 Lotery HE, McClure N, Galask RP. Vulvodynia. *Lancet.* 2004;363:1058-60.
6 Wagner G, Levin RJ. Effect of atropine and methylatropine on human vaginal blood flow, sexual arousal, and climax. *Acta Pharmacol Toxicol*.1980;46:321-5.
7 http://www.neuro.wustl.edu/neuromuscular/nother/autonomic/autonfcn.htm. Accessed 8/28/04
8 Fischer G. Management of vulvar pain. *Dermatol Ther.* 2004;17(1):134-49. Review.
9 Graziottin A, Brotto LA Vulvar vestibulitis syndrome: a clinical approach. *J Sex Marital Ther.* 2004;30: 125-39.
10 Choi YD, Chung WS, Choi HK. The action mechanism of relaxation effect of atropine on the isolated rabbit corpus cavernosum. *J Urol.* 1999;161:1976-9.
11 Rosen T, Schell BJ, Orengo I. Anti-inflammatory activity of antifungal preparations. *Int J Dermatol*. 1997;36:788-92.
12 Nwokolo NC, Boag FC. Chronic vaginal candidiasis. Management in the postmenopausal patient. *Drugs Aging*. 2000;16:335-9.
13 Mock DM, Henrich CL, Carnell N, Mock NI. Indicators of marginal biotin deficiency and repletion in humans: validation of 3-hydroxyisovaleric acid excretion and a leucine challenge. Am J Clin Nutr. 2002;76:1061-8.
14 Baker H, Frank O, Jaslow SP. Oral versus intramuscular vitamin supplementation for hypovitaminosis in the elderly. *J Am Geriatr Soc*. 1980;28:42-5.
15 Strom CM, Levine EM. Chronic vaginal candidiasis responsive to biotin therapy in a carrier of biotinidase deficiency. *Obstet Gynecol.* 1998; 92: 644-6.
16 Schaller JL, Behar D. Liquid medication preparations. *J Am Acad Child Adolesc Psychiatry*. 1998;37:136-7.
17 www.doh.state.fl.us/mqa/pharmacy/ph_home.html; www.dos.state.pa.us/bpoa/phabd/mainpage.htm. Accessed 8/10/2004.

Vitamin D Deficiency and Pain

Vitamin D deficiency has reached epidemic proportions in the U.S. and Canada and may be a major cause of unexplained muscle and bone pain. The populations with the greatest risk include the homebound elderly, people with pigmented skin, people with cultural and social avoidance of the sun, people who live in wintertime in climates above and below latitudes of 35 degrees, and people with gastrointestinal malabsorption. Numerous studies report that low vitamin D levels may precipitate or aggravate chronic pain, including low back pain (LBP). Vitamin D deficiency causes osteopenia and the painful bone disease osteomalacia, precipitates and exacerbates osteoporosis, and should be considered in the differential diagnosis of patients with musculoskeletal pain, fibromyalgia, chronic fatigue syndrome, or myositis. Vitamin D deficiency causes painful softening and bending of the bone ("rickets"), and increases muscle weakness, which worsens the risk of falls and fractures. Studies indicate that men and women who don't have enough vitamin D have lower scores on physical performance tests, especially in hand-grip strength. Because osteomalacia is a known cause of persistent, nonspecific musculoskeletal pain, screening all patients with such pain for "hypovitaminosis D" should be standard practice in clinical care.

A Mayo Clinic study showed that vitamin D deficiency may aggravate chronic pain. In a retrospective study of 267 chronic pain patients, 140 of whom were opioid ("narcotic") users, pain specialists found that about 25% of opioid users with chronic pain were vitamin D deficient. Prevalence of vitamin D deficiency did not differ between opioid users and non-opioid users. However, the opioid users who were vitamin D deficient required significantly more pain medication than those with adequate vitamin D levels: vitamin deficient patients had a mean morphine-equivalent opioid dose that was nearly twice that of the group with adequate vitamin D levels (133.5 mg/day, compared to 70.0 mg/day). Those with inadequate vitamin D levels had also been using opioids significantly longer than those with adequate vitamin D levels. Mean length of use was 71.1 months in vitamin D deficient patients, compared to 43.8 months for those who were not deficient. In addition, opioid users with low vitamin D reported significantly lower health perception and physical functioning than those with normal levels. Study author W. Michael Hooten, M.D., Medical Director at the Mayo Comprehensive Pain Rehabilitation Center, noted: "The implications are that in chronic pain patients, vitamin D inadequacy is not the principal cause of pain and muscle weakness, however, it could be a contributing but unrecognized factor." Dr. Hooten reports vitamin D inadequacy can be treated easily, inexpensively, and with virtually no side effects by taking a prescription supplement once or twice a week for four to six weeks.

Greg Plotnikoff, MD, *et al*. (Department of Internal Medicine, University of Minnesota Medical School, Minneapolis), found that 93% of all patients presenting with persistent nonspecific musculoskeletal pain refractory to standard therapies were deficient in vitamin D, and concluded that all patients presenting with such symptoms should be screened for hypovitaminosis D. In this cross-sectional study, levels of vitamin D in men were as deficient as in women. Of all patients, 28% had severely deficient vitamin D levels (< or = 8 ng/ml), including 55% of whom were less than 30 years and a significant number were women of childbearing age.

According to a report from the Department of Medicine, Johns Hopkins University, there may be a pain syndrome associated with vitamin D depletion that appears as hyperesthesia (extreme sensitivity) worsened by superficial pressure or even small increments of movement. This pain restricts mobility and function and may lead to further complications, such as pressure sores. An unusual pain occurred in five patients in the presence of compromised vitamin D status and resolved 5 to 7 days after supplementation with vitamin D. The pain had a hyperesthetic quality and did not respond to the use of analgesics, including opiate derivatives. Treatment with therapeutic levels of a tricyclic antidepressant did not bring relief of symptoms. In one case, months after treatment and subsequent improvement of vitamin D status and pain, the vitamin D status again declined and the pain recurred. The pain again resolved with vitamin D replacement and improvement of levels.

A study examined hypovitaminosis D and its determinants in female patients with chronic low back pain (LBP) during the childbearing period. Sixty female patients complaining of LBP lasting more than 3 months were clinically studied rheumatologically and neurologically. Biochemical assays of serum calcium, phosphorus, alkaline phosphatase (ALP), parathormone (PTH), and 25-hydroxyvitamin D (25-OHD) were performed and compared to those of 20 matched healthy controls. Patients with LBP had significantly lower 25-OHD levels and significantly higher PTH and ALP than controls. Hypovitaminosis D (25-OHD < 40 ng/ml) was found in 49/60 patients (81%) and 12/20 (60%) of controls. Despite living in a sunny climate, hypovitaminosis D was prevalent among these women in the childbearing period, especially those presenting with chronic LBP, because they had limited sun exposure.

A report in the *Medical Journal of Australia* described two patients with failed spinal fusion for chronic low back pain who were subsequently found to have severe vitamin D deficiency. Both responded positively to vitamin D supplementation. The authors highlighted the need for attending surgeons and physicians to be aware of the potential for vitamin D deficiency in their patients since failure to recognize this easily reversible problem may result in complications of treatment, including failure of spinal fusion surgery, additional morbidity, and the substantial costs of further surgery and hospitalization. Most patients (83%) who attended spinal and internal medicine clinics in Saudi Arabia over a six year period and had experienced low back pain that had no obvious

cause for more than six months had an abnormally low level of vitamin D. After treatment with vitamin D supplements, clinical improvement in symptoms was seen in all of those who had a low initial concentration of vitamin D. The authors concluded that screening of patients with chronic low back pain for vitamin D deficiency should be mandatory.

The Spaulding Rehabilitation Hospital, Boston, reports that vitamin D inadequacy is pandemic among rehabilitation patients in both inpatient and outpatient settings. Male and female patients of all ages and ethnic backgrounds are affected. This is problematic because vitamin D deficiency can present as musculoskeletal pain, which is commonly seen in patient at rehabilitation units. In addition, vitamin D deficiency worsens proximal muscle strength and postural sway. A review of PubMed, Ovid, and MDConsult using the search terms pain, chronic pain, musculoskeletal pain, vitamin D deficiency, and osetomalacia, revealed 51 articles that focused on vitamin D deficiency and noted a direct correlation with musculoskeletal manifestations. At-risk populations are not acquiring enough vitamin D through sun exposure, and the current recommended daily allowances are too low to compensate for this lack of sun exposure. Treatment of vitamin D deficiency produced an increase in muscle strength and a marked decrease in back and lower-limb pain within 6 months. There is a need for better education of health professionals and the general public regarding the optimization of vitamin D status in the care of rehabilitation patients.

Anecdotal reports from rheumatologists in the United Kingdom suggest that patients of South Asian ethnicity are more likely to report widespread body pain. To confirm these reports and to evaluate the relationship of their symptoms with levels of 25-OH vitamin D, two population studies involving over 3135 subjects were carried out in England. The first study confirmed an excess of widespread pain among South Asians, and the second smaller study conducted only among young women also showed a similar excess of widespread pain among South Asians and found that low levels of 25-OH vitamin D (<10 ng/ml) were more common among those with widespread pain. These preliminary results indicate that low levels of vitamin D may be one potentially treatable cause of widespread pain.

Cancer Treatment Induced Bone Loss (CTIBL) is mostly studied in breast cancer and prostate cancer survivors. The cause in these groups is mainly due to treatment-induced reductions in hormones, but other causes of CTIBL include chemotherapy, physical inactivity and inadequate intake of vitamin D and calcium.

In a study involving 150 children and adults with unexplained muscle and bone pain, almost all were found to be vitamin D deficient; many were severely deficient with extremely low levels of vitamin D in their bodies. Humans tend to get most of their vitamin D from exposure to sunlight, so those who avoid the sun completely or who always wear sunscreen to protect themselves against skin cancers are at risk for vitamin D deficiencies, says Michael Holick, MD, who runs the Vitamin D Research Lab at Boston University Medical Center. Dr. Holick notes that the original message from dermatologists was that people should limit their sun exposure, not that they should avoid the sun entirely. The amount of sun exposure needed to get the proper dose of vitamin D depends on a person's skin type, where he lives, time of year, and time of day the exposure occurs. Dr. Holick says it is difficult for people living in northern climates to get the vitamin D they need from the sun in the winter, but in the summer a light-skinned person at the beach should get all the vitamin D she needs in about five minutes.

The recommended dietary allowance (RDA) for vitamin D varies with age, sex, and medical conditions, but in general is 200-600 IU per day. The experts who made that recommendation were basing that recommendation only on vitamin D's ability to prevent rickets. Dr. Holick believes most people need about 1000 IU of vitamin D each day.

Vitamin D deficiency can be prevented by sensible sun exposure and adequate supplementation. Vitamin D can be synthesized by the body, or provided through food and supplements. Recent recommendations suggest that older adults, people with dark skin, and those exposed to insufficient ultraviolet radiation (i.e., sunlight) should consume extra vitamin D. Vitamin D is found in fortified milk, egg yolks, cod liver oil, and saltwater fish (salmon, herring, and sardines). Fifteen minutes of sun exposure a few times per week helps the body to produce adequate vitamin D. Treatment of vitamin D deficiency can produce an increase in muscle strength and a marked decrease in back and lower-limb pain within 6 months.

Vitamin D controls phosphorus, calcium, bone metabolism, and neuromuscular function. The medical literature overwhelmingly supports increasing vitamin D and calcium intake as an effective method for decreasing risk of vertebral and non-vertebral fractures. Health care providers should evaluate vitamin D levels as a possible cause of osteoporosis and treat vitamin D deficiency before resorting to the use of prescription drugs for bone health.

Recently, the literature has revealed many problems associated with low vitamin D levels. Dr. Holick claims there is now a strong epidemiological case linking vitamin D deficiency with a host of cancers including those of the prostate, colon, and breast; and he says vitamin D may also help protect against heart disease, autoimmune diseases, and even type 1 diabetes.

Ask our pharmacist for more information about quality vitamin D supplements.

Clin J Reumatol. 2007 Nov;26(11):1895-901.
Nutr Clin Pract. 2007 Jun;22(3):297-304.
Acta Oncol. 2007;46(4):490-6.
Am J Phys Med Rehabil. 2006 Nov;85(11):916-23.
Ann Rheum Dis. 2005; 64(8):1217-9
BMJ 2005;331:109 (9 July).
Mayo Clin Proc. 2003;78(12):1463-70.
Spine 2003;28: 177-9.
Med J Austr 2002;176: 438-9
Arch Intern Med. 1991 Aug;151(8):1662-4.

Benefits of "Single Subject Clinical Trials"

"Worthwhile clinical effects do not always require proof by placebo-controlled, prospective, randomized trials. In fact, the latter are only required if the benefits are very small, or the treated condition is highly variable. For major effects in stable condition, a 'clinical trial with *n* of one' [one patient trial] is often the best evidence. A highly respectable body of scientific literature exists in support of such single-subject clinical trials. **This is exactly what the compounding pharmacist can perform: a drug trial in each patient, to the satisfaction of the patient, the pharmacist and the physician.**"

An "n-of-1" trial must only be used when the treated condition is stable (to allow a rating of the effectiveness of the therapy); the potential benefit must be substantial, and the outcome to be modified must not be variable.

Customized Medications and Unique Dosage Forms

Our compounding professionals can prepare:

- Unique dosage forms containing the best dose of medication for each individual.
- Medications free of problem-causing excipients such as dyes, sugar, lactose, or alcohol.
- Combinations of various compatible medications into a single dosage form for easier administration and improved compliance.
- Medications that are currently unavailable.
- Novel medication delivery systems.

The optimal dosage form depends upon the specific needs of each patient. Options include:

Transdermal and topical administration are increasingly popular methods of drug delivery.

- Creams and gels can be formulated to provide high local concentrations at the site of application (e.g., NSAIDs for joint pain, morphine mouthwash for radiation mucositis), for trigger point application (e.g., combinations of medications for neuropathic pain), or in a base that will allow systemic absorption. Transdermal medications utilize the skin or mucosa to facilitate absorption. Studies suggest that there are no great restrictions on the type of drug that can be incorporated into a properly compounded transdermal gel.
- Buccal troches
- Sublingual drops

Oral dosage forms can also be customized to meet the specific needs of each patient. We can combine numerous compatible medications into a single dose for ease of administration or simplification of a confusing dosage schedule.

- Lollipops
- Freezer pops
- "Gummy bears"
- Solutions and suspensions, flavored to suit the individual.

Rectal formulations include suppositories, solutions and gels, and enemas. "Rectal rockets" facilitate simultaneous internal and external application of medication for hemorrhoids and other problems.

Nasal preparations are increasingly used as a method of delivering many types of medication.

- Spray
- Gel
- Drops

Solving Problems

Successful long-term pain management requires rapid, flexible, and expert responses to the changing needs of the patient. Patients and their loved ones should never allow pain to continue due to concerns about "being a complainer," medication-related side effects, or fear of addiction or loss of control subsequent to the use of pain medications. Effective pain management is best achieved by a team approach involving the physician, patient, his/her family, and often other health care providers.

Compounding combines an ageless art with the latest medical knowledge and state-of-the-art technology. Using state-of-the-art equipment and the highest grade of chemicals, we can compound a preparation according to your prescription and dispense in a dosage form that will simplify administration and improve patient compliance. Bring us your medication problems!

How to Write a Prescription for a Compounded Medication

Our pharmacists will be happy to discuss formulations and answer any questions.

Rx _____

_____

Compounded Medication*

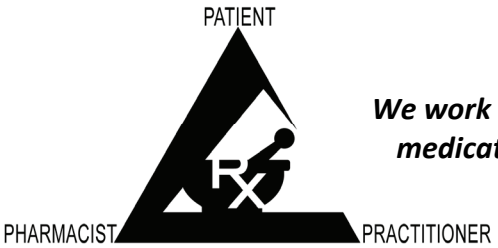
Generic Name of Active Ingredient(s) / Strength or Dose (i.e., mg or %)

Dosage Form (i.e., Suppository, Transdermal Gel, Troche)

Quantity

Directions for Use

*prescription should begin with the phrase “Compounded Medication”



We work together with practitioners and patients to customize medications which solve problems and meet specific needs.