THE TOPICAL PAIN RELIEF REVOLUTION:
PRINCIPLES AND PRACTICE OF COMPOUNDING PHARMACY

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KEY WORDS

# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOREWORD</td>
<td>5</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>7</td>
</tr>
<tr>
<td>NuMedCare: Compounding Excellence</td>
<td>8</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>9</td>
</tr>
<tr>
<td>DRUG OVERDOSE EPIDEMIC</td>
<td>9</td>
</tr>
<tr>
<td>ECONOMICS AND COMPOUNDING PHARMACY</td>
<td>12</td>
</tr>
<tr>
<td>DISADVANTAGES OF ORAL OR PARENTERAL ANALGESICS</td>
<td>13</td>
</tr>
<tr>
<td>ADVANTAGES OF TRANSDERMAL DELIVERY</td>
<td>15</td>
</tr>
<tr>
<td>ADHERENCE TO MEDICATION REGIMENS (COMPLIANCE)</td>
<td>19</td>
</tr>
<tr>
<td>CONCEPTS OF ADJUVANT ANALGESICS</td>
<td>22</td>
</tr>
<tr>
<td>OTC PAIN RELIEF</td>
<td>26</td>
</tr>
<tr>
<td>TOPICAL DELIVERY OF MEDICATIONS</td>
<td>27</td>
</tr>
<tr>
<td>TYPES OF ANALGESICS FOR TOPICAL USE</td>
<td>29</td>
</tr>
<tr>
<td>NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)</td>
<td>30</td>
</tr>
<tr>
<td>TOPICAL PREPARATIONS OF NSAID FOR TENNIS ELBOW</td>
<td>35</td>
</tr>
<tr>
<td>NEUROMODULATORS</td>
<td>37</td>
</tr>
<tr>
<td>OPIOIDS</td>
<td>38</td>
</tr>
<tr>
<td>ANESTHETICS</td>
<td>41</td>
</tr>
<tr>
<td>AMITRIPTYLINE</td>
<td>43</td>
</tr>
<tr>
<td>CAPSAICIN</td>
<td>44</td>
</tr>
<tr>
<td>NMDA RECEPTOR ANTAGONISTS</td>
<td>47</td>
</tr>
<tr>
<td>AMANTADINE</td>
<td>49</td>
</tr>
<tr>
<td>KETAMINE</td>
<td>50</td>
</tr>
<tr>
<td>CLONIDINE</td>
<td>57</td>
</tr>
</tbody>
</table>
FOREWORD

John Salerno DO

This monograph is a very useful guide for all practicing physicians. It provides a contemporary review of how many different pain medications can be used in the effective induction of topical analgesia. Dr. Holt is an internationally acclaimed expert in Integrative Medicine, and he makes valuable contributions to the important subject of topical pain control.

In this overview, the authors teach us that customized options for pain medication provide alternate dosages in topical forms. These medications can be applied directly to the area to be treated. The use of combined formulae may permit the use of medications in localized topical dosage forms with enhanced safety. Synergistic formulations result in an ability to reduce dosages or apply beneficial strength variations.

To further summarize matters, one can refer to the relative advantages of topical pain control:

Topical Versus Oral Benefits

- Reduction in side effects.
- Lack of gastrointestinal side effects.
- Fewer systemic side effects.
- Localized relief of pain and inflammation.
- Dose reductions.
- Reduced addictive potential.
- Increased adherence/patient compliance.

This book highlights the value of alternatives to oral or parenteral use of analgesics with the definition of a special role for the compounding pharmacists. This work is timely
with the recent calls to limit prescriptions of drugs that have the capability of inducing dependence or addiction.

I recommend this book highly for its role as a basic introduction to the topical pain control revolution that is gaining momentum in clinical practice in the U.S.A.

John Salerno DO, 2013
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The authors thank Todd Stephens of NuMedCare LLC, Boca Raton, Florida for his help and support in producing this work. The authors acknowledge the excellent work of several contemporary authors, and they cannot do justice in this short monograph to all current studies in the rapidly expanding literature on this subject which is expanding rapidly. Of special note and reference is the work of Jorge et al., J. Pain Res., 4, 11-24, 2011, Argooff CE, Current Pain and Headache Reports, 7, 34-38, 2003, Current Science, Jamero et al, reference: http://www.uspharmacist.com/content/feature/i/1500/c/282821, and Lusser et al, The Oncologist, 2004;9.
**NuMedCare: Compounding Excellence**

NuMedCare LLC is a research and development corporation that manages and consults with pharmacies providing synergistic topical compounded drug formulations for pain control and other conditions. The company also consults with physicians and other providers in the development of transdermal medication programs that can be tailored to a patient’s need (customized prescriptions).

Physicians and patients using the service of NuMedCare LLC have access to pain management experts and technical pharmacy staff who prepare compounded drugs. Many insurance companies and managed care companies cover the cost of topical analgesics including: HMO’s, PPO’s, workers compensation and personal injury coverage. NuMedCare, LLC has specially trained staff who can work with third party payers to assist in billing claims.

NuMedCare LLC is located in Boca Raton, Florida but is able to service patients and physicians in multiple states. The staff is readily accessible and bilingual (English and Spanish). Patients can contact info@numedcare.com.
INTRODUCTION

Compounding pharmacy has revolutionized the topical control of pain with the provision of effective synergistic analgesia. In these circumstances, tailor made combinations of pain-killing medications are presented in unique dosage forms such as creams, gels, ointments, oral lozenges, delayed release formulations, emulsions or suspensions. This practice permits the use of carefully individualized topical preparations that have advantages over standard oral or parenteral forms of analgesic drugs. Topical preparations can replace standard analgesic drug administration, assist in optimal pain control and improve patient compliance. The objective of this review is to guide the physician and pharmacist in a joint approach to efficient systemic and local pain management.

DRUG OVERDOSE EPIDEMIC

At the time of writing, the media was alive with reports of increasing numbers of overdose deaths from drugs. Reports from the Center for Disease Control (CDC) in Atlanta, Georgia indicate that opiate pain-relieving drug deaths increased dramatically from 1999 to 2010. In preceding times, the majority of overdose deaths from drugs occurred in men as a consequence of the consumption of heroin or cocaine. It now appears that overdose deaths in the United States are increasing rapidly among middle-aged women with prescription pain-relieving medication as the main culprit. This alarming increase in overdose death rates is coincidental with an increase in the
overall use of prescribed pain-killer drugs. The CDC has reported that the number of prescription pain-killer deaths increased among females by a factor of five times in the period of 1999 to 2010. In contrast, death rates from overdose rose about 3.5 times in men in the same period of time.

It would appear that men may take more risks with drugs than women and they may have a higher prevalence of injuries in the work place which result in the prescription of potent analgesic drugs. In 2010, approximately 23,000 deaths from pain killing drugs were noted in men, compared with 15,300 in women. Drug overdose death rates have risen continuously over the last eleven years and most of these are the result of accidents involving the use of addictive painkillers. Sometimes multiple drugs are involved, with alcohol. There have been a number of initiatives taken to try and control the growing use of painkilling drugs but the problem continues with stubborn persistence. In the year 2010, the CDC reported 38,329 drug overdose deaths nationwide and nearly 60 percent of these deaths were caused by prescription drugs. This circumstance overshadows the number of deaths caused by the use of illicit narcotic drugs, such as heroin or cocaine.

It would appear that opioid drugs (oxycontin and vicodin) are the biggest problem because they contribute to three out of four of all prescription medication overdose deaths. Several reasons are responsible for this serious situation. First, these opioid drugs are prescribed too often and patients may be exposed to “pill mills” where adequate care concerning use of dangerous drugs is absent. Patients
may “doctor hop” for drug prescriptions and it is clear that middle-aged women are more likely to have chronic pain which results in the prescription of higher dosages of analgesic, compared with men. This is a dangerous situation because drug toxicity is more likely in women who have a smaller body size than men. There is some evidence that women are more likely to attend multiple doctors and obtain drugs from these physicians. This circumstance of excessive pain-killing drug use persists despite efforts to monitor drug prescriptions. Several solutions have been suggested including counseling on addiction and alternative interventions for chronic pain. Data from drug monitoring programs are available in most states but few physicians avail themselves of this information for patient management. These matters are highly complex because of the need for patient confidentiality.

In January 2013, a federal panel of drug safety specialists recommended that vicodin and many other pain medications be subject to the same restrictions as the narcotic drug, oxycodone. The CDC have focused attention on reporting the dangers of prescription opioids (vicodin and oxycontin), but problems exist with generic forms of these medications, methadone and powerful new drugs such as Opana (oxymorphone). In brief, an alarming finding is the major increase in drug overdose death rates in women ages 45 through 54 and 55 through 64. The rate of deaths for each of these groups of women increased three fold between 1999 and 2010. In response to these problems many hospitals have started to apply appropriate restrictions on the prescription of pain-killing medications.
Much information has appeared in popular literature about the progression of patient’s use of pain-killing medications from prescription drugs to illicit narcotics. Many opioid pain-killing drugs are of high addictive potential and the relief of discomfort felt with these drugs is followed by a downside feeling of withdrawal. This vicious cycle of relief or pleasure perpetuates drug habituation. It is estimated that 12 million Americans use non-medically approved opioid analgesics in the year 2010. The opioids act to release dopamine, an excitatory neurotransmitter, which results in secondary sensations of comfort and satisfaction. The saturation of brain opioid receptors makes it necessary for the patient to increase dosages to gain desired effects.

It is clear that there is a serious threat to public health posed by several pain killing drugs, most notably opioids. One important potential approach to this problem is to use topical pain control when possible. Topical pain control will not produce the same circumstances of potential addiction that occur with standard oral dosing. Any intervention that reduces the exposure of patients to the addictive potential of opioid drugs or other neuromodulating agents can make an important impact on public health.

**ECONOMICS AND COMPOUNDING PHARMACY**

Trevor Stokes (TimesDaily.com, April 2011 and May 2013) reports that drugs delivered through the skin generated revenue of billions of dollars in 2009, according to the independent work of Market Research News. It is
estimated that compounding pharmacists make about 1-3% of the prescription topical drug market which is generating high revenue.

This circumstance has contributed to activity in the pharmaceutical industry where “old drugs” are selected and put through an FDA approval process. Stokes (ibid, 2011 and 2013) points out that this circumstance is very lucrative for the pharmaceutical industry; and he quotes the example of Hydroprogesterone use to prevent pre-term labor where costs per injection escalates one hundred fold ($15 per injection to $1,500 per injection) with this proprietary shift in medication. While concerns exist about the expense of compounding pharmacy, in the presence of such economic shifts, compounding pharmacy may benefit cost-containment in several circumstances.

**DISADVANTAGES OF ORAL OR PARENTERAL ANALGESICS**

There are many classes of standard oral or parenteral analgesic medications. The most common type of oral analgesics includes acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). Acetaminophen preparations may be effective in mild to moderate pain relief, but they have a propensity to cause hepatic toxicity, especially in large dosages.

Acetaminophen overdose is the most common cause of acute liver failure. This has resulted in new warnings on acetaminophen medications with advice to lower daily maximum dosage from 4 grams to 3,250 mg per day. In
2005, studies performed in more than 9,000 participants showed that many individuals took over the counter (OTC) pain relievers such as ibuprofen and aspirin in what has been described as an inappropriate and potentially dangerous manner.

It is notable in reviews of the use of NSAID-type analgesics that many subjects are unaware of the potential side effects of gastro-intestinal upset, headache, renal damage and bleeding from the gastro-intestinal tract. More recent studies in 2012 have found that a significant number of individuals are at risk of overdosing on OTC pain medications (e.g. acetaminophen). Furthermore, two dozen or more non-prescription (over the counter, OTC) non-steroidal anti-inflammatory drugs (NSAIDs) have common and potentially onerous side effects to a degree that they are a major public health concern.

To review the status of NSAID usage, it is apparent that many millions of Americans with bone and joint problems are “gobbling” aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Common side effects of NSAIDs include stomach upset that can herald the onset of peptic ulcer, and the precipitation of life-threatening bleeding from the upper or lower digestive tract. In addition, liver and kidney problems are relatively common with NSAID use. Certain types of NSAIDs are associated with a risk of stroke or heart attack. Unfortunately, the side effects of NSAIDs are sometimes fatal, especially in the elderly, who represent the main target population who take these drugs, and to whom these drugs are often selectively marketed.

For these reasons, many people have sought alternative management strategies for bone and joint health, including
the use of dietary supplements. While dietary supplements for bone and joint health are not drugs or considered substitutes for drugs (at law), many doctors and their patients are using dietary supplements to manage simple arthritis, especially osteoarthritis. This approach can occur only with statements that stress the use of “nutritional support for bone and joint structure and/or function.”

More potent pain killing drugs are limited in their use by their ability to produce dependence or frank addiction. For example, opioids are limited in their use by central nervous system effects, respiratory depression and failure to control arthritic pain in some circumstances-vide infra. The relative advantages and disadvantages of several analgesics are reviewed later in this overview.

**ADVANTAGES OF TRANSDERMAL DELIVERY**

Pain resulting from surgery, traumatic injury, malignant disease, neuropathic diseases (e.g. diabetic, chemotherapy induced, or HIV neuropathy), arthritis, or musculoskeletal pain, are all amenable to the application of topical pain relief compounded preparations. One clear advantage of cutaneous application of analgesia is direct application to the source of the pain. The absorbed pain relief drugs from the topical application can have variable bioavailability, but the cutaneous administration of the drugs tends to produce local pain relief effects. Topical delivery prevents extensive first-pass metabolism that occurs in the liver, most notably when drugs are given by the oral route.
There are many drugs that can be placed into specially compounded emulsions that permit absorption of the active moieties through the skin. Classes of drugs that can be compounded in topical formulations include: tricyclic antidepressant drugs, anticonvulsant compounds, NMDA antagonists, NSAID, muscle relaxants, GABA agonists and anesthetic agents. Examples of the successful use of transdermal medications are shown in table 1.

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>CONCENTRATION (%)</th>
<th>MEDICAL USE</th>
</tr>
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<tbody>
<tr>
<td>Ketamine</td>
<td>5-20</td>
<td>Neuropathic pain, herpetic and myofascial trigger points, neuralgia, by local analgesia.</td>
</tr>
<tr>
<td></td>
<td>May combine with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clonidine, 2 and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gabapentin 6</td>
<td></td>
</tr>
<tr>
<td>Magnesium Chloride</td>
<td>10</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>10-20</td>
<td>Anti-inflammatory effects, low back pain, arthritis</td>
</tr>
<tr>
<td></td>
<td>May combine with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketamine 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclobenzaprine,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and Buvipavaine 0.5</td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>2</td>
<td>Local analgesia</td>
</tr>
<tr>
<td></td>
<td>May combine with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baclofen or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>capsaicin</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>6</td>
<td>Local analgesia</td>
</tr>
<tr>
<td>Medication</td>
<td>Concentration</td>
<td>Local Analgesia</td>
</tr>
<tr>
<td>------------</td>
<td>---------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Clonidine</td>
<td>0.1-0.2</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1-2</td>
<td></td>
</tr>
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**Legend to Table 1. Medications and typical concentrations used for specific disorders, alone or in combination.**

References:

- Schwartz SI. Allin D. Kipness MS: Dose ranging and tolerance study of 0.05% clonidine gel in patients with painful diabetic neuropathy. Program and abstracts of the 19th Annual Scientific Meeting of the American Pain Society: November 2-5, 2000: Atlanta, Georgia. Abstract 671.

Alongside these limited examples of compounded topical pain relief preparations comes information relevant to further advantages of this mode of treatment. Topical pain control appears quite safe except for the occurrence of occasional local reactions (e.g. pain and irritation caused by
agents such as capsaicin) or occasional allergic reactions to a variety of drugs.

Topical delivery can result in short-lived stable levels of drugs, but repeated applications, up to four times daily, may be necessary in several circumstances. The use of topical agents in combination can result in synergistic effects, which tend to enhance pain control.

There is clear and substantial evidence that certain combinations of topical agents can effectively block nociceptive and neuropathic pain. Compliance with cutaneously applied analgesia is good as a consequence of a diminished need to take multiple dosages of oral medication and opportunities for the simplification of dosing. Overall, “topical” application of drugs can reduce the central nervous system effects (cognitive impairment) of many drugs (e.g. opioids) and in some cases it can overcome treatment failure with pain-killer drugs or result in reduced dosages that are required for pain control.

While scientists have discussed the placebo effect of local administration of analgesics to the site of the pain, such an effect is quite advantageous. This is the case even in referred pain from distant sources. Placebo effects can alter clinical outcomes of pain control and ancillary adverse effects, such as nausea or digestive upset. In the case of NSAIDs, which are a common cause of dyspepsia when administered orally, topical application can still result in uncommon occurrences of damage to the gastrointestinal tract, but it is much less than that encountered with oral administration of these drugs.

In summary, evidence has accrued that topical analgesics can often be as effective as pain killing drugs when taken
orally. While most experience with topical analgesia has been derived from studies in adults, there is increasing success in the use of topical pain control in pediatric populations. However, the pharmacokinetic properties of various drugs may differ between adults and children.

**ADHERENCE TO MEDICATION REGIMENS (COMPLIANCE)**

Complex factors determine the extent of matching of a prescribed treatment regimen to a patients’ intake of medication (adherence). In other words, “adherence” is a measure of how well the patient “sticks with” the prescribed regimen. Simple conclusions can be inferred about adherence and have been confirmed in clinical studies. For example, simple dosing regimens (once daily) in patients with chronic symptoms indicate that adherence is substantially higher compared with frequent dosing schedules (Claxton et al., Clin.Ther. 23,8,1296-1310, 2001). A number of co-existing factors alter adherence to medication (Jorge et al, J. Pain Res, 4, 11-24, 2011):

- presence of depression or substance abuse history
- social support systems
- socioeconomic status
- patient – clinician relationships
- chronicity of disease
- symptom burden
- mechanisms of healthcare delivery
- characteristics of treatment regimens.
The above listed circumstances should be optimized to produce good clinical outcome with topical pain treatments. Adjustment of dosing schedules to avoid side effects is important because a principal barrier to compliance is high dosing with attendant side effects. It appears that long half-lives of certain drugs may favor compliance by reducing the complexity or number of dosages required in one day. This knowledge reinforces the value of synergistic topical analgesic programs.

Other factors that can assist in ensuring adherence include consultation with relatives who can assist in the compliance of the patient, and supportive psychotherapy. Furthermore, close patient follow up and telephone or written prompts may be of value, but these latter attempts to improve compliance may result in variable success. More studies are required with the application of topical pain relief to identify important variables in clinical outcome.

Jorge et al (ibid 2011) have summarized a description of different strategies, that vary by disease, to improve patient adherence. Many of these examples of improving adherence can be modified and made portable to circumstances of topical pain control. The following is quoted from Jorge et al 2011.

- Patient awareness of breast cancer has increased and physicians are required to provide information regarding treatment goals and adverse effects of drugs, which are frequent and disabling. These issues influence compliance.
- Among patients with cardiac failure, the main predictor for cardiac rehabilitation was the physician’s endorsement of the effectiveness of program. Adherence increase when patients were actively referred, educated, highly self-motivated, and when programs were easily accessible.

- The major barriers for a good glycemic control include low efficacy of oral hypoglycemic drugs, fear of hypoglycemia, issues related to convenience of treatment (subcutaneous route, invasive blood sugar monitoring), poor access to health services, and lifestyle, leading to low adherence.

- Educational sessions, psychotherapeutic interventions, and phone prompts in community psychiatric services increase adherence of psychotic patients.

- Factors associated with poor treatment adherence among patients undergoing renal replacement therapy or under dialysis are frequent dosing, patient’s perception of treatment benefits, poor patient-physician communication, lack of motivation, and low socioeconomic background. Strategies for compliance are not well established, but some are suggested: treatment regimen simplification, establishing a partnership with the patient, and education.

- The most striking barrier to medication adherence in multiple sclerosis is forgetfulness to take pills, coping with adverse effects and perceived lack of efficacy. Validated strategies include good provider-patient
relationship, continuous education, and reinforcement regarding the benefit of treatment.

- Non-adherence of chronic obstructive pulmonary disease in 40%-60% as opposed to asthmatic patients, who adhere to inhalers and rescue medication. Economic factors and health beliefs influence device selection.

- Long-term adherence for asymptomatic conditions such as arterial hypertension is 50%. For these patients, adverse effects related to antihypertensive therapies and costs threaten treatment adherence. The most commonly used method to increase compliance in dyslipidemia and hypertension is dosing schedule modification from twice to once a day dosing.

DIFFERENT STRATEGIES IMPROVE PATIENT ADHERENCE IN A VARIETY OF DISEASES

CONCEPTS OF ADJUVANT ANALGESICS

In an excellent reviewed article, Lussier et al discussed the characteristics and use of adjuvant analgesics in cancer
pain management. The term “adjuvant analgesic” refers to drugs that have a primary indication other than pain treatment, but they have analgesic properties in some painful disorders. While they can be used alone to manage pain, they are usually administered with other pain killing medications e.g. acetaminophen, NSAID and Opioids. In this circumstance, the use of adjuvant analgesics is referred to as “co-analgesics”. This use of co-analgesia may result in the reduction of the dosage of a pain killer and improve pain that has not responded to the primary analgesic drug. Sparing the dosage of opioids is particularly valuable in reducing drug side effects.

Many different types of drugs can be used as adjuvant analgesics and some are multi-purpose in their function. Types of adjuvant analgesics include: antidepressants, corticosteroids, a2-adrenergic agonists, neuroleptics, whereas others are specific for neuropathic pain (anti-convulsants, local anesthetics, N-methyl-D-aspartate receptor antagonists), bone pain (calcitonin, bisphosphonates, radio-pharmaceuticals), musculoskeletal pain (muscle relaxants), or pain from bowel obstruction (octreotide, anti-cholinergics).

There have been few direct comparisons of the relative benefits of adjuvant analgesics. The clinician should attempt to select the optimal adjuvant analgesic by consideration of the underlying diagnosis and satisfaction
so that the drug addition is compatible with the patient’s status. Certain types of pain match individual categories of adjuvant analgesic and sometimes other disorders associated with the painful addition may benefit from the use of a specific drug. For example, the drug Cymbalta® is an antidepressant with specific benefit in patients with pain from diabetic peripheral neuropathy. This drug not only affords pain relief but it also exerts antidepressant effects. Chronic pain is often associated with depression.

There is general agreement that it is advantageous to start treatment with one drug at a time so that additive toxicity can be avoided (Lussier et al (ibid, 2004). Factors that guide the use of adjuvant analgesic in the management of cancer pain are listed below and taken verbatim from the review article by Lussier et al (ibid), 2004.

1. **Consider optimizing the opioid regimen before introducing an adjuvant analgesic.**
2. **Consider the burdens and potential benefits in comparison with other techniques used for pain that is poorly responsive to an opioid, including: A) opioid rotation. B) more aggressive side-effect management. C) a trial of spinal drug administration, and D) trials of varied non-pharmacologic approaches for pain control (e.g. nerve blocks, rehabilitative therapies, and psychological treatments).**
3. Select the most appropriate adjuvant analgesic based on a comprehensive assessment of the patient, including inference about the predominating type of pain and associated factors (co-morbidities) or symptoms.

4. Prescribe an adjuvant analgesic based on knowledge of its pharmacological characteristics, actions, approved indications, unapproved indications accepted in medical practice, likely side effects, potential serious adverse effects, and interactions with other drugs.

5. The adjuvant analgesics with the best risk-benefit ratios should be administered as first-line treatment.

6. Avoid initiating several adjuvant analgesics concurrently.

7. In most cases, initiate treatment with low doses and titrate gradually according to analgesic response and adverse effects.

8. Reassess the efficacy and tolerability of the therapeutic regimen on a regular basis, and taper or discontinue medications that do not provide additional pain relief.

9. Consider combination therapy with multiple adjuvant analgesics in selected patients.
OTC PAIN RELIEF

Before reviewing prescribed compounded topical analgesics, it is relevant to briefly review over-the-counter (OTC) pain relief products. These products are not as potent as prescription medication and often have limited absorption of certain ingredients, thus nullifying their effect.

Unlike topical compounded pain products, few of these OTC products have delivery mechanisms that would drive an analgesic through the skin. That said, some products have temporary pain relief actions with potential effects on mild to moderate local pain. The most common effects of OTC pain relievers is to mask pain by producing a heating or cooling effect that may also be achieved variably by hot or cold-pack treatments.

Ingredients in over-the-counter (OTC) topical pain medications include capsaicin (from hot peppers), salicylates (aspirin-like compounds) and essential oils (camphor or menthol). Capsaicin has special uses in compounded pain creams. It is derived from hot peppers and produces a burning sensation when eaten or applied on a topical basis. It will be described in more detail later in this review. Examples of commercially available, low dose capsaicin topical products include Capzaisin® and Zostrix®.

Salicylates are the prime example of NSAIDs and are available as Aspercreme® and Biofreeze®. It is important not to mix OTC analgesic products with compounded pharmacy preparations for fear of interaction.
The stratum corneum of the skin provides a barrier that limits the cutaneous absorption of many compounds. In topical pain control substances, the pharmacist may add agents that facilitate the transport of drugs through the skin. Physico-chemical factors of additives to pain creams work in different ways including: increasing absorption, diluting drug concentrations, retaining the drug at the target site, decreasing drug clearance and enhancing permeation, with attempts to decrease drug toxicity. One overriding objective is to reduce systemic absorption, in comparison to oral or parenteral administration, without interfering with analgesic effects. As mentioned earlier, the compounded preparation, when applied topically, can reduce first pass hepatic metabolism and sometimes contribute to stable blood concentrations of the administered drug. However, topical analgesia is capable of being produced by many agents that have negligible systemic bioavailability.

The effects of topical drug administration are altered by many factors, other than the relatively impenetrable barrier of the stratum corneum. These factors include: inter-individual (and some degree of intra-individual) difference in absorption (drug penetration amounts and rates), the degree of penetration into the subcutaneous areas and toxic or allergic properties of delivered drugs. Factors such as blood flow, lymphatic flow, the presence of carrier substances and ambient conditions can all affect transdermal transfer of drugs.
The site of application of the topical drug can affect absorption amounts and rates, as can specific factors such as pH, temperature, lipophilic or hydrophilic properties of the drug etc. As noted earlier, differences in response can be expected in children versus adults, and special caution should be applied in pediatric care.

Physical factors have been variably applied to modulate the transdermal uptake of drugs using electricity (iontophoresis), sound waves (phonophoresis) and even simple massage. Massage is to be avoided because of inconsistent effects. Special combinations of cooling (hypothermia) with iontophoresis have shown to increase levels of topically applied sodium diclofenac and prednisone in synovial fluids (Sammeta et al, Pharm. Res, 26, (11), 2535-40, 2009). Many studies in animals have confirmed the ability of physical methods to enhance drug concentrations in joints.

Innovations in the delivery of analgesic drugs include the use of biodegradable, implantable, controlled- drug delivery systems, and the addition of novel agents to topical preparations. Specially compounded emulsions can help in drug absorption. Pure powdered medications are obtained by pharmacies from licensed vendors which can be blended and placed into a gel or cream base. Milling of the preparations to a small particle size is an important step in enhancing transdermal bio-availability of drugs.

For example, lecithin or ganogel provides a suitable matrix for transdermal drug absorption, and pluronic lecithin ganogel (PLO) mixed with isopropyl palmitate acts as a surfactant with low toxicity and little irritation to the skin (Brown S, Tech. Reg. Anes and Pain Mgmt., 12, 199-
121, 2008). Other valuable additives to topical pain preparations include wetting agents, (e.g. ethoxy diglycol), which assist in the deposition and holding of medication within the skin (Ritschel et al, Skin Pharmacol, 4, 235-245, 1991, cited by Brown S, ibid, 2008).

A number of different patches have been developed for the topical delivery of a variety of analgesics. Some may cause minor irritation with occasional severe local inflammatory reactions. In general, the use of single agents is most common, and they are produced with a variety of additives to improve transdermal transfer, but the “power of synergy” in analgesic combinations is most advantageous – vide infra.

**TYPES OF ANALGESICS FOR TOPICAL USE**

Different properties of analgesics permit the selection of combination creams, gels or lotions which may possess different carrier mechanisms. The main classes of medication used in compounded pharmacy preparations are summarized below (Table 2).

<table>
<thead>
<tr>
<th>CLASS OF MEDICATION</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Steroidal Anti Inflammatory Drugs (NSAID)</td>
<td>Diclofenac, Ibuprofen, Ketoprofen, Piroxicam, Baclofen, Ketorolac (Tromethamine), Naproxen Flurbiprofen</td>
</tr>
<tr>
<td>Opioids</td>
<td>Buprenorphine, Fentanyl</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Lidocaine, Prilocaine, Tetracaine</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Zostrix®Qutenza® Capzasin P®</td>
</tr>
<tr>
<td></td>
<td>Zostrix HP®</td>
</tr>
<tr>
<td>Nitroglucerin</td>
<td>Organic nitrate, Nitro Dur®, Nitrodisc®, Transderm - Nitro®Glyceryl Trinitrate</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Kealar®, Ketanest®, Ketaset® (with hydrogel or ganogel, Pluronic®, PLO)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Catapres TTS®</td>
</tr>
</tbody>
</table>

Legend to Table 2. Examples of classes of drugs that are used in topical analgesic preparations produced in a compounding pharmacy.

NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Direct comparisons of the safety and effectiveness of topical NSAIDs have not occurred in a systematic manner. Each NSAID has unique pharmacokinetic and pharmacodynamic properties when given orally, but topical dosages of NSAIDs (creams, gels or sprays) are designed to
produce peripheral (local) effects on pain without significant systemic absorption and bio distribution.

The application of topical NSAIDs is to improve patient tolerance, especially with reduction of gastrointestinal side effects. As tolerance improves, compliance should improve. In one systematic review of 3455 individuals with musculoskeletal disorders (mainly sprains) good levels of pain control were encountered without the adverse systemic effects of orally administered NSAIDs (Massey et al, Cochrane Database Syst Rev. June 16, 6, CD 607402, 2010, cited by Jorge et al; ibid 2011).

The topical application of NSAIDs results in the development of high concentrations of the administered drug in subcutaneous tissues and local muscles, with considerable reduction in gastrointestinal side effects. In addition, there is a reduction in blood levels of the drug to a level of 5-15% of the levels encountered with a systemically administered drug. It is noted that synovial levels of NSAIDs increase when topical application occurs. This assists in producing prolonged analgesic effects.

Topical NSAIDs provide valuable relief in chronic pain of osteoarthritis (Jorge et al ibid 2011). Jorge et al (ibid 2011) quote the opinions of the European League Against Rheumatism and the International Osteoarthritis Research Society that topical NSAID for mild to moderate knee and
hand arthritis are preferred over oral NSAIDs, in patients with “sensitivity” to oral compounds. Other guidelines concur with those opinions. For example, in Great Britain, guidelines (NICE) suggest a preference for the use of acetaminophen alone or in combination with topical NSAIDs, compared with opioids or oral Cox-2 inhibitor drugs or oral NSAID (Conaghan et al, BMJ, 336, 502-3, 2008).

The effects of various topical NSAIDs on the induction of analgesia have been pieced together from a variety of animal experiments, with controlled observations mainly of single agents (NSAIDs) in humans. For example, in an in vitro inflammatory/pain model, Ketorolac Tromethamine gel, delivered by phonophoresis, had a lower permeability coefficient than Ibuprofen, Piroxicam and Diclofenac, delivered in the same way (Yang et al, Arch. Pharm Res. 31, 511-7, 2008). More studies of this type are required to compare absorption of topical NSAIDs, but extrapolation of the results from animal experiments to humans are sometimes problematic.

Evidence has accumulated that NSAIDs work by a local action. For example, a patch containing diclofenac epolaine (DE) (Flector ®) was able to provide analgesia for musculoskeletal disorders within one hour, at a time when no drug would be expected to have systemic distribution. Studies of diclofenac confirm efficacy in the management of joint stiffness and pain in osteoarthritis (OA) of the knee.

Ketoprofen works by stabilizing the membranes of lysosomes, antagonizing bradykinin and cox inhibition. Placebo controlled trials show its benefits when applied topically in cases of traumatic injury and rheumatic diseases. It can cause skin irritation when administered in patch form (Mazieres B, Drugs RD, 6,337-44, 2005). In a multi-center randomized controlled trial, Ketoprofen in topical patch format was equivalent in actions, in OA of the knee, to 100mg of oral celecoxib (Rother et al, Ann Rheum Dis, 66, 1178-83, 2007).

Ibuprofen is a popular NSAID that penetrates well into synovial fluid and, as mentioned earlier, it is believed that this results in a prolonged action on joints. It is often used in chronic arthritis and post-exercise pain; and it has less adverse effects than aspirin or indomethacin at equivalent pain-control dosages. Two types of ibuprofen topical preparations (Dolgit® cream and Nurofen® gel) are of demonstrated value in acute pain following injury and knee osteoarthritis (OA).
To reiterate, the objective of using topical NSAIDs is to provide analgesic and anti-inflammatory effects without systemic side effects. In a review of 47 studies (Massey et al Cochrane Database syst. Rev. Jun 16, 6, CD 007402, 2010) that mainly compared topical NSAIDs (creams, gels and sprays) with placebo, it was observed that, in 3455 patients, topical NSAIDs produced overall good pain relief in a mixture of different musculo-skeletal disorders. In brief, it was found that topical application of diclofenac, ibuprofen, ketoprofen and piroxicam were of equivalent effectiveness at pain control but indomethacin and benzydamine were not superior to placebo. There were few side-effects, but the data could not result in a reliable comparison of efficacy of each topical NSAID with each other, or with the same NSAID, administered by the oral route.

Moore and Rabbie (Cochrane Data Base Syst Rev, Sep 12, CD 007400, 2012), of the University of Oxford, England, performed a detailed analysis of chronic musculoskeletal pain, using information from 7688 individuals in 34 studies, derived from 32 publications. It was concluded that topical NSAIDs provided good pain relief and topical diclofenac solution was found to be equivalent in efficacy to oral NSAID in the treatment of knee and hand osteoarthritis (OA). An important finding was that changes in formulation were found to influence levels of topical analgesia. While the occurrence of local side effects of topical NSAID
application occurred, gastrointestinal complaints and events were significantly reduced compared with the application of oral NSAIDs.

This short review of NSAID applications in topical pain relief shows efficacy of several preparations, but comparisons are difficult due to difference in study design, variable controlled observations and several other factors.

**TOPICAL PREPARATIONS OF NSAID FOR TENNIS ELBOW**

Lateral epicondylitis (or tennis elbow) is one of the most common overuse injuries in clinical practice. In this condition there is inflammation of adjacent tendons and soft tissues which often results in its treatment by NSAIDs. Gastrointestinal (GI) intolerance of NSAIDs and other side effects limit the oral use of these drugs and GI upset occurs in up to one in three users (Polisson R, JAMA, 100, suppl 2A, 315-36, 1996 cited by Burnham et al, Clin J. Sports Med, 8, 78-81, 1998).

Burnham et al (ibid, 1998) studied the effectiveness of topical diclofenac 2% in a liposomal delivery system (pluronic-lecithin liposomal organogel, PLO) in 14 subjects with chronic lateral epicondylitis. The gel (2% diclofenac) provided effective reduction in elbow pain during the time of its administration and improved elbow discomfort and wrist extensor weakness that was due to the chronic epicondylitis (tennis elbow). Other studies have confirmed
the benefit of selected topical NSAIDs in the treatment of epicondylitis.

One of the most frequently asked questions about the use of topical drugs is how far they penetrate tissues to achieve maximal effects. Until recently, no studies have measured NSAID concentrations in tendon, bone, periarticular, and periosteal tissues after both topical and oral administration.

In excellent studies, Shuken Kai et al (British J. Clin. Pharmacol, 75: 3, 799-804, 2012) compared the tissue concentrations of flurbiprofen (an NSAID) as a consequence of oral and topical administration (according to standard and approved dosing schedules). In these studies, 16 patients were randomly assigned to the topical application or oral administration of flurbiprofen by tape or tablet, respectively.

There were no adverse effects experienced with the test drug, and specific laboratory testing remained normal throughout the studies. Flurbiprofen concentrations were higher in the tissues examined after topical versus oral administration, but systemic levels of the drug were predictably higher following oral administration. Thus, the flurbiprofen concentrations were significantly higher following cutaneous (tape) application in fat, muscle, tendon and periosteum. Concentrations of flurbiprofen
were higher in bone after oral administration compared with topical application. Flurbiprofen tapes for topical pain relief are available in Japan as Zepolos ® Tape (Mikasa Seiyaku, Tokyo).

Calculations of the topical to plasma drug concentration ratios were much higher in topical treated groups, but measures of pain control were not assessed in this study. These findings indicate that flurbiprofen was delivered to the tissues by blood and other transport systems. Recent research implies that both dermal blood flow and lymphatic vessel flow play a significant role greater than simple direct diffusion of NSAID into deeper tissue (Anirmov and Roberts, Pharm Res., 28, 2119-29, 2011 and Sammeta et al Pharm. Res, 26, 2535-40, 2009). These data offers strong support for the use of flurbiprofen, and perhaps other NSAID, in the effective topical delivery to multiple tissues adjacent to the body surface.

**NEUROMODULATORS**

Richards et al (Cochrane Database Syst Rev, Jan 18, 1, CD008921, 2012) examined, in a literature review, the ability of neuromodulators to control pain in rheumatoid arthritis. Several drugs were included in the review process including: anticonvulsants (gabapentin, pregabalin, phenytoin, sodium valproate, lamotrigine, carbamazepine, levetiracetam, oxcarbazepine, tiagabine and topiramate), ketamine, bupriopion, methylphenidate, nefopam, and
capsaicin. Following a computer-assisted search of several databases, four trials were included (Richards et al, ibid, 2012). The four selected trials were considered to have a high degree of potential bias. Two of the four trials studied oral nefopam, and one studied topical capsaicin.

Oral nefopam was superior to placebo, but there were side-effects of the medication (nausea and sweating). Topical Capsaicin was also superior to placebo in pain control, but local burning reactions were common and 2% withdrew because of this troublesome side effect. Overall, the benefits of the investigated neuromodulators were perceived to be modest.

**OPIOIDS**

The two opioids that have received most use and research attention in topical analgesia are buprenorphine and fentanyl. Buprenorphine and fentanyl are synthetic opioids. While the effects of these drugs are largely on the central nervous system, there are peripheral receptors involved in pain control that interact with these opioids. Observations in humans on the effects of topical opioids on pain have produced mixed results, but support for their potential actions comes from the recent discovery of mu and delta opioid receptors at the endings of sensory afferent neurons.
Morphine administered topically may relieve mucositis related pain in individuals undergoing chemotherapy for head and neck cancer (Hassan et al Neuroscience, 55, 185-95, 1993), but topical opioids may have limited effects on pain from skin ulcers, bladder pain and pain from dental procedures (cited by Jorge et al ibid 2011, Cerchietti et al, Pain, 105, 265-73, 2003).

Fentanyl interacts with mu opioid receptors. It is lipid soluble and of low molecular weight which makes it ideal for transdermal use. Fentanyl has most use in the treatment of chronic malignancy-related pain but it has been used in more general forms of pain control (e.g. post-operative pain) following major abdominal surgery. In contrast, buprenorphine has a long half-life and potent anti-hyperalgesic effects. It is available as Butrans® and it is used most often for musculoskeletal and chronic cancer pain. (Jorge et al, ibid, 2011).

Buprenorphine is a partial agonist of mu, delta and kappa receptors and it is an efficient agonist of opioid receptor-like receptor 1 (ORL1). Thus, it differs in its pharmacological action from other opioids. The success achieved with Buprenorphine in neuropathic pain is explained by its effect as an agonist of Kappa receptors. Overall, clinical trials show improved pain control outcome with general benefits of better sleep and less need for extra pain control interventions, especially when Buprenorphine
is used for the management of cancer pain. (Jorge et al, ibid, 2011).

Both Buprenorphine and Fentanyl can cause onerous side effects in high dosages. Respiratory depression can be a problem with both medications, but Buprenorphine can cause renal impairment. In fact, Buprenorphine has a greater propensity to cause respiratory depression and renal dysfunction than other opioids, such as methadone, hydromorphone, morphine and fentanyl. The key to controlling side effects is dosage adjustment, but topical administration generally limits the side effect profile of opioids, compared with oral or parenteral administration.

In common with Buprenorphine, the most frequent adverse effects of fentanyl are nausea, vomiting, headaches, skin irritation and occasional flushing. Fentanyl carries a modest risk of respiratory depression. The side effect profile of the use of Buprenorphine and Fentanyl are substantially similar in several respects, but arguably Fentanyl has less adverse effects.

There is a considerable amount of research on transdermal patch matrix compositions for delivering opioids. Fentanyl has been administered by patient-controlled iontophoretic (electricity) transdermal systems (Fentanyl ITS®). This system is approved by the Food and drug Administration (FDA) for the treatment of
postoperative pain (induced by surgery) (Jorge et al, ibid, 2011).

This system of self-controlled treatment differs from a standard Fentanyl patch which is fabricated mainly to produce a controlled release of the drug over a 72 hour period. This patch design is more suitable for chronic pain than the acute fluctuating pain suffered by the post-surgical patient (Jorge et al, ibid, 2011). In brief, much more research is required on the use of Fentanyl which has been increasingly applied for pain control in a topical form in FDA-off label usage.

Whittle et al (J. Rheumatol. Suppl, Sep, 90, 40-6, 2012) performed an analysis of 11 studies of patients with rheumatoid arthritis (RA). These studies were all of short duration and had a high risk of outcome bias. In brief, these studies showed the marginal benefit of the use of opioids, administered by any route, in Rheumatoid Arthritis (RA); and adverse events were quite common. Adverse events were considered to reduce overall benefits after short term use in RA and long term risks of the use of opioids in RA are not well defined.

**ANESTHETICS**

Topical anesthetics in common topical use include lidocaine, prilocaine and tetracaine. These anesthetics are available in gel, cream and patch preparations, with the
most popular combination use of prilocaine 2.5% and lidocaine 2.5% (EMLA cream-2).

EMLA can be applied to the skin prior to invasive procedures (most notably minor surgical interventions) and it has been used (FDA – off-label) for the treatment of neuropathic pain (post-herpetic neuralgia). Anesthetic ‘topicals’ can all cause skin irritations and some cause significant allergic skin eruptions, perhaps from both the anesthetic content and additives, such as parabens or propylene glycol (Jorge et al, ibid, 2011).

The topical analgesic Ametop® is a tetracaine base product which is widely used for cutaneous pain relief in both children and adults. It has been applied successfully in skin needle insertion in children. While topical anesthetics are useful in reducing pain of intravenous catheter insertion or needle puncture of blood vessels, they have not been used routinely, largely because of the time taken for their onset of analgesia (Jorge et al, ibid, 2011).

The patch Rapydan®, containing 70 mg of Lidocaine with 70 mg of Tetracaine, has been used with a heat delivery system for rapid onset of action. This system of topical pain control is approved in Europe for pain relief during blood vessel cannulations and minor surgical procedures.

Lidocaine is often available in 5% patches (Lidoderm®) and it is approved for the treatment of post-herpetic
neuralgia and other neuropathic conditions. It is recommended for use when other treatment are ineffective, such as failure of antidepressants or anticonvulsants e.g. Lyrica®, Cymbalta® or opioids. These suggestions for the use of expensive drugs, with common attendant side effects as first line options, may be misguided.

Lidocaine patches (5%) have been shown to be valuable in the management of sub-acute or chronic low backache when administered on a daily basis for six weeks. Overall, lidocaine patches have a low incidence of adverse effects and they are unlikely to cause drug interactions. They have a high degree of tolerance and adherence (Jorge et al, ibid, 2011).

**AMITRIPTYLINE**

Amitriptyline is a more potent topical local analgesic than Bupivacaine and Lignocaine. It has a longer action after cutaneous infiltration than bupivacaine and both drugs are enhanced in their action by the co-administration of Epinephrine (Mohammed et al, Anesthesiology, Jan, 96, 1, 109-116, 2002). Furthermore, prolonged cutaneous analgesia is achieved with the topical application of Amitriptyline and Capsaicin in a manner that is superior to Amitriptyline alone.
In several studies, the co-administered Capsaicin prolongs cutaneous analgesia by facilitating the passage of Amitriptyline into pain receptor locations (nociceptors) and the co-applied capsaicin could theoretically counteract the vaso-constrictive effects of topically applied Amitriptyline (Calvin et al, Regional Anesthesia and Pain Medicine, 36, 3, 236-40, 2005).

**CAPSAICIN**

Capsaicin is a derivative of hot pepper plants. Capsaicin interacts with sensory nerve afferents via vanilloid receptors (VRI). These receptors are cation channels that are part of the transient receptor potential family (Jorge et al ibid, 20110). In addition, capsaicin can deplete substance P at nervous afferent endings and it decreases the density of nervous fibers in the skin. Chronic topical use of Capsaicin both stimulates and desensitizes cation channels thereby interfering with sensory nerve afferents.

Several reviews confirm the benefit of topical Capsaicin in different strengths of 0.75% and 8%. In one overview of 1566 subjects with neuropathic or musculoskeletal pain, improvements in neuropathic pain occurred in 57%, whereas 42% relief of pain occurred in the placebo group. In the study group with musculoskeletal pain, 38% improvement was observed with a Capsaicin patch (0.25%) with only a 25% improvement in the placebo group (cited by Jorge et al ibid, 2011).
Overall, improvement in neuropathic pain can be expected with 0.75% strength of Capsaicin cream or single patch application of 8% Capsaicin. Improvements have been noted in several disorders including: post-surgical pain, post-herpetic neuralgia, diabetic neuropathy, HIV neuropathy and Guillain-Barre syndrome (Mason et al, BMJ, 328, 991-5, 2004, Derry et al, Cochrane Data Base Review, CD007393,4,2009, Ellison et al, J. Clin Oncol, 15,6,2974-80,1997).

Common side effects of Capsaicin include a burning sensation at the site of application with redness of the skin and an occasional rash. There are uncommon severe reactions, especially when there is a need for the use of capsaicin on a frequent basis (4 x per day). Frequent use of Capsaicin affects compliance in an adverse manner. One can expect to see some local irritation in 33% of patients and 10% may have to withdraw from capsaicin therapy due to considerable discomfort.

Moore DS (Cochrane Database Syst. Rev, Sep 12, CD010111, 2012) investigated the use of low dose (<1%) topical Capsaicin creams in the management of chronic neuropathic pain. Six studies were found to have compared low dose 0.075% Capsaicin cream with placebo. In these studies, there was much variation in outcome with different measures of beneficial outcome. Only two studies reported at least 50% pain relief. The outcome of this research
review did not permit conclusions to be made about the efficacy of low dose Capsaicin cream, but apart from local irritation there were few systemic side effects (Moore DS, ibid, 2012).

Derry et al (Cochrane Database Syst Rev, Feb 28, 2, CD007393, 2013) have produced a recent review of the safety and effectiveness of high concentration (8%) topical Capsaicin for the management of chronic neuropathic pain. These authors reviewed six studies which examined 2073 participants in comparisons of 8% topical Capsaicin versus a control of 0.04% topical Capsaicin. As anticipated, mild to moderate local adverse effects were common, but serious side effects were not significantly greater in the high capsaicin concentration versus low concentration treated individuals.

The authors Derry et al (ibid, 2013) concluded that high concentration topical capsaicin (8%) was effective in inducing pain relief in patients with post-herpetic neuralgia and Human Immunodeficiency Virus (HIV) induced peripheral neuropathy. There were added benefits in the responsive group including: better sleep, reduced fatigue, lightening of depression and improvements in quality of life (QOL). The authors commented that unknown risks of chronic application of high dose Capsaicin exist, most notably a risk of disruption and damage to cutaneous innervation.
NMDA RECEPTOR ANTAGONISTS

A noxious stimulus to the peripheral parts of the body releases glutamate. Glutamate is a neurotransmitter that interacts with the N-methyl-d-aspartate (NMDA) receptor and serves to antagonize its actions. The stimulation of NMDA receptors produces three main effects. First, it causes hyperalgesia and, second it contributes to neuropathic pain. The third effect is to reduce the actions of opioid receptors. Neuropathic pain and hyperalgesia result from spinal neuron sensitization. The reduction in the function of opioid receptors contributes to opioid tolerance. This tolerance to opioids results in a need to use higher dosages of opioids to induce adequate pain control.

A number of NMDA receptor antagonists are available for use in topical or systemic dosing. These antagonists include ketamine, methadone, memantine, amantadine, and dextromethorphan. Table 4 gives examples of NMDA receptor antagonists and their recommended dosages and potential side effects. It is apparent that ketamine is the most potent NMDA antagonist, but it is more likely to induce central nervous system side effects which may include dizziness, fatigue, headache, nightmares and sensory changes. These circumstances have led to a preference for the use of amantadine.
Table 4. NMDA Antagonists for Pain Management

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Analgesic Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>IM: 2-4 mg/kg&lt;br&gt;IV: 0.2-0.75mg/kg&lt;br&gt;Continuous iv infusion: 2-7 Mcg/kg/min</td>
<td>CNS effects: Hallucinations, confusion, dreamlike state, irrational behavior. Other effects: Respiratory depression, increased CSF pressure, hypertension, Tachycardia, tremor, nystagmus, myocardial Depression</td>
</tr>
<tr>
<td>Methadone</td>
<td>Opioid naive: Initial dose: 2.5-10 mg q8-12(^{th}) (interval may range from 4-12 h as analgesic duration is short during initial therapy, although it increases with prolonged therapy). Opioid-tolerant: Oral morphine to oral methadone conversion is variable</td>
<td>CNS depression, respiratory depression, QTc prolongation, constipation, nausea and vomiting, dizziness, disorientation</td>
</tr>
<tr>
<td>Memantine</td>
<td>PO: 10-30 mg/day</td>
<td>Hypertension, dizziness, drowsiness, confusion, anxiety, hallucinations, cataract</td>
</tr>
<tr>
<td>Amantadine</td>
<td>IV:200 mg infused over 3h PO: 100-200 mg/day</td>
<td>Orthostatic hypotension, dry mouth, drowsiness, agitation, confusion, hallucinations, dyskinesia.</td>
</tr>
<tr>
<td>Dextromethor Phan</td>
<td>PO:45-400 mg/day</td>
<td>Light-headedness, drowsiness, confusion, nervousness, visual disturbances, serotonin syndrome</td>
</tr>
</tbody>
</table>

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AMANTADINE

Amantadine is an anti-viral drug which is sometimes used in the treatment of Parkinson’s disease. It is a non-competitive NMDA antagonist that is used on a chronic basis in humans because of its relative safety. Case studies and preliminary trials show that amantadine can result in significant reduction of surgical-induced neuropathic pain in cancer patients (Macres SM, Understanding Neuropathic Pain) http://www.spineuniverse.com/conditions/chronic-pain/understanding-neuropathic-pain.

Pud et al (Pain, 1998, 75,349-354) performed a randomized placebo-control trial of amantadine in cancer patients who were experiencing surgical neuropathic pain. The amantadine was given by infusion, and there was an 85 percent reduction in pain with the administration of amantadine compared with 45 percent following the administration of placebo. In this study, pain intensity at two days prior and two days following treatment resulted in a 31 percent reduction in pain compared with only 6 percent reduction in pain in the placebo group.

Amin P and Sturrock NDC (Diabetic Medicine, 20,: 114-118. Doil: 10.1046/j.1464-5491.2003.00882.x) studied the effects of amantadine in the treatment of painful diabetic peripheral neuropathy. Amantadine was given by intravenous infusion to 17 patients and it resulted in reduction of the pain experienced from diabetic
neuropathy. Favorable pain relief was present for at least one week following the infusion of amantadine. In this study, perception of pain relief was 10-fold greater following amantadine administration compared with placebo.

Not all studies with amantadine have shown positive outcome in pain control. For example, Fukui et al (J.Anesth,2001,15,179-181) studied the use of oral amantadine in patients who had failed to respond to several conventional treatment for neuropathic pain. In this study, only 2 of the 19 patients experienced significant pain reduction and side effects were experienced in 52.6 percent of the patients. Side effects consist of drowsiness, hallucinations, irritation, dizziness and dyskinesia.

**KETAMINE**

Ketamine is a glutamate receptor antagonist that causes analgesic effects in doses less than those used for anesthesia. This drug works as a non-competitive, N-methyl – aspartate (NMDA) receptor antagonist with some degree of opioid activity. The analgesic effects of Ketamine are complex and they are dependent on: calcium channel blockage, actions on opioid receptors, cholinergic or monoaminergic effects and glutamate receptor activity. Glutamate receptors are present on afferent nerve terminals in the peripheral nervous system and on membranes of unmyelinated peripheral axons.
Table 4 summarizes four topical (alone or in combination) Ketamine studies:

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Patient population and numbers</th>
<th>Design/Methodology</th>
<th>Outcomes</th>
<th>Withdrawal/Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barton (2011)</td>
<td>DB RCT PLC</td>
<td>N-208: Chemo-therapy associated peripheral neuropathy for 1 month</td>
<td>Topical Gel of 10 mg baclofen, 40 mg amitriptyline and 20 ug ketamine vs placebo 10ml applied daily x 4 weeks</td>
<td>Statistically significant improvement in motor neuropathy symptoms on CIPN-20 questionnaire; trend towards improvement in sensory neuropathy symptoms</td>
<td>No significant difference in adverse events between placebo and treatment</td>
</tr>
<tr>
<td>Lynch (2003)</td>
<td>DB RCT PLC: subsequent open label prospective in &quot;ketamine responder s” subgroup</td>
<td>N=20; Chronic neuropathic pain</td>
<td>Topical ketamine cream (0.5%) vs. topical amitriptyline cream (0.1%) vs. combination cream vs. placebo 5ml daily x 2 days: subsequent 7 day open</td>
<td>No difference on McGill Pain Questionnaire or VAS between treatment arms in 2 day trial; open label arm showed significant decrease in pain by day</td>
<td>2 patients Experienced “minor” side effects</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Intervention</td>
<td>_outcome</td>
<td>Adverse Events</td>
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<tr>
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</tr>
<tr>
<td>Lynch (2005)</td>
<td>DB RCT PLC</td>
<td>N=92: Diabetic neuropathy, Post- Herpetic neuralgia or Post traumatic neuralgia</td>
<td>Topical ketamine cream (0.1% vs. Topical amitriptiline cream (0.2%) vs. combination cream vs. Placebo (emulsant only); all creams 4 ml TID x 3 Weeks</td>
<td>No statistically significant difference in pain reduction on NRS- PI scale between 1-1.5 decrease in spontaneous pain</td>
<td>1 episode of local skin irritation; 1 swollen feet; 2 episodes of drowsiness</td>
</tr>
<tr>
<td>Vranken (2005)</td>
<td>DB RCT PLC</td>
<td>N=33 Central Neuropathic Pain</td>
<td>Iontopatch administered 50 mg ketamine vs. 75 mg ketamine vs. placebo (NS) over 24hr x 5 days</td>
<td>No significant difference between any groups in change of VAS scores after 7 days; significant improvement in PDI, EQ-5D and SF-6 scores in the 75 mg ketamine group</td>
<td>3 patients in ketamine arms reported sedation, 1 each of nausea/vomiting, confusion, dizziness, vivid dreams</td>
</tr>
</tbody>
</table>
Table 5. A summary of four controlled observations of topical ketamine effects when given alone or in combination. Reproduced from Presentation by Horsha Shanthanna, Assistant Professor, Anesthesiology and Pain Medicine, St. Joseph’s Hospital, McMaster University: 2013 accessed.

In summary, the value of topical ketamine for pain control can be summarized (Shanthanna H, 2013), verbatim.

- “There is some evidence to argue for peripheral NMDA activation via glutamate.

- The potency of local anesthetic action needs more investigation

- Animal studies have shown the decreased pain behaviors with peripheral ketamine, can it still be systemic?

- Human studies have not been conclusive.

- The topical application is not used on its own in any study (in any RCT’s).

- It is difficult to say that there is any good evidence for topical ketamine application (Class III). Proper well designed studies with adequate patients are needed.” (Shanthanna H, McMaster University, 2013).
Ketamine (Ketalar®, Ketanest®, Ketaset®) comes in intravenous and intramuscular preparations, but studies have been undertaken with intranasal, transdermal and rectal administration to evaluate its analgesic effects. Ketamine is a phencyclidine analogue and it is not routinely used as an anesthetic. Transdermal varieties of the drug include complexes with PLO (Pluronic® lecithin organogel). These preparations come in liposomal (phospholipid) emulsions, oil and water base 0.5% or a 1% cream or basic emulsion. The most efficient delivery system appears to be the PLO form (Jorge et al, ibid, 2011).

Complementary trials to those listed in Table 4 include the use of 0.5 – 1% Ketamine cream for postoperative pain and cancer pain. In this context, limited observations have shown synergistic benefits of ketamine 0.5% with amitriptyline 2.5% in treating rectal pain of unknown cause (cited by Jorge et al, ibid, 2011).

The resistance of neuropathic pain to opioids has led to the application of other analgesic agents for neuropathic pain e.g. antidepressants, anticonvulsants and local anesthetics (Gammaitoni et al, J. Pain, Oct 6, (10), 644-9, 2005). These latter authors describe the role of central sensitization or pain “wind up” that may contribute to the continuity of chronic neuropathic pain, even in the absence
of peripheral neuropathy (Gammaitoni et al, ibid, 2005). The phenomenon of “wind up” is considered to be a cause of alldynia, hyperpathia and hyperalgesia, as a consequence of action through various receptors e.g. NMDA, AMPA.

The ability of Ketamine to interact with NMDA receptors has led to its use for the treatment of neuropathic pain. It is suggested that Ketamine has an action on peripheral receptors in opioid and Na⁺ K⁺ channels. In a small study of five patients with neuropathic pain, Ketamine was shown to substantially reduce numerical pain scores (range 53-100%) with patient reports of significant pain relief accompanied by relaxation, altered temperature sensation and “decreased tension” at the site of application. Other more recent studies have confirmed these findings on the benefit of ketamine gel in chronic neuropathic pain.

The “power of synergy”, involving the combined use of Ketamine and Amitriptyline, is apparent in a study by Lynch et al (J. Pain, Oct 6, (10), 644-9, 2005). In this latter study, 28 individuals with moderate-severe but refractory pain from peripheral neuropathy received topical Amitriptyline 2% containing Ketamine 1%. There was no significant absorption of the drugs and regular use of the topical cream resulted in up to 12 months of perceived analgesic effects. At the termination of the study 89% of the
participants rated their level of satisfaction at 3 out of 5 or greater and 2 subjects were pain free.

This study combines two medications with multiple pharmacological effects that variably contributed to the successful outcome. Together these drugs exert the following actions blocking peripheral N-methyl-D-aspartate receptors, local anesthetic effects and interactions with adenosine systems. This and other studies suggest that synergy among drugs with different actions, can be used to amplify benefits of combination topical formulations that are produced by principles of compounding pharmacy.

Topical ketamine has been found useful in the management of neuropathic pain as a consequence of multiple causes including: complex regional pain syndrome CRPS, lumbar radiculopathy, post-surgical neuropathic pain, post herpetic neuralgia and idiopathic proctodynia.

It has been suggested that Ketamine works by a mechanism of central sensitization but its action is most likely due to local causes (Finch et al, Pain, Nov, 146, (1-2), 18-25, 2009). Ketamine even when applied at a concentration of 10% is not detectable in the systemic circulation and when applied to healthy limbs it has no effect on separate painful limbs. These findings provide support for the valuable local effects of ketamine which blocks N-methyl-D-aspartate receptors and Na⁺ and Ca⁺
channels. In addition, ketamine blocks tissue edema response of inflammation. Ketamine applied topically is ideal for delivering pain relief without significant side effects.

**CLONIDINE**

When administered in a topical format clonidine (creams or patches, Catapres TTS®) produces central and peripheral analgesic effects. It works by blocking the emerging pain signals at peripheral terminals (via alpha – 2 adrenoceptors).

This blocking circumstance avoids the central adverse effects of clonidine which when given orally can produce sedation, hypotension and rebound hypertension. While the effect of clonidine is generally analgesia, in the presence of peripheral nerve damage, hyperalgesia may occur or worsen. That said, topical clonidine has been applied for the control of hyperalgesia in complex regional pain syndromes (CRPS) (cited by Jorge et al, ibid, 2011).

The effects of clonidine in topical analgesia appears to be localized and it can be administered in a transdermal therapeutic system consisting of a multilayered film of the drug that is designed for slow and continuous release, over a seven day period (Jorge et al ibid, 2011).
SYNERGY IN PAIN CONTROL

According to the Webster Unabridged Dictionary: Synergy, [Gr. Synergia, joint work, from synergein, to work together.] is combined or co-operative action or force: specifically, in medicine, (a) the combined or correlated action of different organs or parts of the body, as in performing complex movements; (b) the combined or correlated action of two or more drugs.” Synergy is a very important concept in compounded topical pain control agents.

Who said that a ‘little bit’ of this combined with a “bit” of that provided a better treatment outcome than a lot of this or that alone? An acknowledgment of the therapeutic power of synergy may answer this “gobbledygook” question. The power of synergy is apparent when one considers the common therapeutic failure of single receptor drug interventions and the complex biochemistry or physiology of the “harmony of life” (Claude Bernard, circa 1860). All body functions and structure rely upon carefully coordinated cascades of biological or physiological events. These “cascades” cannot be completely responsive to a unitary intervention such as single drug, nutrient or botanical compound. These notions form the basis of the “completeness” of treatment approaches (holism) that must be present in the practice of Integrative Medicine. Welcome to the domains of “synergy”.

Synergy (synergism) may be best understood as the addition or reinforcing actions of separate agents that can
produce a greater overall effect than when such agents are used in a single manner (singly). While I focus on the notion of using therapeutic agents in a synergistic manner, the principles under discussion apply specifically to drug use or even the interactions of organs in the coordinated harmony of body functions.

Proposals about “the power of synergy” are neither novel nor new. They are well known to scholars of “classic” therapeutics. The power of synergy in therapeutics is “crystal clear”, but it is often forgotten. An extension of the concepts of synergy underlies the practice of Topical Pain Relief. Pain is a complex cascade of bio-physiological events that require multipronged (synergistic) interventions.

**CLINICAL APPLICATIONS**

Charles Argoff (Argoff CE, Current Pain and Headache Reports 7, 34-38, 2003, Current Science) has provided a valuable review of the clinical applications of topical analgesics in a variety of circumstances. Argoff (ibid, 2003) has coined the useful term “targeted peripheral analgesics” which he defines as “the use of analgesics whose mechanisms of action appears to be primarily through reducing pain transmission within the peripheral nervous system”.

The terms used by Argoff (ibid, 2003) are not redundant because in addition to differentiating the actions of targeted peripheral and systemic analgesics, Argoff (ibid, 2003) distinguishes topical and transdermal analgesics. For example, some transdermal preparations are used as a way
of delivering systemic concentrations of analgesics (eg. fentanyl patch), whereas targeted peripheral analgesics are used only for the accumulation of local concentrations of pain killing or anti-inflammatory drugs.

One clear advantage of the use of targeted peripheral analgesics is to avoid systemic side effects and potentially eliminate drug-drug interactions. Many patients have necessary polypharmacy and lack of drug interactions is sometimes important for the induction of optimal pain control without the development of adverse drug events (Gammaitoni AR and Davis MW, Ann. Pharmacother. 36, 236-240, 2002).

**CLINICAL CONCEPTS OF PAIN CONTROL**

Table 6 gives a list of common clinical pain disorders that are amenable to treatment by topical analgesics.

- Acute sports injuries.
- Allodynia
- Arthritis
- Chemotherapy-Induced Peripheral Neuropathy.
- Complex regional pain syndrome (CRPS).
- Diabetic Neuropathy.
- Epicondylitis (Tennis Elbow).
- Failed back syndrome.
- Fibromyalgia.
- Idiopathic Proctodynia.
- Musculoskeletal pain.
- Osteoarthritis.
- Lumbar radiculopathy.
- Phantom limb pain.
- Plantar fasciitis.
- Post herpetic neuralgia.
- Prior to minor surgery.
- Post-surgical pain.
- Trigeminal neuralgia.
- Tendonitis (Tennis elbow).
- Tendinosis.

**Legend to Table 6. Clinical circumstances in which compounded topical pain creams are advantageous for management.**

It is valuable to reiterate earlier concepts on the value of topical pain management which is generally applied to the following clinical circumstances:

- Neuropathic pain
- Soft tissue injuries
- Low back pain
- Myofascial pain
- Osteoarthritis pain
- Surgical pain
- Pain from inflamed tissue (e.g. RA)

The use of topical peripheral analgesics carries few risks of adverse effects and it is possible to avoid significant blood levels of the applied substances. Also, even with continuous use, there tends to be little systemic accumulation of the administered drug (Argoff, ibid, 2005). Local anesthetics, e.g. lignocaine, (lidocaine) 5% patches can be expected to benefit pain without delivering systemic levels of the drug that may alter cardiac function.
Compounded Products: An Overview

The compounding pharmacy can create synergistic combinations of several agents that can be effective in pain control by a mechanism of targeted topical delivery. Table 7 gives examples of several substances that can be used in variable combinations.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mode of action.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantadine</td>
<td>NMDA receptor antagonist</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Sympatholytic</td>
</tr>
<tr>
<td>Baclofen</td>
<td>GABA(p) agonist</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Alpha 2 agonist</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Glutamate antagonist</td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA receptor antagonist</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Anesthetic</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>L type calcium channel</td>
</tr>
<tr>
<td></td>
<td>Antagonist</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>NMDA receptor antagonist</td>
</tr>
<tr>
<td>Pentoxiphylline</td>
<td>TNF 1 alpha antagonist</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Anesthetics</td>
</tr>
</tbody>
</table>

Table 7. Medications that can be used for effective topical pain control. Some of these agents can be used together. In view of different modes of actions it is possible to use them in a synergistic manner. The prescribing physician should always check compatibility and drug interaction potential with the compounding pharmacist.

In Table 8 a number of combination creams and lotions used by NuMedCare LLC are shown in example format. Information in Table 8 displays only examples. Ingredients and dosages can vary depending on the Physicians requirements.
<table>
<thead>
<tr>
<th>Sports Injuries</th>
<th>Standard</th>
<th>Flurbiprofen 20%, Tramadol 5%, Clonidine 0.2%, Cyclobenzaprine 4%, Bupivacaine 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced</td>
<td>Standard</td>
<td>Flurbiprofen 20%, Tramadol 5%, Clonidine 0.2%, Cyclobenzaprine 4%, Bupivacaine 1%</td>
</tr>
<tr>
<td>Advanced with Neuropathic</td>
<td>Flurbiprofen 10%, Gabapentin 6%, Nifedipine 7%, Pentoxifylline 5%, Lidocaine 3%, Clonidine 0.2%</td>
<td></td>
</tr>
<tr>
<td>Chemo-induced Neuropathy RSD/CRPS General Neuropathy Post-Herpetic Neuralgia Diabetic Neuropathy</td>
<td>(Ketamine (C-III) 10% or Amantadine 15%), Gabapentin 6%, Tramadol 8%, Amitriptyline 4%, Cyclobenzaprine 4%, Clonidine 0.2%</td>
<td></td>
</tr>
<tr>
<td>Chemo Neuropathic</td>
<td>Flurbiprofen 20%, Baclofen 4%, Cyclobenzaprine 2%, Gabapentin 6%, Lidocaine 5%</td>
<td></td>
</tr>
<tr>
<td>Standard Neuropathic</td>
<td>Flurbiprofen 10%, Gabapentin 6%, Nifedipine 7%, Pentoxifylline 5%, Lidocaine 3%, Clonidine 0.2%</td>
<td></td>
</tr>
<tr>
<td>(Ketamine (C-III) 10% or Amantadine 15%), Gabapentin 6%, Nifedipine 7%, Pentoxifylline 5%, Lidocaine 3%, Clonidine 0.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic Neuropathic</td>
<td>(Ketamine (C-III) 10% or Amantadine 15%), Gabapentin 6%, Tramadol 8%, Amitriptyline 4%, Cyclobenzaprine 4%, Clonidine 0.2%</td>
<td></td>
</tr>
<tr>
<td>(Ketamine (C-III) 10% or Amantadine 15%), Gabapentin 6%, Nifedipine 7%, Pentoxifylline 5%, Lidocaine 3%, Clonidine 0.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>Standard with anti-muscle spasm</td>
<td>Flurbiprofen 20%, Tramadol 5%, Clonidine 0.2%, Cyclobenzaprine 4%, Bupivacaine 1%</td>
</tr>
<tr>
<td>Myofascial Pain Fibromyalgia Post Laminectomy Pain</td>
<td>Flurbiprofen 20%, Baclofen 4%, Cyclobenzaprine 2%, Gabapentin 6%, Lidocaine 5%</td>
<td></td>
</tr>
<tr>
<td>Advanced Formulation</td>
<td>(Ketamine (C-III) 10% or Amantadine 15%), Gabapentin 6%, Tramadol 8%, Amitriptyline 4%, Cyclobenzaprine 4%, Clonidine 0.2%</td>
<td></td>
</tr>
<tr>
<td>Flurbiprofen 20%, Baclofen 4%, Cyclobenzaprine 2%, Gabapentin 6%, Lidocaine 5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Numedcare formulations.
TOWARDS THE APPLICATION OF TOPICAL AGENTS

Most custom compounding pharmacies focus attention on the development of combination topical agents. Lotions or creams or gels are applied to clean dry areas of the skin and it is important that the person administering the topical wash their hands both before and after applications. It is important not to touch the eyes, mouth or other sensitive areas of the body especially if capsaicin is used. Intense burning and itching with skin rashes can occur as a consequence of capsaicin applied to sensitive areas of the integument. It is important to educate the patient in the correct application of topical analgesics otherwise compliance and adherence with medication will not occur.

Under no circumstances whatsoever should a topical analgesic be applied to an open wound. Most compounded creams (or lotions or emulsions) come with a way of measuring applications e.g. by a syringe or by the use of a pump device that will allow metered dispensation. For example, there are pump applicators that will deliver one gram of cream for every manual pump. For optimal outcome the preparation should be rubbed into the skin, in a thorough manner, for one to two minutes. Optimal application will have occurred when the sensation of friction is felt after rubbing. It is important to check with
your physician on the best site of application for each specific type of pain.

**Dermatomal Directions**

A dermatome is an area of skin that is mainly supplied by a single spinal nerve. These nerves relay pain from the skin and adjacent tissues directly to the brain. Figure 1 shows examples of dermatomes.

It is important to cover the area of pain and the area innervated in each dermatome in cases of referred pain. This will result in maximum effects, but pain can cross over a dermatome segment.

For example, inspecting figure 1 shows the extent of dermatome e.g. L2 and L3. These dermatomes are located on the inner and front aspect of each thigh and covering much of the area of the dermatome is ideal. However, one can see that the dermatome L2 and L3 is close to the scrotum (or vagina) in its upper reaches and it is important to avoid these sensitive areas of skin. Equally the trigeminal nerve area of innervations is close to the eye and mouth and these areas are to be avoided. The prescribing physician should take care to explain optimal site of administration of topical pain control agents, preferably by using a dermatome chart.
Fig 1  Examples of dermatomes
Payment for Compounded Pain Medications.

In many cases, medical insurance will pay for the cost of the medication but the amounts of co-payments required vary from one prescription plan to the other. The staff of NuMedCare, LLC is dedicated to assisting you and your physician to obtain reimbursement. Sometimes insurance companies hold the opinion that all standard forms of therapy e.g. oral NSAID should be used in place of topical NSAID, but many people have stubborn pain that has not responded to standard treatments and decisions by insurance companies can be appealed.
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