



Natural Therapies & Prescriptions That Enhance Life.™

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## Customized Therapies for Chronic and Neuropathic Pain

Chronic pain, whether arising from viscera, bone, or any other tissue or structure, is often the result of a variety of pain mechanisms, and therefore there is no simple formula available to manage chronic complex pain states. Trials of novel medications and adjuvants may be clinically appropriate for refractory pain. Therapies for cutaneous allodynia/hyperalgesia include topical NSAIDs, gabapentin, carbamazepine, and mexiletine. According to the patient's clinical condition and pain mechanism, practitioners may want to consider an empirical trial of one or more of the emergent topical therapies. Topical clonidine may be considered for sympathetically maintained pain. A major rationale for introducing adjuvants is to better balance efficacy and adverse effects.<sup>1</sup>

The following scenarios should prompt the use of adjuvant analgesics in clinical practice:

- The toxic limit of a primary analgesic has been reached.
- The therapeutic benefit of a primary analgesic has plateaued, eg, treatment has reached its true efficacy limit or pharmacodynamic tolerance has developed.
- The primary analgesic is contraindicated, eg, substance abuse, aberrant behavior, organ failure, allergy, etc.
- Symptoms demand broader coverage.

Existing commercially-available treatments may have limited effectiveness and produce relatively frequent adverse effects. Patients often convey that different medications will impart distinct analgesic benefits. Presence of side effects such as insomnia, depression, anxiety, and fatigue can diminish the patient's quality of life, and justify a change to a customized therapy.

Topical therapies and combination preparations may have many advantages over systemically administered analgesics, including the ability to provide effective analgesia with reduced systemic drug levels, a factor particularly beneficial to the elderly. Fewer side effects coupled with convenient and painless administration results in improved patient acceptance and compliance, and ease of use may reduce overall treatment costs. Because they are applied directly to the target site, topical administration can provide therapeutic levels in the tissues under the area of application, with minimal serum levels. Lower systemic drug levels potentially lower the risk of organ toxicity. In addition, first pass hepatic metabolism and other variables associated with the gastrointestinal tract are avoided. Topical therapy is a viable solution which often avoids the need for injections when oral dosing is not feasible because the patient is nauseated or unconscious.

There is a growing body of evidence on the efficacy and safety of topical agents in a variety of pain disorders, including the most prevalent neuropathic pain conditions. The molecular basis for the usage of peripheral analgesics in neuropathic pain and the available clinical trial evidence for a wide variety of topical agents are reviewed in an excellent article<sup>2</sup> by Oscar A. de Leon-Casasola, MD, Department of Anesthesiology and Critical Care Medicine, Roswell Park Cancer Institute, School of Medicine and Biomedical Studies, State University of New York at Buffalo. Agents "that profoundly reduce neurotransmitter release from nociceptors generating ectopic pulses, such as topical local anesthetics and anticonvulsants, may relieve neuropathic pain. Likewise, increased peripheral sensitivity mediated through the release of prostaglandin E2 and substance P at the peripheral level results in spontaneous discharges that may be inhibited by topical drugs, such as **nonsteroidal anti-inflammatory drugs (NSAIDs)**... Additionally, topical substance P inhibitors and **ketamine** can reduce the effects of

substance P, while sympathetic afferent activation can be modified by the topical administration of a beta-blocker and **clonidine**. Topical antihistamine may decrease the release of histamine and serotonin, thereby limiting the inflammatory process and hindering vasodilation. Topical **opioids** can target the opioid receptors present on nociceptive fibers and mast cells. Binding of opioid receptors can inhibit the release of the calcitonin gene-related peptide (CGRP) and substance P from nerves, thereby preventing the feed-forward mechanism of pain that typically results in sensitization at the site of injury (primary hyperalgesia).” **Pentoxifylline** has effectively provided relief for some neuropathic conditions when applied topically. “Topical tricyclic antidepressants, such as **doxepin** and **amitriptyline**, have demonstrated efficacy in a number of neuropathic pain states.”

Neuropathic pain is often resistant to opioids, so other medication classes - such as **tricyclic antidepressants, anticonvulsants, and local anesthetics** - are often used. Central sensitization, or pain “wind-up”, may perpetuate chronic neuropathic pain even when ongoing peripheral sensory input is absent. Wind-up is thought to cause allodynia, hyperalgesia, and hyperpathia. Receptors such as NMDA, AMPA, and M-glu have recently been identified for their role in central sensitization and antagonists of these receptors have produced pain relief.<sup>3</sup>

The analgesic effect of **tricyclic antidepressants** 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 was described in a randomized, double-blind, placebo-controlled study of 200 adult patients. Fewer side effects were reported compared with oral administration.<sup>4</sup>

**Topical NSAIDs** are widely used to treat acute musculoskeletal conditions due to their potential to provide pain relief without associated systemic adverse events. Massey et al of the University of Oxford, UK, reviewed the medical databases for randomized, double-blind, active or placebo-controlled trials in which treatments were administered to adult patients with acute pain resulting from strains, sprains or sports or overuse-type injuries (twisted ankle, for instance). Forty-seven studies with 3455 participants were included in a meta-analysis. Clinical success was defined as 50% pain relief. For treatment periods of 6 to 14 days, topical **diclofenac, ibuprofen, ketoprofen, and piroxicam** were of similar efficacy. The analysis concluded: “Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs...”<sup>5</sup>

Researchers at the University of Connecticut School of Medicine examined the effect of a topical cream consisting of cetylated fatty acids (**cetyl myristoleate**) on functional performance in patients diagnosed with osteoarthritis (OA) of one or both knees. Forty patients were randomly assigned to receive topical cetylated fatty acid (CFA) or placebo and were evaluated at baseline and after treatment. Significant improvements were noted for knee range of motion (ROM), ability to ascend/descend stairs, ability to rise from sitting, walk and sit down, and unilateral balance.<sup>6</sup>

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**Sample prescriptions:** These are examples of medications that have been prescribed; however, medications can be added to or removed from the combination, and in most cases, the strength/dose/frequency can be changed.

#### Sample Prescription

##### Compounded Medication

Ketoprofen 5%, Diclofenac 5%, Cetyl Myristoleate 2%, DMSO 10% Cream  
Disp the following days supply (circle): 15 Days 30 Days 90 Days  
Sig: Apply a pea-sized amount (1 gram) to the affected area 3 to 4 times each day.

#### Sample Prescription

##### Compounded Medication

Speed Gel (Guaifenesin 10%, Dextromethorphan 10%)  
Disp the following days supply (circle): 15 Days 30 Days 90 Days  
Sig: Apply 4 to 6 drops (0.5 ml) to the affected area four times daily and rub in.

#### Sample Prescription

##### Compounded Medication

Ketamine\* 10%, Clonidine 0.2%, Gabapentin 6%, Imipramine 3%, Mefenamic Acid 3%, Lidocaine 2% Cream  
Disp the following days supply (circle): 15 Days 30 Days  
Sig: Apply a pea-sized amount (1 gram) to the affected area 3 to 4 times each day.  
\*Note: Ketamine is a C-III drug. Amantadine 8% can be substituted if desired.

#### References:

- <sup>1</sup> Med Clin North Am. 2007 Jan;91(1):113-24.
- <sup>2</sup> J Pain Symptom Manage. 2007 Mar; 33(3):356-64.
- <sup>3</sup> Reg Anesth Pain Med 2003 Jul-Aug;28(4):289-93
- <sup>4</sup> Pain Clin 2000;12(1):47-50.
- <sup>5</sup> Rheumatology (Oxford) 38(6):564-7
- <sup>6</sup> J Rheumatol. 2004 Apr;31(4):767-74.