Palliative Care
Customized Medications for Pain Management, Symptom Control, & Wound Care

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**This booklet contains numerous ideas to stimulate discussions regarding palliative care. We welcome the opportunity to work together with other health care professionals, patients and their families, caregivers, and hospice team members, to customize medications to meet each patient’s specific needs.**

*Your questions are always welcome!*

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**INTRODUCTION**

The World Health Organization has defined palliative care as: "the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is the achievement of the best possible quality of life for patients and their families.

Palliative care:

- Affirms life and regards dying as a normal process
- Neither hastens nor postpones death
- Provides relief from pain and other distressing symptoms
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement.

Radiotherapy, chemotherapy and surgery have a place in palliative care, provided that the symptomatic benefits of treatment clearly outweigh the disadvantages. Investigative procedures are kept to a minimum."

**Customized Medications Offer Alternatives & Advantages for Palliative Care**

- **Change in Route of Administration** - A medication may only be commercially available as an oral or injectable product, but we can often simplify home administration for someone who is NPO by compounding an alternate dosage form, such as a transdermal gel.
- **Combination Preparations** - It is often possible to combine several compatible drugs into a single dosage form, such as a capsule, troche, transdermal gel, or suppository. This can simplify the medication administration schedule, and improve compliance.
- **Discontinued or “Unavailable” Medications** - When a commercial medication is out of stock, temporarily unavailable, or discontinued (for reasons such as declining use or lack of financial incentive for a manufacturer), we can utilize pharmaceutical grade chemicals to prepare the needed medication in the best strength and dosage form for a particular patient.
- **Flavoring** - Often, we find that hospice patients are unable to tolerate sweetness, but would prefer a medication with a bitter flavor - like coffee, for example. We can flavor each medication to please the individual’s palate, and eliminate aftertastes.
- **Elimination of Problem-Causing Excipients** - Medications can be formulated free of dyes, sugar, lactose, alcohol, and preservatives.
- **Dosage Modification** - We can compound a medication that contains the most appropriate strength of medication to provide therapeutic benefit but minimize the risk of adverse effects. This can be particularly beneficial for a patient with kidney failure or liver disease.
- **Change in Dosage Form** - Medications can be altered to meet each patient’s needs. Suppose it is most desirable to continue oral administration, but the patient has difficulty swallowing a tablet or capsule. With consideration of the medication’s solubility and stability, we can compound an alternate dosage form. A liquid medication such as a flavored solution, suspension, or concentrate can simplify titration when doses need to be gradually increased to control pain or other symptoms. Freezerpops, lozenges, or lollipops are particularly useful when it is desirable to prolong medication contact with the oral mucosa, such as when a patient has “thrush”.

**Transdermal Therapy**

Absorption through the skin or oral or rectal mucosa is currently regarded as an important alternative to traditional methods of drug delivery. This can be accomplished in many ways; the optimal delivery system depends upon the specific needs of each
patient. Our compounding pharmacy can formulate a medication into a cosmetically-appealing cream or gel for topical or transdermal administration. The medication and the desired rate and extent of absorption are considered when selecting the most appropriate base.

- **Pluronic Lecithin Organogels (PLO gels)** have many properties which make them desirable vehicles. Studies suggest that there are no great restrictions on the chemical structure of the drug that can be incorporated into a properly compounded PLO gel.
- **Anhydrous Gel Base** is useful for administering medications used to treat neuropathic pain, and is particularly beneficial when a drug is unstable in an aqueous vehicle.

**Advantages of Transdermal, Sublingual, Buccal, and Rectal Drug Administration**

Various dosage forms permit medications to be absorbed without passing through the gastrointestinal system. Although the parenteral route is a traditional alternative to oral administration, transdermal and mucosal absorption offer many advantages:

- When medication is absorbed directly into the bloodstream without first entering the gastrointestinal system, first-pass liver metabolism is bypassed, and therefore a smaller amount of active ingredient may be required for therapeutic effect. This can be especially important in patients with hepatic disease, where changing liver function often necessitates frequent dosage changes.
- Direct application and absorption at the target site can mean higher levels of drug in local tissues and lower blood levels.
- Side effects such as GI irritation can be eliminated.
- Various types of physical drug interactions may be avoided when medications are administered by different routes.
- Numerous medications can easily be administered to patients who are NPO or nauseated.
- Discomfort, anxiety, and the need for caregiver training associated with injectable therapies can often be avoided.
- Most of these dosage forms provide a rapid onset of action, are cost effective, and convenient.

**Sublingual/Buccal/Rectal dosage forms include:**

- Troches and Mini-troches
- Sublingual drops
- Tablet triturates
- Rapid Dissolve Tablets
- Enemas
- Suppositories

**More Dosage Forms...**

- **Lip Balms and Applicator Sticks** can be used to apply medication directly to the affected site.
- **Metered Nasal or Sublingual Sprays** administer a measured dose of medication.
- **Non-aerosol Topical Sprays** are useful for administering medications such as analgesics, anesthetics, or corticosteroids.
- **Suppositories and Enemas** can provide a rapid effect. Many drugs are well-absorbed when administered rectally or vaginally. The unique “rectal rocket” can facilitate simultaneous internal and external administration of medications to treat hemorrhoids and other conditions.
- **Irrigations** can be prepared to contain ingredients of the prescriber’s choice.
- **Sustained Release formulations** can prolong effect and reduce the incidence of side effects caused when medications are absorbed too rapidly.
- **Inhalation solutions** can be compounded to contain multiple ingredients and concentrated to ease therapy.

**PAIN MANAGEMENT**

Effective pain management must be individualized, and is best achieved by a team approach involving the patient, his/her family, and health care providers. Successful long-term pain management requires rapid, flexible, and expert responses to the changing needs of the patient. As soon as pain begins, it is important that the patient meets with a knowledgeable, experienced practitioner. Pain control is crucial because even when the underlying disease process is stable, uncontrolled pain prevents patients from working productively, enjoying recreation, or taking pleasure in their usual role in the family and society. Patients and their loved
ones should never allow pain to continue due to concerns about “being a complainer,” medication-related side effects, or fear of addiction or loss of control subsequent to the use of pain medications.

Kathleen Foley, M.D., professor and neurologist at Memorial Sloan-Kettering Cancer Center states: “Pain can be managed. Physicians must determine the severity and frequency of their patients’ pain experience to prescribe the most appropriate and effective pain management regimen.” The goal of the initial assessment of pain is to characterize the pain by location, intensity, and aggravating and relieving factors. Frequently, a 10-point Numeric Pain Intensity Scale or Visual Analog Scale is used to facilitate communication between the patient and health care professionals, and to monitor the adequacy of therapy. Regular follow-up should occur and routine recording of pain intensity along with other vital signs is recommended.

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

“Combination therapy is frequently the only effective approach for managing the complex array of chemical mediators and other contributors to the individual pain experience. As topical formulations are developed, they provide hope for more effective drug combinations, with fewer systemic adverse drug effects and drug-drug interactions.”

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

**Opioids**

Preclinical studies suggest opioids may produce benefits when applied topically to somatic sites. In a clinical setting, the analgesic effect of opioids has also been reported when applied to painful ulcers and skin lesions. Systemic use of opioids may cause adverse effects; therefore, the topical application of opioids, with potentially fewer systemic effects, is an alternative that physicians may wish to consider. The type of base used is critical to the success of this therapy, and can significantly affect the extent of transdermal absorption. The low pH of necrotic wounds limits the use of local anesthetic agents for treating severe pain from skin and mucous membrane disease. Morphine (pKa 9.8) is very stable at low tissue pH and therefore may be suitable for the treatment of local wound pain.

**Opioid Responsive vs. Opioid Resistant Pain**

Maureen Carling, R.N., developed an algorithm to demonstrate how the patient’s description and duration of pain can determine the type of pain that is being experienced and if that pain will be responsive to opioids, thereby helping a practitioner to initiate the most appropriate therapy.

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Responsiveness to Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>visceral</td>
<td>usually responsive</td>
</tr>
<tr>
<td>soft tissue</td>
<td>usually responsive</td>
</tr>
<tr>
<td>bone</td>
<td>semi-responsive</td>
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<tr>
<td>nerve compression</td>
<td>semi-responsive</td>
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<tr>
<td>pleuritic</td>
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<td>colic</td>
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<tr>
<td>muscle spasm</td>
<td>resistant</td>
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<td>nerve destructive or deafferentation</td>
<td>resistant</td>
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**NMDA receptor antagonists**

NMDA receptor antagonists such as dextromethorphan and ketamine can block pain transmission in dorsal horn spinal neurons and reduce noiception. Elliot et al. of Cornell University Medical College showed that the NMDA receptor antagonist dextromethorphan can modulate morphine-mediated analgesic (opioid) tolerance in pain patients. The use of dextromethorphan can therefore reduce the amount of opioid that is needed to control pain. Dextromethorphan is a common ingredient in cough and cold preparations; however, for this purpose, it would be problematic to get an adequate dose of dextromethorphan by using these commercially-available products. Our compounding pharmacy can prepare a formulation containing the most appropriate dose of dextromethorphan.

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

Here are examples of customized pain therapies that have been compounded to meet specific patient needs:

**Hydrocodone without acetaminophen**

Hydrocodone is often an effective analgesic, but commercially available hydrocodone preparations have the drawback of containing acetaminophen. Often, to receive adequate doses of hydrocodone, the patient would have to consume potentially toxic doses of acetaminophen. To avoid the risk of liver damage, the physician can prescribe a compounded preparation containing the most appropriate dose of hydrocodone to control the individual’s pain, but with less or no acetaminophen.

**Intranasal ketamine for the treatment of breakthrough pain**

Noting that few placebo-controlled trials have investigated the treatment of breakthrough pain (BTP) in patients with chronic pain, Carr et al. of the Department of Anesthesia, Tufts-New England Medical Center, evaluated the efficacy and safety of intranasal ketamine for BTP in a randomized, double-blind, placebo-controlled, crossover trial. Twenty patients with chronic pain and at least two spontaneous BTP episodes daily self-administered up to five doses of intranasal ketamine (dose = 0.1 ml of 10% aqueous solution of ketamine with 0.002% benzalkonium chloride in a metered nasal spray pump) or placebo at the onset of a spontaneous BTP episode (pain intensity > or =5 on a 0-10 scale). Patients reported rapid, safe and effective relief for breakthrough pain. Intranasal ketamine was well tolerated with no serious adverse events. “Although BTP is typically treated with opioids, patients chronically receiving opioids may display progressive intolerance, and so the use of non-opioid agents to treat BTP on a long term basis is an attractive option… The safety and efficacy of ketamine as an anesthetic and analgesic agent is well documented… and low (analgesic) doses of ketamine have minimal impact upon cardiovascular or respiratory function.”

**Topical Anesthetics: Customized Dosages, Lollipops, Sprays, and Combination Preparations**

Topical anesthesia is an essential need, and a form of therapy that aptly demonstrates how compounding pharmacists can work together with physicians to provide the most appropriate therapy for each patient. Commercial products are limited, and sometimes unavailable.

Oral viscous lidocaine is useful for the treatment of symptoms induced by oral inflamed mucosa, such as radiation- or chemotherapy-induced mucositis. However, toxic reactions associated with accidental overdose have been reported in pediatric cases. Also, Yamashita et al. reported a case of lidocaine toxicity in a 22-year-old man following frequent viscous lidocaine use. However, toxic reactions associated with accidental overdose have been reported in pediatric patients with cancer and in those dying of non-malignant diseases such as chronic obstructive airway disease.”

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Topical anesthetic sprays and creams can also be compounded to contain the most appropriate combination of anesthetics, for use on wounds or prior to dressing changes.

“Good pain management is one of the central pillars of good palliative care. Pain is a prevalent and feared symptom – both in patients with cancer and in those dying of non-malignant diseases such as chronic obstructive airway disease.” Uncontrolled pain can cause physical as well as psychological distress. Fortunately, pain can be controlled in most patients with individualized therapy. Knowledge about pain management is paramount in the comprehensive treatment of patients with terminal illness.

Pain syndromes can occur as several different types of pain and as a consequence may be treated according to the nature of the pain. Cancer pain may be classified as nociceptive pain, which can then be further grouped as bone pain and visceral pain. Nociceptors can be activated by a number of chemicals liberated by tissue damage and/or inflammation. Tissue injury can trigger the local release of algogenic substances; prostaglandins, bradykinin, adenosine, cytokines, and others. Neurologic pain is generated ectopically by abnormal peripheral nerve fibers involved with pain transmission or abnormal foci in the central nervous syndrome, which is then responsible for neuropathic pain. Both types of pain can be present at the same time in cancer patients, and it is often difficult to distinguish nociceptive from neuropathic pain.

“Patients experiencing difficult cancer pain syndromes require treatment plans tailored to their individual problems. As the patient becomes less functional, a more aggressive intervention based on titration and combination therapy is necessary. The treating physician needs to balance efficacy, safety, and tolerability of several drugs, often used on an ‘off label’ basis.”
Neuropathic Pain

Patients may present with allodynia, hyperalgesia, numbness, tingling, weakness, burning, abnormal sensations, or radiation of pain. Clinicians should evaluate neuropathic pain as it may signal the progression of disease or an evolving neurologic emergency.

Pharmacologic Strategies to Relieve Neuropathic Pain

**Anti-Epileptic Drugs**: These are the first line of therapy for neuropathic pain due to their ability to decrease neuronal excitability.

**Antidepressants**: Tricyclic antidepressants (TCAs; such as amitriptyline, nortriptyline, and desipramine) have established efficacy in treatment of neuropathic pain. SSRIs such as paroxetine and fluoxetine have not proven to be effective analgesics.

**NMDA Receptor Antagonists**: NMDA (N-methyl-D-aspartate) receptor stimulation is responsible for most cases of neuropathic pain, and the emergence of intractable pain may notably be due to the activation of NMDA receptors located in the central nervous system. NMDA antagonists such as ketamine are often used, followed by adjuvants such as sodium channel blockers, alpha-2 agonists, or substance P blockers, resulting in significantly improved pain control. Ketamine has shown a particular role as an adjuvant to opioids in cancer neuropathic pain. Because NMDA receptors have been found in local tissues, compounded topical preparations have shown positive outcomes in the management of chronic pain. NMDA antagonists also may prevent or counteract opioid tolerance.

**Anti-Inflammatory Drugs**: Corticosteroids are prescribed to relieve severe inflammatory pain due to cancer infiltration of the brachial or lumbosacral plexus, roots, and trunks, and work by decompressing nervous structures. Non-steroidal anti-inflammatory drugs (NSAIDs) have been used to treat mild-to-moderate bone pain, but have little value in the treatment of neuropathic pain.

**Opioids**: Opioids were once considered ineffective for neurologic pain; however, efficacy has been demonstrated in recent clinical trials. Opioid receptors are located throughout the body but in high concentrations in the central nervous system and in the primary dorsal horn.

Methadone has an intrinsic NMDA antagonist effect, which may add adjuvant analgesia in neuropathic pain. Methadone is a mu opioid, and offers an alternative when more frequently used opioids fail to provide adequate analgesia in patients with complex cancer pain syndromes. “Methadone has many positive attributes: it lacks neuroactive metabolites, its clearance is independent of renal function, it has excellent oral bioavailability, and the cost is less than many other opioid analgesics.”

Meperidine use is NOT recommended “because the toxic metabolites, specifically normeperidine, accumulate with prolonged use or in the higher dose range, even in patients without renal or hepatic insufficiency. This can result in central nervous system toxicity, including the possibility of dysphoria, seizures and death.” Mixed opioid agonist-antagonists, such as pentazocine and dezocine, are not recommended due to potential for CNS toxicity and psychomimetic and ceiling effects, and because they can precipitate a noxious withdrawal event in opioid-tolerant patients.

**Bone Pain**

Bone metastasis is the most common cause of pain in cancer patients.

Pharmacologic Intervention

**Anti-Inflammatory Drugs**: As noted previously, corticosteroids are prescribed to relieve severe inflammatory pain due to cancer infiltration of the brachial or lumbosacral plexus, roots, and trunks, and work by decompressing nervous structures. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of mild-to-moderate bone pain.

Laura Shaiova, MD, of the Department of Neurology, Division of Pain and Palliative Care, Memorial Sloan-Kettering Cancer Center, New York, recommends use of the following algorithm for treatment of moderate-to-severe bone pain:

- Opioid/opioid rotation + IV bisphosphonate
- ± Corticosteroids
- ± Gabapentinoids, antidepressants, mexiletine, NMDA antagonists
Visceral Pain
Visceral pain is commonly caused by cancer infiltration causing compression or distention of an organ or inflammation of mucosa.

Therapy for Visceral Pain
“Treatment includes a wide range of modalities from opioid analgesics, steroids, anticholinergics, octreotide (which relieves bowel obstructive symptoms by decreasing gastric secretions), and adjuvant analgesics given for the neuropathic component, to neuroaxial analgesia via intrathecal pumps or tunneled intraspinal catheter systems, neurolytic blockades, neuroablative procedures, and palliative surgery.”

Conclusion
Management of severe neuropathic, bone, and visceral cancer pain is often difficult and challenging. Expertise is required to titrate doses appropriately, while assessing the pain and recognizing and managing drug-related side effects. As soon as pain begins, it is important that a patient talks to a health care provider who is knowledgeable in pain management. Besides mitigating suffering, pain control is crucial because, even when the underlying disease process is stable, uncontrolled pain prevents patients from working productively, enjoying recreation, or taking pleasure in their usual role in the family and society.

Medication schedules should meet the needs of the patient and caregiver. “Generally, unless the pain is very acute and unpredictable, around-the-clock medication should be used to prevent the pain from recurring, rather than ‘catching-up’ or ‘chasing after’ pain control…[A] continuous schedule of analgesic delivery will generally better control the pain compared with intermittent dosing. Sustained-release medication can be very helpful in decreasing the frequency of medications required, facilitating sleep at night. Once the daily opioid requirement is known and stable for a couple of days, the transition can be made from the immediate- to the sustained-release opioid. With the goal of avoiding ‘catch-up’, doses for breakthrough pain should be [readily] available…”

When patients are unable to take oral medications but wish to avoid parenteral therapy, transdermal, sublingual or oral transmucosal, or rectal (may be contraindicated in neutropenic and/or thrombocytopenic patients) dosage forms are often prescribed. When a medication is not commercially available in the needed dosage form, compounding pharmacists can work together with the physician to determine the most appropriate formulation and dose.

1 Australian Family Physician, October 2006; 35(10):762-765

Our compounding specialists offer many unique options for pain management. Regardless of origin, and whether the pain is acute or chronic, our efforts are directed at meeting the specific needs of each patient. We work together with patient and physician to reach treatment goals. Please call our compounding pharmacy regarding individualized pain therapy to meet your patients’ specific needs.

Trigger Points and Dermatomes
The International Association for the Study of Pain defines a dermatome as “the sensory segmental supply to the skin and subcutaneous tissue.” A dermatome is the area of skin supplied by a spinal nerve by way of its dorsal root. Often, pain does not arise at the point or organ where pain is perceived. Rather, pain may originate at the spinal level, and follow the path along the entire dermatome to the trigger point. When touching a pain trigger point lightly even with a cotton swab, pain is elicited that feels as if it arises deep within the terminal area of the nerve - for example, the leg or abdomen. Dermatome maps and trigger point application may be useful when a practitioner chooses to administer medications transdermally. A properly-formulated cream or gel can be applied as a thin film over the sites of pain, then the dermatomes can be traced around to the back where the gel can also be applied at spinal level, with the sites marked for ease of future application.

Topical Medications for Chronic Pain Patients
Stephen P. Hersh, M.D., F.A.P.A.  Director, Medical Illness Counseling Center  
Clinical Professor, G.W.U. School of Medicine • Member, American Pain Society

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

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

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

Excellent Outcomes using Medications in Topical Gel for Neuropathic Pain
Maureen A. Carling, R.N.

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

Assessment revealed pain in the posterior-lateral aspect of both sides of the chest wall, with pain shooting down into the pelvis and inward to the spine; pain in the left sacroiliac joint and pain in both great toes, which extended up into the arches. His pain was severe and uncontrolled.

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

Assessment revealed pain, which was described variously as: “Intermittent ache; occasional burning, shooting, stabbing; worse on movement.” This suggests neuropathic and bone pain.

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

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

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

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

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

Transdermal Lidocaine & Ketoprofen for Pain Management
Babak Arvanaghi, M.D., Pain Management Clinic, Suburban Hospital, Bethesda, MD

“I have used Lidocaine 10%/Ketoprofen 20% in many pain syndromes including diabetic polyneuropathy, post-herpetic neuralgia, and osteoarthritis of the hands, toes, knees, and shoulder. Conventional therapies include the use of NSAIDs with their significant side effect profile (especially in the elderly) and trials of neuropathic medications for the neuropathic pain syndromes, again with their own side effects. The lidocaine/ketoprofen preparation has been used in dozens of patients. Side effects have been essentially non-existent, and a significant number of patients have had good results to the point that a trial of topical medication has become one of my standard approaches in the treatment of patients suffering from chronic pain.”

Note:
The preparation that Dr. Arvanaghi uses is a lotion titrated to proper pH for transdermal absorption. It is typically dispensed in a quantity of 30 grams, and is applied three to four times daily to the affected area. The strength of the lotion can be titrated to achieve the desired response in each patient. Depending upon the symptomatology, a number of other medications may be included in the preparation, including cyclobenzaprine (for muscle relaxant) or guaifenesin (for spasms). The lotion is well-absorbed through the skin, leaving no greasy film or residue. This preparation can not simply be compounded by placing the required ingredients in a base such as white petrolatum or Unibase™. This transdermal lotion contains a number of ingredients not found in most pharmacies, which together with significant physical agitation, increases micelle formation to optimize the therapeutic benefit. (Micelles are spaghetti-like structures that produce a macroscopic viscosity, increasing the transdermal penetration.) Appropriate mixing requires the use of an ointment mill or other homogenization process which we use in our compounding laboratory.

Relief of Nerve Pain with Compounded Gabapentin Cream
Bruce Zagnit, R.Ph., Bethesda, Maryland

Case One: A hospice patient had severe post-herpetic (shingles) nerve pain on his back and sides. He was on Oxycontin® and Percocet® which adequately controlled his cancer pain. However, it did not relieve his nerve pain which he had endured for months. He was prescribed Gabapentin 6%, Clonidine 0.2%, and Lidocaine 10% cream, to be applied to the affected areas three times daily. He stated he had immediate relief on the first day of application.

Case Two: A hospice patient with tumor involvement of the brachial plexus suffered severe stabbing, burning pain secondary to nerve compression in her arm. On a 0-10 scale, she rated her pain as 10. Her pain was so severe that she asked if her arm could be amputated. She was receiving Duragesic® 500mcg (five 100mcg patches applied every three days) and Roxanol® 50 mg PRN for breakthrough pain. At times, the opioids would take the edge off the pain, but never afforded substantial relief. After consultation with the compounding pharmacist, a cream containing Gabapentin 10%, Clonidine 0.2%, and Lidocaine 10% was prescribed, 1cc to be applied three times daily to her affected shoulder and axilla. After the second application, her pain rating was decreased to 2-3. After the fourth application, she had no more nerve pain in her arm.

Transdermal Clonidine for Pain

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

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

Gabapentin and Clonidine Transdermal for Pain
Carole Knubel, BBN, CRNH

A 79 y.o. woman was admitted to hospice home care with peripheral vascular disease and a chief complaint of extreme pain in her toes. She had a BKA of her right leg and refused to have the other leg amputated. The primary goal of the patient, MD and hospice was pain control. At the time of admission, she was on IV Fentanyl® with a CADD pump and converted to Oxycontin® in ever increasing doses to 180mg q 12 hours with Oxy IR® 60 mg PRN breakthrough pain which she took 3-4 times/day. Patient adamantly refused introduction of any other pain medication in spite of many efforts to help her understand that her nerve pain could not be managed solely by narcotics. Her pain increased as her condition worsened and she reluctantly agreed to have new meds introduced. After consulting with her physician and compounding pharmacist, she was started on dextromethorphan 60mg capsules orally twice daily to reduce tolerance to the analgesic effect of the narcotics. This was increased to QID over a three month period. She then agreed to take nortriptyline which was titrated from 10mg to 100mg over a two week period. She experienced some pain relief but continued to take Oxy IR 60 mg BID - QID for breakthrough pain. At this point, a transdermal gel containing gabapentin 6% and clonidine 0.2% was started (1 ml was applied topically to her great toe and adjacent area TID). The response has been amazing. After a few days, she no longer needed her breakthrough pain med and the Oxycontin has been reduced to 40mg q 12 hours. She maintains the gel is a miracle. She and I are both grateful to our compounding pharmacist for the help in managing this difficult pain management problem.
Transdermal Gels for Neuropathic Pain Management - a case study
Submitted by Dana Reed-Kane, Pharm.D., FIACP

Hx: 70 y.o. male presented with neuropathic pain after herpes zoster ("shingles"). His physician prescribed Amitriptyline 2% / Baclofen 2% / Ketoprofen 20% / Lidocaine 10% / Ketamine 5% in a PLO gel, with instructions to apply a small amount to the affected area four times daily and rub in well.

S: Patient applies this "cream" around the navel and waist area. He is now quite comfortable, stating "I think the pain is finally going to go away." He now rates his pain as "not even a 1" on a scale of 1 to 10, noting it is "more like an awareness of tingling, but not painful." He continues to take oral Neurontin® 300 mg TID, and occasionally Aleve®.

O: NKA

A: Patient’s pain is well controlled with the transdermal formulation and oral Neurontin®.

P: The patient’s plans are to continue with his current therapy.

Topical Opioids in Palliative Care
This case report was excerpted from an article by Krajnik et al published in Pain. 1999 Mar;80(1-2):121-5.

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

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

Hydrocodone without Acetaminophen
by Alan Spanos, M.D., M.A.

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

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

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

Dr. Spanos is a pain specialist, and director of Blue Ridge Clinical Associates, Raleigh, NC. He spoke at the PCCA International Seminar for Compounding Pharmacists in Houston, Texas on “Advanced Pain Treatment: The Pharmacist’s Role.”
**Ibuprofen 500 mg. Rectal Suppositories for Bone Pain**  
*C. Spencer, M.D., Oncologist, California*

**Patient/Hx:** 25 y.o. Caucasian diagnosed with osteosarcoma L5, under hospice treatment with severe pain and nausea. S/P three cancer-related surgeries. Patient rated pain at 8 (on a scale of 1-10) despite therapy with MS Contin® 900mg every 8 hours for weeks.

**Compounded Medication:** Ibuprofen 500 mg Suppositories - one administered rectally every 6 hours. (As patient was nauseated most of the time, oral ibuprofen therapy was not considered a good option.)

**Outcome:** Within hours of administration of the first suppository, pain level dropped from 8 to 1. The patient died one month later with pain level still between 1 and 2.

**Advantages of Compounded Medication:** Less sedation, less constipation, non-oral administration (nauseated patient).

**Dextromethorphan May Attenuate and Reverse Morphine Tolerance**

Elliot et al. of Cornell University Medical College showed that dextromethorphan, an NMDA receptor antagonist, can modulate morphine-mediated analgesic tolerance. Administration of subcutaneous dextromethorphan prior to an escalating morphine dosage schedule prevented a 5-fold increase in the morphine ED50 value observed on treatment day 4. In a trial involving morphine tolerant mice, administration of dextromethorphan resulted in an almost complete return of the morphine ED50 value to the opioid naive value. A study of post-operative pain relief using PCA in women undergoing hysterectomy indicates that patients who are poor metabolizers of dextromethorphan (or in whom the O-demethylation is competitively inhibited by other medication) may not experience any effect from the narcotic.

*Pain* 1994 Dec;59(3):361-8  

**Dextromethorphan Single Agent Preparations**

Dextromethorphan is an NMDA (N-methyl-D-aspartate)-receptor antagonist. Ongoing research indicates that drugs in this class can block pain transmission in dorsal horn spinal neurons and reduce nociception. However, most commercially-available dextromethorphan preparations have drawbacks to use for pain management. Dextromethorphan is frequently combined in cough/cold preparations with various antihistamines, decongestants, expectorants, or analgesics. Decongestants may raise concerns for hypertensive patients, and antihistamines may cause problems for those with BPH or glaucoma. Liquid “cough syrups” often contain sugar and/or alcohol, and have an unpleasant taste.

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

**SYMPTOM CONTROL**

**Nausea & Vomiting**

Persistent nausea can often be effectively controlled by using a combination of medications tailored to meet a patient’s specific needs. Antiemetic dosage forms include transdermal gels, suppositories, lollipops, and more. A variety of medications which target various pathways such as vagal nerve stimulation, the vomiting center, and the chemoreceptor trigger zone (CTZ) can be combined for a synergistic effect. Researchers at Memorial Sloan-Kettering Cancer Center have studied the antiemetic activity and safety of the antiemetic regimen of metoclopramide, dexamethasone, and diphenhydramine in patients receiving standard outpatient chemotherapy. Vomiting was prevented in over 70% of patients. Lorazepam, diphenhydramine, haloperidol, and metoclopramide (known in combination as “ABHR”) have been prepared as a rectal suppository and other transdermal dosage forms.

**Palliative Care: Treatment of Nausea, Vomiting, Retching, and Intestinal Obstruction**

Nausea, vomiting, and retching (NVR) are common and distressing complaints and 50-60% of patients with advanced cancer suffer from one or more of these. An understanding of the emetic process and the main neurotransmitters involved is helpful in assessing and treating patients who are vomiting. Antiemetic drugs are predominately neurotransmitter blocking agents which are effective at different receptor sites and therefore treat different causes of vomiting. As there is often a combination of causes in the palliative care setting, 30% of patients require two or more antiemetics. Effective management of individual symptoms during initial and continued therapy profoundly influences symptom response throughout the course of cancer therapy. Persistent
nausea may decrease gastric emptying, with a resultant decrease in drug absorption. Nausea can be treated with oral drugs, but alternative routes are needed for patients with severe vomiting.

Common causes of vomiting in patients with advanced cancer (and potential treatment)

- Drugs, especially chemotherapy (numerous treatment options) and opioids (during initial period of opioid treatment, metoclopramide and haloperidol may be administered prophylactically)
- Gastritis or ulceration (stop NSAID therapy, give omeprazole or H2 receptor antagonist)
- Functional gastric stasis due to external pressure (prokinetic drugs)
- Constipation (stool softeners and laxatives)
- Renal failure (haloperidol)
- Hypercalcemia (rehydration and bisphosphonates)
- Raised intracranial pressure
- Vestibular disturbance (sublingual or transdermal scopolamine)
- Anxiety (explanation and reassurance, possibly anxiolytic drugs)

Neuropathophysiology of Chemotherapy-Related NVR

Afferent input to the emetic center originates primarily from four sources:

- the cerebrocortical pathway, which is stimulated by learned associations.
- the chemoreceptor trigger zone (CTZ) that is located in the area postrema in the cortex and is sensitive to chemical stimuli from the cerebrospinal fluid and blood.
- the vestibular pathway, which activates the emetic center via body positional changes (as in motion sickness).
- the peripheral pathway, which is activated by neurotransmitter receptors found in the gastrointestinal tract where the vagus nerve communicates with the emetic center.

Vomiting occurs when efferent impulses are sent from the vomiting center to the salivation center, abdominal muscles, respiratory center, and cranial nerves. The mechanoreceptors in the bowel wall also may be stimulated by the stretch, distortion, or direct invasion of the gastrointestinal tract by a tumor.

Neurotransmitters, e.g., dopamine, acetylcholine, histamine, and serotonin (5-HT), are involved in the emetogenic pathways stimulated by chemotherapy and radiation. The gastrointestinal tract, the CTZ, and the emetic center are rich in receptors for these neurotransmitters. The serotonin or 5-hydroxytryptamine type-three (5-HT3) receptors are found in peripheral tissues, the nucleus of the solitary tract, and the CTZ where the majority of vagal afferents enter the brain. Neurokinin receptors, particularly the NK-1 receptor which is stimulated by substance P, are also involved with emesis.

5HT3 antagonists (e.g. ondansetron, tropisetron, granisetron, dolasetron) are effective for chemotherapy/radiation induced nausea and vomiting, but are not the first line of therapy for nausea and vomiting due to other causes. Although the 5-HT3 receptor antagonists represent a major improvement in the management of chemotherapy-induced NVR, clinical experience indicates that the antiemetic efficacy of 5-HT3 antagonists (given as single agents or in combination with dexamethasone) is not always maintained over multiple chemotherapy cycles.

Drugs with antiemetic effects include butyrophenones (e.g., haloperidol and droperidol), antihistamines (histamine H1 receptor antagonists, e.g., diphenhydramine, and cyclizine and promethazine), and corticosteroids. An advantage of these drugs is that some can be administered transdermally as well as orally or parenterally. Medications that block dopamine receptors (phenothiazines, metoclopramide, butyrophenones) prevent or reduce the emetic response associated with mild to moderately emetogenic chemotherapeutic regimens, and are used effectively in various combinations. Corticosteroids are useful in heightening the effects of antiemetic agents; for example, adding dexamethasone to tropisetron-containing combinations, or tropisetron alone, increased the anti-emetic effectiveness. The efficacy of benzodiazepines (e.g., lorazepam and alprazolam) may be derived from their sedative, anxiolytic, and amnesic properties, which enhance the effectiveness of antiemetic regimens.

Antiemetics need to be chosen based on the causes of nausea. Adequate symptom management may require combination therapy.

Nonpharmacologic Management of NVR may involve modification of diet and environment, acupuncture/acupressure, music therapy, progressive muscle relaxation, and guided imagery.
One of the areas where compounded medications can be most useful is symptom management of the terminally ill patient. For example, persistent nausea can often be effectively controlled by using a combination of medications tailored to meet that individual’s specific needs. A variety of medications which target various pathways such as vagal nerve stimulation, the vomiting center, and the CTZ can be considered.

ABHR for Refractory Nausea: Tolerability in Hospice Patients

Various formulations of ABHR (lorazepam, diphenhydramine, haloperidol, metoclopramide), such as topical creams, lozenges, and suppositories, have been used to treat chemotherapy-induced nausea and vomiting. Dexamethasone is sometimes added, and has been substituted for haloperidol in an intravenous preparation. There is significant rationale for prescribing ABHR/dexamethasone: each medication has a different site and mechanism of action. These drugs are synergistic in their inhibition of nausea and vomiting.

An oral combination of metoclopramide, dexamethasone, and diphenhydramine was given to patients with small cell lung cancer receiving standard outpatient chemotherapy programs. Vomiting was prevented in 15 of 21 patients receiving cisplatin and 21 of 31 individuals given cyclophosphamide plus doxorubicin. Adverse effects were mild and transient.1

To determine the tolerability of ABHR in both younger and elderly hospice patients, a retrospective cohort study analyzed a total of 11,181 ABHR prescriptions dispensed to 8600 hospice patients in the home care setting. A total of 42 ABHR prescriptions were discontinued secondary to adverse drug reactions (ADRs) in 39 patients. Only 0.1% of all prescriptions discontinued secondary to an ADR were consistent with an extrapyramidal reaction. The study concluded that compounded ABHR is generally well tolerated in the majority of hospice patients.2

ABHR for Chemotherapy-Induced Nausea/Vomiting

Various formulations of ABHR (lorazepam, diphenhydramine, haloperidol, metoclopramide), such as topical creams, lozenges, and suppositories, have been used to treat nausea and vomiting. Dexamethasone is sometimes added, and has been substituted for haloperidol in an intravenous preparation. There is significant rationale for prescribing ABHR/dexamethasone: each medication has a different site and mechanism of action. These drugs are synergistic in their inhibition of nausea and vomiting.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Site of Antiemetic Action</th>
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<tbody>
<tr>
<td>diphenhydramine</td>
<td>vomiting center and cerebral cortex</td>
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<tr>
<td>lorazepam</td>
<td>cerebral cortex</td>
</tr>
<tr>
<td>haloperidol</td>
<td>chemoreceptor trigger zone (CTZ) dopamine receptors</td>
</tr>
<tr>
<td>metoclopramide</td>
<td>CTZ and periphery (dopamine and serotonin receptors)</td>
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Cleri et al of Memorial Sloan-Kettering Cancer Center, New York, studied the antiemetic activity and safety of the oral combination antiemetic regimen of metoclopramide, dexamethasone, and diphenhydramine in patients with small cell lung cancer receiving standard outpatient chemotherapy programs. Vomiting was prevented in 15 of 21 (76%) patients receiving cisplatin and 21 of 31 (71%) individuals given cyclophosphamide plus doxorubicin. Adverse effects were mild and transient and included sedation, loose stools, akathisia, and hiccoughs.

ABHR Cream for Uncontrolled Nausea

by Nicole Christenson, R.N., Hospice Nurse

A 54 y.o. female with ovarian cancer and liver metastases was admitted to hospice with IV PCA and IV hydration due to uncontrollable nausea/vomiting of two weeks duration. ABHR Cream (lorazepam, diphenhydramine, haloperidol, metoclopramide) was initiated 0.5 ml was applied to the wrist and nausea subsided within 15 minutes. The medication was reapplied every six hours. The patient was able to tolerate clear liquids that day and held down p.o. Propulsid® and Decadron® that evening. The following day she was receiving a manicure and pedicure and went to the beach for four “wonderful” days before she died, according to her family.

I have used ABHR with at least four patients, all of whom were greatly relieved by the cream. All of the families have been amazed by the effectiveness of this compounded medication.
Aggressive Pharmacological Treatment for Reversing Malignant Bowel Obstruction

A combination of propulsive and antisecretory agents can act synergistically to allow a fast recovery of bowel transit without inducing unpleasant colic. Fifteen consecutive advanced cancer patients with inoperable bowel obstruction received a combination of drugs including metoclopramide, octreotide, dexamethasone and an initial bolus of amidotrizoato. Patients were hydrated and metabolic alterations were corrected. Patients received a drug combination composed of metoclopramide 60 mg/day, octreotide 0.3 mg/day, and dexamethasone 12 mg daily as an intravenous infusion. An initial bolus of 50 mL of amidotrizoato was administered orally. Almost all the patients surveyed showed a recovery of intestinal transit within 1-5 days, more commonly within 2 days, and vomiting generally disappeared within 24 hours. When successful, the treatment was maintained after hospital discharge, using a continuous infusion pump which was refilled once a week. Symptom control was prolonged, and some patients were able to resume eating and drinking. Patients died free of gastrointestinal symptoms.


Nausea Control for Hospice Patients
Samer Bibawi, M.D. and Sandra J. Shubel, R.N.

A 62 year old female with metastatic lung cancer (including mets to brain) had tried all commercially available anti-nausea medications, as well as a compounded scopolamine transdermal gel with no improvement. Following discussion with our compounding pharmacist, an “ABHR with dexamethasone suppository” (containing lorazepam 1 mg, diphenhydramine 12.5 mg, metoclopramide 20 mg, haloperidol 2 mg, and dexamethasone 6.67 mg) was prepared for administration three times daily. All nausea stopped. When the patient became confused (perhaps due to disease progression, as she expired two weeks later), the dosage was decreased to twice daily.

Metoclopramide

Metoclopramide (MTC) 40 mg by nasal spray 2 hours before chemotherapy, followed by the same dose at 4 hours and 8 hours proved to be therapeutically equivalent to MTC 20 mg i.v. at time zero, and MTC 20 mg i.m. after 4 hours and 8 hours in patients who experienced grade 2 nausea and/or vomiting subsequent to cisplatin administration. No extrapyramidal effects were reported. It was concluded that MTC nasal spray represents an effective, safe, easily managed and low-cost therapeutic alternative for the prophylaxis and treatment of emesis induced by low-dose chemotherapy. In a separate study, intranasal MTC 80 mg significantly reduced the frequency of acute vomiting in 43 patients receiving highly emetogenic chemotherapy.


Administration of high dose metoclopramide suppositories achieved plasma drug concentrations that are associated with the effective treatment of cytotoxic drug-induced nausea and vomiting. Suppositories are convenient and may be advantageous in the treatment of medical oncology out-patients.


A pharmacokinetic study of high-dose metoclopramide suppositories

Hardy F, Warrington PS, MacPherson JS, Hudson SA, Jefferson GC, Smyth JF
Department of Pharmacy, Heriot-Watt University, Edinburgh, Scotland.

The pharmacokinetics of high-dose rectal metoclopramide have been studied in nine patients after administration of 150-mg suppositories. The results have been compared to the pharmacokinetics of the drug in five patients who received the same dose of metoclopramide intravenously. Administration of a metoclopramide suppository achieved plasma drug concentrations that are associated with the effective treatment of cytotoxic drug-induced nausea and vomiting. In three patients who received the drug by both routes the systemic availability of the suppository appeared to be complete. High-dose metoclopramide suppositories are convenient and may be advantageous in the treatment of medical oncology out-patients.

Intranasal metoclopramide for the control of chemotherapy-induced emesis

The nasal formulation of metoclopramide (MTC), an established and effective antiemetic drug, is now commercially available in Australia and Europe. In a study of 12 patients, MTC 40 mg by nasal spray 2 hours before chemotherapy, followed by the same dose at 4 hours and 8 hours proved to be therapeutically equivalent to MTC 20 mg i.v. at time zero, and MTC 20 mg i.m. after 4 hours and 8 hours in patients who experienced grade 2 nausea and/or vomiting subsequent to cisplatin administration. No adverse reactions were observed at any time during the course of the study, and all 12 patients judged the acceptability of the new formulation as optimal. It was concluded that the use of MTC nasal spray represents an effective, safe, easily managed and low-
cost therapeutic alternative for the prophylaxis and treatment of emesis induced by low-dose chemotherapy. In a separate study, intranasal MTC 80mg significantly reduced the frequency of acute vomiting in 43 patients receiving highly emetogenic chemotherapy.

A pilot study suggested that intranasal metoclopramide, with or without dexamethasone, may reduce cisplatin-induced delayed emesis. In a randomized crossover trial in 40 patients, intranasal metoclopramide or oral metoclopramide, both with dexamethasone, were equally effective in the control of delayed emesis induced by moderately-emetogenic chemotherapy.

One 30 patient study suggests that intranasal metoclopramide has similar efficacy to oral metoclopramide in the treatment of functional dyspepsia.

Intranasal metoclopramide caused minor irritation of the nasal membrane and unpleasant taste in some patients, but was otherwise well tolerated. None of the more serious extrapyramidal effects sometimes associated with metoclopramide were reported.

*Drugs* 1999 Aug;58(2):315-22; discussion 323-4  

**Oral combination antiemetics in patients with small cell lung cancer receiving cisplatin or cyclophosphamide plus doxorubicin.**

Cancer 1995 Sep 1;76(5):774-8

Cleri LB, Kris MG, Tyson JB, Pisters KM, Clark RA, Gralla RJ

Department of Medicine, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, NY, NY

**BACKGROUND.** Intravenous antiemetic combinations containing a 5-HT3 receptor antagonist (like metoclopramide, ondansetron, or granisetron) with dexamethasone have become the standard therapy for the treatment of acute chemotherapy-induced vomiting. Intravenous antiemetics, however, can be more costly and take more time to prepare and deliver, and therefore are not preferred for home, outpatient, or office use. The objective of this study was to determine the antiemetic activity and safety of the oral combination antiemetic regimen of metoclopramide, dexamethasone, and diphenhydramine in patients with small cell lung cancer receiving standard outpatient chemotherapy programs.

**METHODS.** Fifty-two patients receiving initial cisplatin (60 mg/m2) or cyclophosphamide (600-1500 mg/m2) plus doxorubicin (30-45 mg/m2) received an oral regimen of metoclopramide (3 mg/kg x 2 then 2 mg/kg x 2 or 4 doses), dexamethasone (50 mg) and diphenhydramine (50 mg x 2 or 3 doses) (oral MDD), beginning 30 minutes before chemotherapy. RESULTS. Vomiting was prevented in 15 of 21 (76%) patients (95% confidence interval [CI], 53%-92%) receiving cisplatin and 21 of 31 (71%) individuals (95% CI, 52%-86%) given cyclophosphamide plus doxorubicin. Adverse effects were mild and transient and included sedation, loose stools, akathisia, and hiccoughs. CONCLUSIONS. The oral MDD antiemetic regimen prevented acute emesis in 73% of the patients entered and was well tolerated in this population of patients with small cell lung cancer.

**Five-drug antiemetic combination for cisplatin chemotherapy.**


Sridhar KS, Hussein AM, Hilsenbeck S, Cairns V

Department of Oncology, Sylvester Comprehensive Cancer Center, University of Miami School of Medicine, Florida

A combination of metoclopramide, dexamethasone, droperidol, lorazepam, and diphenhydramine was used in prophylaxis of high-dose (greater than or equal to 100 mg/m2) or moderate dose (greater than or equal to 50 mg/m2) cisplatin. Sixty minutes prior to starting cisplatin, 16 mg dexamethasone, 50 mg diphenhydramine, and 0.5 mg lorazepam were given orally (PO). Droperidol 1 mg was given intramuscularly (IM) 15 minutes prior to beginning cisplatin. Repetitive doses of intravenous (IV) metoclopramide, 2 mg/kg in 75 ml 5% dextrose in water over 15 minutes was given 30 minutes prior to, and at 1 1/2, 4 1/2, and 7 1/2 hours after beginning cisplatin chemotherapy. Only patients with nausea and/or vomiting received subsequent doses of 2 mg/kg metoclopramide IV every 3 hours as needed. Patients refractory to metoclopramide were given 1 mg droperidol IM and 50 mg of diphenhydramine PO every 6 hours. There were 19 men and 9 women with a median age of 58 (range 31-75) years. Complete protection from nausea and vomiting in all courses of treatment occurred in 77 (61%) patients. In 63% and 70% of the 57 evaluable courses, there was neither nausea nor vomiting, during the first 24 hours after cisplatin. When present, nausea was mild and the median number of vomiting episodes was 2 (range 1-3). This antiemetic regimen was well tolerated. Toxicities were mild and occurred in 3 patients (angioneurotic edema, transient episode of facial twitching, and heaviness of tongue, respectively). The five-drug antiemetic combination can prevent cisplatin-induced nausea and vomiting in a majority of patients.

**Promethazine** 50mg (12.5mg/0.1ml PLO), when applied topically to the wrist was absorbed systemically, although it produced much lower serum concentrations and also less sedation than parenteral administration.1 Promethazine is commonly compounded for topical or transdermal application to treat nausea, vomiting, and vertigo. Promethazine gel can be dispensed in a calibrated topical syringe (without needle), and should be stored at room temperature. The viscosity of some preparations such as PLO gels is temperature dependent: they may liquefy when refrigerated and if too warm, these gels can become more viscous and resistant to rubbing.2


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Promethazine Transdermal Gel for Nausea
Mark Seratt, M.D., Family Medicine, Locust Grove, OK

Promethazine can be compounded into a pluronic lecithin organogel for transdermal administration. I have found this to be a superior alternative to commercially available preparations in the majority of cases for many reasons:

- Rapid onset - This preparation usually provides relief from nausea and vomiting in 10-15 minutes.
- Lack of side effects - My patients have reported less drowsiness compared to oral preparations.
- There is no question how much medication is absorbed; this is often a problem if the patient has an emesis or bowel movement shortly after administration of an oral or rectal medication.
- No concern with diarrhea - Since many patients with “flu-like” symptoms have N/V and diarrhea simultaneously, topical absorption avoids the problems encountered with rectal administration.

Patients apply the prescribed amount of promethazine gel (usually 0.25ml -0.5 ml of a 50 mg/ml gel) to the wrist. In the last two years, I have prescribed this for over 200 patients, with only two failures. It has become my “first-line” anti-emetic therapy because it is so convenient for my patients and it works very well. The “secret” to the efficacy of this product lies in the preparation of the “PLO gel” which facilitates adequate penetration and transdermal absorption.

Dyspnea

When illness is incurable or the cause is irreversible and the goal is palliation, systemic opioids are the first-line therapy for symptomatic management, along with other general comfort measures (positioning, cool air movement, calming environment). A study at St. Christopher’s Hospice in London found that titrated oral morphine improved dyspnea in 60% of patients with terminal cancer. Improvement in dyspnea with the use of morphine may be related to its depressant effect on the hypoxic and hypercapnic ventilatory drives.1

To determine the efficacy of oral morphine in relieving the sensation of breathlessness in patients in whom the underlying etiology is maximally treated, a randomized, double blind, placebo controlled crossover study was conducted at four outpatient clinics at a hospital in South Australia. Participants (mean age 76, predominantly chronic obstructive pulmonary disease) who had not previously been treated with opioids were randomized to four days of 20 mg oral sustained-release morphine followed by four days of identically-formulated placebo, or vice versa. Laxatives were provided as needed. Participants reported significantly different dyspnea scores when treated with morphine and also reported better sleep. The conclusion was that sustained-release oral morphine at low dosage provides significant symptomatic improvement in refractory dyspnea in the community setting.2

When prescribed appropriately, respiratory depression is not a significant concern. Research has demonstrated that opioids will relieve the distress of breathlessness in many patients without a measurable effect on their respiratory rate or blood gas concentrations. The precise mechanism by which opioids exert this effect is unclear. There may be both central and peripheral effects. In the opioid-naive patient, doses lower than those used to relieve pain may be effective, yet the effect of opioids on dyspnea may be of shorter duration than analgesia. When an effective dose has been established, dosing can be simplified by converting to an extended-release preparation. When opioids are used to manage breathlessness, pharmacologic tolerance is not a clinically significant problem. Opioid treatment for dyspnea is consistent with good medical practice, and when widely accepted dosing guidelines are followed, is unlikely to be associated with hastened death or abuse behaviors.

It must be stressed that the studies which show that administration of opioids resulted in respiratory depression have been on either opioid-naive patients with acute pain or normal experimental subjects without pain. Morphine slows the respiratory rate and decreases tidal volume and increases arterial pCO2. Pain is a potent stimulus to respiration and an effective antagonist to opioid-induced respiratory depression. Patients in pain being treated with high dose opioids and with normal respiration may develop respiratory depression following rapid pain relief from other means, e.g., addition of coanalgesics, or sudden complete spinal cord compression. However, chronic ventilatory failure appears neither common nor clinically significant in advanced cancer patients who are pain-free on stable doses of oral morphine even in the presence of pre-existing respiratory disease. Clinical experience supports efficacy and safety when dosed appropriately. A Cochrane review of the literature found “statistically strong” evidence that opioids are effective in relieving dyspnea in both cancer and COPD, but opioids must be appropriately titrated to symptom relief to minimize the possibility of depressing respiration. Toxicity should be monitored carefully; however, unrealistic fears or excessive caution should not prevent appropriate palliative management of this distressing symptom.3

Mild dyspnea
For mild dyspnea in patients taking no opioid analgesics, treatment options include:

- hydrocodone, 5 mg po q 4 h with a breakthrough dose of 5 mg q 2 h prn
- codeine 30 mg po q 4 h with a breakthrough dose of 30 mg q 2 h prn
- children or elderly may require lower doses (can be titrated using a syrup or a compounded preparation)

Severe dyspnea
In the opioid-naive patient, oral treatment options include:

- morphine (as elixir or tablets), 5–15 mg q 4 h and titrate
• oxycodone, 5–10 mg q 4 h and titrate
• hydromorphone, 0.5–2 mg q 4 h and titrate

In patients receiving an opioid on a fixed schedule, an additional dose of a short-acting opioid (eg, morphine) equivalent to 30%–50% of the amount of the baseline opioid taken over 4 hours can be tried q 1 h, and titrated to effect. Chlorpromazine and promethazine have both been reported to improve breathlessness, particularly when combined with opioids.

Prescribers should use caution in prescribing oral medications that contain an opioid in combination with acetaminophen, due to the potential for acetaminophen toxicity when an appropriate dose of opioid is administered. We can compound acetaminophen-free preparations.

Common side effects of opioids include constipation, nausea, vomiting, dry mouth, and sedation. Tolerance to these side effects develops rapidly, except for constipation. It is important that a patient begin routine utilization of a stool softener and mild laxative when initiating opioid therapy.4

**Nebulized opioids**

Nebulized opioids have been used for dyspnea after anecdotes and case reports suggested benefit. The mechanism is thought to be through direct action on opioid receptors in the large airways. A report of the use of nebulized opioids in patients with pulmonary fibrosis, lung, and tracheal cancer achieved significant improvement in dyspnea, exercise tolerance, and general well-being. Several randomized trials failed to demonstrate benefit of nebulized opioids over saline, although these have been criticized for failing to titrate the doses used. Advantages of nebulized opioids include (1) ease of administration, (2) preservation of patient independence and autonomy, (3) limited systemic absorption and toxicity, (4) rapid onset, (5) noninvasiveness, (6) relative inexpensiveness, and (7) reported efficacy of “as-needed” dosing. Disadvantages include (1) lack of unequivocal evidence and (2) slightly longer time to onset of action compared to parenteral opioids. Bronchospasm may occur with nebulized morphine possibly due to stimulation of histamine release, but is uncommon with therapeutic doses by other routes.5

**Oral Naloxone to Prevent or Reverse Opioid-Induced Constipation**

Opioid analgesics are the cornerstone of pain management for moderate-to-severe cancer pain and, increasingly, chronic non-cancer pain. The use of opioids is commonly associated with dose-limiting constipation that seriously impacts patients’ quality of life. Agents currently used to manage opioid-induced constipation (OIC), such as laxatives, do not address the underlying opioid receptor-mediated cause of constipation and are often ineffective. Therefore, a significant need exists for more effective treatment options. A novel approach for selectively and locally antagonizing the gastrointestinal effects of opioids involves the coadministration of a mu-opioid receptor antagonist with negligible systemic availability, such as oral naloxone. Combination therapy with prolonged-release (PR) oxycodone plus PR naloxone has been shown to provide effective analgesia while preventing or reducing constipation. This novel strategy has the potential to significantly improve the quality of life of patients suffering from chronic pain, affording patients the benefit of full analgesia, without the burden of OIC.1

A randomized controlled trial involving 202 patients with chronic pain under stable oral prolonged-release (PR) oxycodone therapy (40, 60 or 80mg/day) were randomized to receive PR oral naloxone (10, 20, 40mg/day) or placebo. After a 4 week maintenance phase, patients received oxycodone only for 2 weeks. Pain intensity was evaluated using a numerical analogue scale and bowel function was assessed. No loss of analgesic efficacy with naloxone was observed; mean pain intensity scores were comparable for placebo and all doses of naloxone and remained unchanged during treatment. Naloxone 20 mg and 40 mg significantly improved bowel function at the end of the maintenance phase compared with placebo. The 2:1 oxycodone/naloxone ratio was identified as the most suitable. The conclusion: co-administration of PR oral naloxone and PR oral oxycodone is associated with a significant improvement in bowel function compared with PR oral oxycodone alone, with no reduction in the analgesic efficacy of oxycodone.2

A small double-blind, randomized, placebo-controlled study of 9 patients evaluated the effects on constipation and analgesia of low doses of oral naloxone (4 mg, 2 mg, or placebo) given three times daily in patients taking stable doses of opioids with complaints of constipation. All the patients who received oral naloxone had some improvement in their bowel frequency. Two patients experienced partial reversal of analgesia, and one patient had complete reversal of analgesia. Patients using high doses of opioids appeared to be the most vulnerable to reversal of analgesia by oral naloxone.3

In 4 of 17 patients with chronic pain receiving oral opioids, moderate side effects (sweating, shivering, or abdominal cramps) of short duration (30 minutes to 6 hours) were observed in patients who received single doses of 6 to 20 mg of immediate release oral naloxone. To prevent systemic opioid withdrawal symptoms, therapy should be started with low doses and patients carefully monitored during titration.4

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2 BMJ. 2003 Sep 6;327(7414):523-8
3, 5 Am J Hosp Palliat Care 2003; 20; 57
4 EPEC Project, 1999. The Project to Educate Physicians on End-of-life Care from the Institute for Ethics at the American Medical Association.

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Oral naloxone, particularly when formulated as an extended release preparation, may provide an option for relief of opioid-induced constipation in patients who desire to avoid subcutaneous injections of methylnaltrexone.

Dry Mouth & Stomatitis

Loss of saliva (xerostomia) is one of the most common complaints among patients who have received radiation therapy of the head and neck. Xerostomia contributes to radiation induced periodontal infection, dental caries, osteoradionecrosis, and poor digestion of carbohydrates.

There are many factors that can interfere with the ability to eat when a person is receiving chemotherapy. Malnutrition may result, yet it is often preventable. Our pharmacy can compound medicated dosage forms to help to combat the mouth tenderness and infections experienced by many patients, which in turn may enable them to enjoy eating again. How about a lollipop or freeze pop that can dissolve in the mouth, and provide sustained contact with a helpful medication? It’s often much easier than swishing a suspension.

Should the patient need an oral rinse, we can compound a preparation that will be soothing and refreshing and taste good, too. Commercial mouthwashes often contain alcohol and may burn or sting. Our compounding professionals can prepare alcohol-free, sugar-free, and dye-free medications.

Pilocarpine LA for Xerostomia

W. James Nethery, D.D.S.
Dental Oncology/Maxillofacial Prosthetics, Loma Linda and Santa Ana, California

One of the most common complaints among irradiated head and neck cancer patients is the loss of saliva - xerostomia. Xerostomia contributes to post radiation decay, radiation induced periodontal infection, osteoradionecrosis, and poor digestion of carbohydrates. For over 30 years I have attempted to provide relief with limited success. The artificial solutions to replace saliva have offered minimal results. Most patients use drinking water due to the costs of medications, unpleasant tastes, and failure of these products to adequately moisturize their mouths.

At my request, my local pharmacy compounded a time-release pilocarpine in two doses, 7.5 mg and 10 mg capsules. It is taken orally once in the morning and at bedtime. Based on my patients' comments, the adverse effects of this form are minimal in comparison to those of commercially available immediate-release pilocarpine (which include sweating, hot flashes, and headaches). More importantly, my patients report improvement in their continuous saliva stimulation with the time-release pilocarpine. (The effective salivary stimulation period of the immediate release product is only about 30 minutes.)

Being able to provide patients with an improvement in their quality of life using a preparation like Pilocarpine LA is most important, because it not only provides relief from their dry mouths, but is also cost effective.

Glutamine Suspension to Prevent Mucositis in Patients Undergoing Bone Marrow Transplant

Oral mucositis is a common and debilitating side effect of the regimens that use high-dose chemotherapy with or without radiation for bone marrow transplantation. There has been limited success in preventing or treating mucositis. Administration of glutamine, which is a nitrogen-rich amino acid found in the body, has emerged as a possible method of preventing oral mucositis in patients undergoing bone marrow transplantation.

Glutamine is a nutrient for rapidly dividing cells and the major energy source for intestinal epithelium. Administration of glutamine suspension 2 g/m²/dose (maximum dose of 4g), swish and swallow twice daily on days of chemotherapy and for at least 14 additional days, resulted in significant amelioration of stomatitis (duration of mouth pain was 4.5 days less when compared to placebo). The severity of oral pain was also reduced significantly when glutamine was provided with chemotherapy: the amount of days mucositis restricted oral intake to soft foods was 4 days less with glutamine. No toxicity of glutamine was observed. Oral glutamine offers a safe, simple and useful measure to increase the comfort of many patients at high risk of developing mouth sores as a consequence of chemotherapy.


Amphotericin B and Nystatin Mouthrinses

Amphotericin B and nystatin are potent antifungal agents which are active against most pathogenic fungi like Aspergillus and Candida. Mouthrinses containing these drugs are used for preventive and curative treatment of fungal infections like oral candidiasis, which can cause multiple diseases, especially in cancer patients. Mouthrinses are usually prepared in aqueous, saline or alkaline medium. Alkaline medium is effective against hyposalivation and acidity which contribute to the development of mucocutaneous candidal infections.
Groeschke et al investigated the stability of extemporaneously compounded mouthrinses containing amphotericin B (7.4 mg/ml) and nystatin (4580.2 IU/ml) in 1.4% sodium bicarbonate (sodium hydrogen carbonate). The stability of these solutions was tested at different temperatures (4 to 37 degrees C) with or without exposure to light and in two types of containers (glass and polypropylene) over a 15-day period. The preparations were also monitored for color change and pH. Amphotericin B and nystatin were quantified by high-performance liquid chromatography (HPLC). At 4 degrees C (refrigeration), amphotericin B and nystatin were stable for 15 days in polypropylene containers. When stored in polypropylene at 37 degrees C (room temperature), with or without light protection, amphotericin B and nystatin were stable for 3 and 4 days, respectively.

J Pharm Biomed Anal. 2006 May 30 (E-pub ahead of print)

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

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

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

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

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

**Chemoradiotherapy-Induced Esophagitis Pain Relieved by Topical Morphine**

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

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

**Delirium**

Delirium may herald the last days of life in a hospice patient with irreversible illness and interferes with meaningful communication and interaction with family and friends as well as professional care givers (health care providers, clergy, counselor).

If delirium occurs close to the time of death, the patient's agitation may simply be observed, with attention given to preventing physical harm. Hospice workers have noted that a changed mental status is more pronounced in patients who have been undergoing a significant psychosocial or spiritual struggle. Many would argue that sedation is not appropriate in this setting. For families, however, the open, staring eyes and agitated movement of a patient, which may give the perception of uncontrolled pain, may not be emotionally tolerable, resulting in a request for something to "quiet" the patient.

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Patients' descriptions of "visits" by loved ones who have died before them should not be mistaken for delirium or confusion. Although labeled by some as hallucinations, these encounters usually appear to be comforting to dying patients and consequently may not require medical treatment. The comfort of the person suffering from delirium is paramount. Extensive work-up including CT scans and X-rays may be warranted but the decision must be made in light of the overall situation. Symptomatic and supportive therapies are indicated when the burden of evaluation and treatment of the underlying causes of the delirium outweighs the benefits.

**Treatment for specific reversible causes of delirium**

- Fluids (IV, PO, SC)
  Dehydration is usually asymptomatic in terminally ill patients; however, when dehydration results in delirium, gentle rehydration may be beneficial if there is a need for the patient to be more alert.
- Caution must be exercised with IV fluids.
- Placement of IV line and restraints to protect the access may traumatize the patient.
- Fluid overload with edema and pulmonary congestion can add to suffering at end of life.
- Antibiotics
- Oxygen
- Lactulose
- Bladder catheterization
- Disimpaction

**Medical management of delirium**

In patients with delirium, discontinuing unnecessary drugs or prolonging the dosing interval for necessary drugs may help to clear the sensorium. Opioid analgesics, required in most patients with advanced disease, are among the psychoactive agents that precipitate delirium most frequently. Patients with delirium should be assessed for other symptoms that suggest opioid neurotoxicity. Intervention in the form of dose reduction or opioid switching in association with assisted hydration typically allows for clearing of the offending opioid or its metabolites.

Therapy for delirium may include the use of neuroleptics, benzodiazepines, anticholinergics, antiemetics, and steroids. Haloperidol is the pharmaceutical agent of choice for the management of delirium. Treatment with benzodiazepines (lorazepam) for agitation associated with delirium may lead to a vicious cycle of escalating doses that only worsens the underlying delirium.

**Neuroleptics**

- Haloperidol – Physicians may wish to consider transdermal preparations when oral or injectable administration is not feasible.*
- Chlorpromazine
- Risperidone
- Olanzapine

**Benzodiazepines**

- Lorazepam – Physicians may wish to consider transdermal preparations when oral or injectable administration is not feasible.*
- Midazolam (used to achieve deep sedation, especially in a terminal hyperactive or mixed delirium when agitation is refractory to other treatments)

The decision to use a deep level of pharmacologically induced sedation in the treatment of agitated delirium often raises ethical concerns. The time between onset of sedation and death has been consistently reported as 1 to 6 days. Consistent with the goals of care, it is important that appropriate efforts are made to assess the reversibility of delirium, clarify the intent of sedation (the relief of refractory symptoms), and maintain clear communication with family members and healthcare team members regarding rationale and process.

**Nonpharmacologic interventions** include discrete efforts at reorientation such as a well-lit room with familiar objects, a visible clock or calendar, limited staff changes, reduced noise stimulation, and the presence of family. A family member or caregiver might remain with the patient to encourage relaxation and prevent physical harm. Use of physical restraints should be avoided unless absolutely necessary to prevent self-harm or physical aggression. If required, restraints should be used in conjunction with sedation. Environmental strategies have been proposed to reduce the symptomatic distress associated with


**WOUND CARE**

**Decubitus Ulcers**

Phenytoin has been used topically to speed the healing of pressure sores and other wounds. Ketoprofen may be used to control inflammation and pain, lidocaine provides topical anesthesia, and pentoxifylline may improve microcirculation. Misoprostol, a prostaglandin analog, is often included in wound care formulations to promote healing.

**Malignant Cutaneous Wounds**

Malignant cutaneous wounds are emotionally traumatic and can cause great distress and embarrassment for patients. These difficult-to-manage lesions may occur due to infiltration of cancer into the skin of patients with end-stage disease and are highly exudative, malodorous, and bleed easily. Quality of life is a goal of therapy.

**Odor Control**

Topical metronidazole has been used to eliminate wound odor, greatly improving the patient’s quality of life. Exudate and associated cellulitis have also decreased significantly with topical antimicrobial therapy.

**Skin Irritation**

Numerous topical preparations containing cholestyramine or sucralfate have been applied for their protectant properties or for treatment of a variety of problems, including oral and esophageal ulcers, peristomal and perineal excoriation, decubitus ulcers, and radiation-induced rectal and vaginal ulcerations.

**Wound Care** involves debridement (removal of dead tissue), cleansing (usually accomplished by irrigating the wound), maintenance of a moist environment, prevention of infection and further injury, and provision of materials needed to improve healing.

**Topical dosage forms such as gels and sprays** are used in conjunction with various dressings to treat wounds. Each time a wound needs to be cleaned, there is the potential for disruption of new tissue growth. Gels, which are more water soluble than creams or ointments and tend to keep the area moist, may be preferable for wound use because a gel can be rinsed from the wound by irrigation. Almost any active ingredient can be formulated into a gel. Solutions can be used for irrigation, baths, soaks and sprays. An advantage of sprays is that the wound area does not need to be touched and sprays can have a cooling effect. Although some medications are commercially available as creams, creams may be more difficult to remove from the wound cavity and may affect the granulation process. Ointments may contain polyethylene glycol (PEG), which can be absorbed from open wounds and damaged skin. If the wound is quite large and too much PEG is absorbed, it can lead to renal toxicity. Therefore, it may be preferable to compound the active ingredients into a gel or solution, or when an ointment is desired, the compounding pharmacist may be able to formulate a less toxic preparation. Medications can also be prepared as powders that can be dispensed in a bellows bottle and puffed onto the affected area. Another useful dosage form is the “polyox bandage” - which can be puffed onto a wound and will adhere even if exudate is present. A polyox bandage can be compounded to contain the active ingredient(s) of your choice.

**Aloe Vera** has been utilized for many years to treat wounds and burns. Aloe improves blood flow to the wound and may work as a free radical scavenger. One study showed that, compared to those who received no treatment, wounded rats treated with topical aloe vera had 93% more collagen in the healing wound. Topical aloe vera has also been shown to have a synergistic effect with other medications used for wound healing.

**Antibiotics** can be included in wound preparations to prevent or treat infections, and can be selected based on sensitivities of bacteria from wound cultures. **Metronidazole** is effective topically against anaerobic bacteria that cause foul and distressing wound odors. Elimination of these embarrassing odors can greatly improve the patient’s quality of life. Exudate and associated cellulitis have also been observed to decrease significantly with topical metronidazole therapy. Adverse reactions characteristic of oral metronidazole have not been reported. Metronidazole oral rinse may alleviate odor associated with oral lesions.

**Benzoyl Peroxide** is a powerful oxidizing agent with broad spectrum germicidal activity and good liposolubility that may be useful for treatment of decubitus ulcers and prevention of wound infection in areas with high density of sebaceous glands.
Topical treatment of pressure sores with 20% benzoyl peroxide in an oil in water emulsion has yielded very satisfactory results. In another study, 10% benzoyl peroxide gel was used prophylactically once a day for 7 days before surgery. The researchers concluded that topical benzoyl peroxide is an efficacious, harmless, and inexpensive agent for prevention of wound infections in seborrheic regions.

**Calcium Channel Blockers**, in properly compounded topical preparations, have been shown to hasten wound healing and improve blood flow to diabetic ulcers. The advantages and successful use of topical nifedipine and diltiazem for healing both acute and chronic anal fissures have been reported often in the medical literature. Topical nifedipine has also been used to improve healing of foot wounds. Topical therapy with calcium channel blockers is preferred over oral administration for wound care due to the lesser incidence of side effects such as hypotension, flushing and headaches.

**Estrogen**, when applied topically, has been found to reduce wound size, increase the rate of wound healing, and stimulate collagen production in both the male and female patients.

**Glyceryl Trinitrate** (GTN, nitroglycerin) has been used successfully to speed healing after hemorrhoidectomy and to treat chronic anal fissures. However, in comparison to topical calcium channel blockers, topical GTN use has been associated with a higher incidence of side effects such as headaches.

**Honey** may be beneficial when used topically for wound healing, but both the type of bee and plant source of the honey are important. Honey that is used therapeutically must be crude and unsterilized because sterilization eliminates much of its antibacterial activity. Honey generates an organized matrix similar to hyaluronic acid which allows for faster epithelialization and reduced scar formation. Therapeutic manuka honey has also been shown to kill *Pseudomonas* bacteria in burn wounds, including strains that were resistant to many antibiotics.

**Hyaluronic Acid** has been applied topically to improve the healing rate in chronic venous leg ulceraions. Research has shown the benefit of using an ester of hyaluronic acid to accelerate the healing process and effectively treat diabetic foot ulceration and other difficult-to-heal chronic wounds.

**Pentoxifylline** reduces blood viscosity and thus can improve circulation to the wound. When used topically, pentoxifylline may improve the rate of wound healing by improving the ability of medications such as calcium channel blockers to reach the wound tissue.

**Phenytoin** may be used topically to promote wound healing by a number of mechanisms, including stimulation of fibroblast proliferation, facilitation of collagen deposition, glucocorticoid antagonism, and antibacterial activity. Topical phenytoin has been used to heal pressure sores, venous stasis and diabetic ulcers, traumatic wounds, skin autograft donor sites, and burns, and has compared very favorably with, and in some aspects was superior to, occlusive dressings. Studies have not reported any significant adverse effects secondary to topical phenytoin therapy.

Rhodes et al compared the healing of stage II decubitus ulcers with topically applied phenytoin and two other standard topical treatment procedures in 47 patients in a long-term care setting. Ulcers were examined for the presence of healthy granulation tissue, reduction in surface dimensions, and time to healing. Topical phenytoin therapy resulted in a shorter time to complete healing and formation of granulation tissue when compared with DuoDerm dressings or triple antibiotic ointment applications. The mean time to healing in the phenytoin group was 35.3 +/- 14.3 days compared with 51.8 +/- 19.6 and 53.8 +/- 8.5 days for the DuoDerm and triple antibiotic ointment groups, respectively. Healthy granulation tissue in the phenytoin group appeared within 2 to 7 days in all subjects, compared to 6 to 21 days in the standard treatment groups. The phenytoin-treated group showed no detectable serum phenytoin concentrations.

Anstead et al. described a patient with a massive grade IV pressure ulcer that was unresponsive to conventional treatment, yet responded rapidly to treatment with topical phenytoin. Song and Cheng reported phenytoin improved wound breaking strength in normal and radiation-impaired wounds. The results of their study indicated that topical phenytoin accelerated normal and irradiation-impaired wound healing by increasing the number of wound macrophages and improving the macrophage function. Pendse et al evaluated the effectiveness of topical phenytoin in healing chronic skin ulcers in a controlled trial of 75 inpatients. At the end of the fourth week, 29 of 40 phenytoin-treated ulcers had healed completely versus 10 of 35 controls. They concluded: "topical phenytoin appears to be an effective, inexpensive, and widely available therapeutic agent in wound healing."

The effectiveness of topical phenytoin as a wound healing agent was compared with that of OpSite and a conventional topical antibiotic dressing (Soframycin) in a controlled study of 60 patients with partial-thickness skin autograft donor sites on the lower extremities. Mean pain scores were lower and mean time to complete healing (complete epithelialization) was best in the phenytoin-treated group (6.2 +/- 1.6 days). Topical phenytoin compared very favorably with, and in some aspects was superior to, occlusive dressings.

**Sucralfate**, commonly used as a protectant, can be formulated as a cream to treat second and third-degree burns, and has been shown to improve healing time by 25%. Topical sucralfate has also been used successfully to treat bleeding and diarrhea caused by radiation-induced proctitis.

*A wide variety of compatible anti-infectives, anesthetics, protectants, and agents that promote wound healing can be*
Example- Compounded Topical Therapy Containing Multiple Medications for Treating Decubitus Ulcers

Phenytoin has been used topically to speed the healing of decubitus ulcers. Ketoprofen may be used to control inflammation and pain, lidocaine provides topical anesthesia, and pentoxifylline may improve microcirculation at the wound margins and promote healing of the injured area. Misoprostol, a prostaglandin analog, is often included in wound care formulations to promote healing. Debridement of necrotic eschar with 40% urea paste may also speed healing.

Healing of wounds involves increased cellular activity, which causes an intensified metabolic demand for nutrients such as arginine, glutamine, protein, vitamin A, vitamin C, pantothenic acid, zinc and copper. Appropriate dietary supplementation may be beneficial to promote wound healing in the shortest time possible, with minimal pain, discomfort, and scarring to the patient. Ongoing research involves the use of various growth factors and immune response modulators.

Malignant Cutaneous Wounds: a Management Protocol

Ostomy Wound Manage 1997 Jan-Feb;43(1):56-60, 62, 64-6
Haisfield-Wolfe ME, Rund C
Johns Hopkins Oncology Center, Baltimore, MD, USA.

Malignant cutaneous wounds are emotionally traumatic and difficult to manage lesions which occur secondary to infiltration of cancer into the skin. They occur in patients with end-stage disease and are highly exudative, malodorous, and bleed easily. Quality of life is the goal for treatment, which includes radiation, chemotherapy, surgery, and local wound care. Odor is addressed with varying levels of success through wound cleansing, external deodorizers, charcoal-impregnated dressings, topical antimalarial therapy, and metronidazole. Exudate is managed with highly absorbent dressing materials, topical steroids or hyoscine (a drying agent). Light bleeding is controlled with local pressure and hemostatic dressings; heavier bleeding may require ligation or cautery. Cosmetic appearance and other psychosocial issues must be assessed on an ongoing basis. Creative dressing techniques can help restore the look of symmetry to the patient’s body. Effective wound management, debridement, and antimicrobial therapy can reduce the risk of infection. Wound cleansing, through irrigation or flushing, should not cause pain, further trauma or bleeding. Dressings should maintain a moist wound environment and not traumatize the wound upon removal. A protocol is included which can be individualized to the needs of each patient and addresses assessment, interventions, patient teaching, documentation, and expected outcomes.

Topical Metronidazole for Malodorous Wounds

Odor from malignant cutaneous wounds, ulcerated tumors, fungating tumors and benign cutaneous ulcers can cause great distress and embarrassment for patients. Elimination of this odor can greatly improve the patient’s quality of life. Clinical research using topical metronidazole over the past 20 years clearly indicates that metronidazole is effective against the anaerobic bacteria that cause these foul and distressing odors. Exudate and associated cellulitis were also observed to decrease significantly with topical therapy. Adverse reactions (nausea, dizziness, metallic taste) characteristic of oral metronidazole have not been reported.

A metronidazole oral rinse has been shown to alleviate odor associated with oral lesions.

Use of metronidazole gel to control malodor in advanced and recurrent breast cancer

Department of Surgery, Tokai University School of Medicine, Kanagawa, Japan.

Intolerable malodor emanating from ulcerated tumors as a result of anaerobic infection is a serious problem in the management of advanced and recurrent breast cancer. Metronidazole can control this malodor, but its oral use may cause adverse reactions. We therefore formulated a metronidazole gel, since no equivalent preparation is commercially available in Japan, and used it in five female patients (four with advanced cancer and one with recurrent cancer) admitted to our hospital between March 1994 and July 1995. The patients were aged between 47 and 71 (median: 59) years, and the duration of morbidity in the four patients with advanced cancer ranged from 10 months to four years. In three patients, the tumors were larger than 10 cm x 10 cm. Metronidazole gel was applied to the surface of ulcerated tumors once or twice daily. Independent assessments by the patient, doctor and nurse were unanimous, and revealed that the malodor was alleviated in one patient after three days, and removed in four patients after two to five (median: four) days of metronidazole gel treatment. Culture of swabs showed a decrease or disappearance of anaerobic colonies. Adverse reactions characteristic of metronidazole did not occur. The topical use of metronidazole in a gel form will improve the quality of life for patients with malodorous ulcerated tumors and facilitate intensive
treatment of the underlying disease.

Lidocaine - Tetracaine Spray  
Submitted by Michelle Orr, R.N.

Case # 1
83 y.o. Caucasian male with Cerebro-Vascular Accident (stroke) and Peripheral Vascular Disease.
Each day, this confused patient would attempt to push the nurse away due to pain caused by a dressing change for a stasis ulcer on his left heel. The dressing change protocol involved debridement of loose eschar, silver nitrate to hypergranulated areas, application of Silvadene®, and dry gauze.
After consultation, Lidocaine - Tetracaine Spray was prescribed with directions to spray the ulcerated area prior to each dressing change. Once this therapy was initiated, the fighting stopped, and the patient presented with only occasional grimaces.

Case # 2
76 y.o. Caucasian male with liver cancer and edema. Enlarged scrotum was excoriated and weeping.
Lidocaine - Tetracaine Spray was prescribed with directions to spray the affected area every four hours as needed and prior to treatments. His pain decreased, which was comforting to the patient and allowed him to rest. The analgesia also enabled the therapist to use elevation and ice packs three times daily to decrease edema without pain. The analgesia produced by the Lidocaine - Tetracaine Spray usually lasted about 30 to 45 minutes. As the patient was able to tolerate treatments, healing was more rapid.

Miscellaneous Therapies to Benefit Patients Receiving Palliative Care

Carbon Dioxide Evacuant Suppository  
Simulates an enema, but without the mess.
Carbon dioxide-releasing laxatives (e.g., potassium bitartrate and sodium bicarbonate) are suppositories that encourage bowel movements by forming carbon dioxide. This gas pushes against the intestinal wall, causing contractions that move along the stool mass. Results often may be obtained with carbon dioxide–releasing suppositories in 5 to 30 minutes. The suppository is typically not associated with cramping or irritation and is easy to administer. It can be more aesthetically acceptable to patients than a liquid enema, and does not interfere with normal digestion. Any undissolved suppository will be passed when the bowel movement occurs, thereby eliminating the worry of residual bowel movements that may occur hours after application.

Stomach Pain Relieved with Compounded Mixture  
by Raymond Magee, M.D., Topeka, KS
A 58-year-old man was diagnosed with squamous cell carcinoma of the lung, adrenal and bone metastases, pulmonary fibrosis, gastro-intestinal ulcer and reflux (GERD). The patient had generalized pain from the cancer and bone metastases. He was allergic to morphine sulfate and nalbuphine hydrochloride and was taking fentanyl transdermal system, lactulose, cisapride, sucralfate and omeprazole. Despite this therapy, the patient continued to have stomach pain and experienced difficulty eating. Patient was given 5 to 10 cc four times daily of a mixture containing the following ingredients: sucralfate 1 gm/10 ml suspension, lidocaine 0.5%, and aluminum hydroxide/magnesium hydroxide suspension. The suspension was given four times a day, in addition to the medications the patient was already taking.
The stomach pain stopped immediately and the patient was able to resume eating. The prescription was refilled ten times. Relief was obtained when nothing else had worked.

Sucralfate in Adhesive Paste
Numerous topical sucralfate preparations have been applied for their protectant properties or for treatment of a variety of dermatologic and mucosal problems, including oral and esophageal ulcers, peristomal and perineal excoriation, decubitus ulcers, radiation-induced rectal and vaginal ulcerations, and second and third degree burns.

Cholestyramine Ointment for Severe Ostomy or Buttocks Rash
If high concentrations of bile acids are contained in the stool, they can irritate the anus and buttocks in a manner similar to the
skin irritation experienced by patients with ostomies. When applied topically, cholestyramine, a bile acid sequestrant, can irreversibly bind the bile and bring relief to the patient. A two-month old boy with reflux and regurgitation was treated with the promotility agent cisapride. He developed a rash on his buttocks and anal irritation that progressed in severity despite the use of numerous topical products and extended diaper-free periods. A topical cholestyramine ointment was compounded and administered, resulting in complete resolution within three days.

Six patients status post continent reservoir operation and ileoanal anastomosis developed severe perianal skin inflammation resistant to ordinary therapy. Twice daily treatment with cholestyramine ointment resulted in a “cure” within ten days.

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Dis Colon Rectum  30(2):106-107

**Misoprostol Suppositories for Prevention of Radiation Proctitis**

Radiation proctitis is a known complication of radiation therapy for prostate cancer. Available medical treatment is usually ineffective and has focused on relieving symptoms after damage has occurred. A prospective, randomized, placebo-controlled, double-blinded trial was conducted by the Department of Radiation Oncology, State University of New York Hospital at Stony Brook to evaluate the use of misoprostol rectal suppositories in the prevention of acute as well as chronic radiation proctitis symptoms. Patients (n=16) with recently diagnosed stages B and C prostate cancer who underwent external beam irradiation received either a misoprostol (n=9) or a placebo (n=7) suppository one hour before each radiation session. A 12-point radiation proctitis symptom score was obtained from each patient at 4, 8, 12, and 36 weeks after radiation therapy, and the difference between the two groups was statistically significant. The authors concluded that misoprostol rectal suppositories significantly reduce acute and chronic radiation proctitis symptoms in patients receiving radiation therapy for prostate cancer.


**A Leader in Customized Formulations For Hospice Patients**

The late Dr. W.I. Smith, former medical director of Hospice of Acadiana (Louisiana), locally pioneered many therapies that provide substantial pain relief and symptom management for terminally-ill patients. Following are several examples.

**Hydromorphone Sublingual Drops for pain control:** For patients who are unable to swallow, concentrated hydromorphone drops can be used buccally or sublingually. Hydromorphone drops can be used alone and titrated to achieve pain relief, or in conjunction with intravenous or transdermal opioids for breakthrough pain. Hydromorphone SL drops are quickly absorbed and provide rapid pain relief.

**Lorazepam Transdermal Gel for anxiety or terminal agitation:** Patients who are terminally ill and severely agitated may refuse oral medications. Trying to forcibly medicate them may only increase their anxiety. Patients are soothed when lorazepam transdermal gel is applied to the inner wrist or neck (carotid) region. The typical dose is 2mg (1ml) topically every four hours as needed for anxiety or agitation.

**BDR (Diphenhydramine 25mg, Dexamethasone 2mg, Metoclopramide 10 mg) Suppositories for nausea and vomiting:** This combination of medications that acts synergistically on the various vomiting centers has been very useful, particularly in patients who are nauseated or unable to swallow, or obstructed or NPO for other reasons. The suppositories are typically prescribed to be administered every four hours as needed for nausea and vomiting.

Dr. Smith was one of the first physicians in his region to prescribe customized dosages for his patients. Instead of using a medication that required the patient to swallow four to five tablets to receive the needed dose, he contacted his local compounding pharmacy to prepare a single formulation that contained the amount of drug that the patient needed. To simplify administration for patients who were unable to swallow, Dr. Smith frequently prescribed topical or transdermal medications for pain, inflammation, or control of symptoms such as nausea and vomiting.

*At our pharmacy, all prescriptions for compounded medications are prepared by specially-trained professionals using state-of-the-art equipment and the finest quality chemicals. We work together with physicians, nurses, patients, caregivers, and the entire palliative care team to customize medications that will meet each patient’s specific needs and solve problems. Your questions are always welcome.*