Pain Management Today

VOLUME 1, NUMBER 1 — CONTROLLING PAIN, IMPROVING LIVES

INSIDE THIS ISSUE

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NATIONAL INITIATIVE ON PAIN CONTROL

Opioid Analgesics in Nonmalignant Pain

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... pain is not well-managed and the JCAHO's concerns are well-founded.

THE CURRENT popularity of OxyContin® (oxycodone) as a drug of abuse has led to concerns that opioid analgesics are prescribed too frequently. Yet, juxtaposed against this growing concern are the new rules of the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) that address the significant undertreatment of pain.[1]

These guidelines, which elevate pain to a fifth vital sign, recognize that the undertreatment of pain is a significant problem that requires regulatory oversight. When one considers that 50% of patients dying with cancer still suffer moderate-to-severe pain,[2] it is clear that pain is not managed well and that the JCAHO's concerns are well-founded. Ironically, the fear of regulatory oversight led to the undertreatment of pain. Physicians are worried that prescribing opioid analgesics will put them at risk of being investigated by the Drug Enforcement Agency (DEA) or their state medical board.[3-5] Importantly, both the DEA and state medical boards recognize that opioid analgesic therapy can be used appropriately in patients with nonmalignant pain.

In addition to regulatory concerns, a number of other barriers prevent the appropriate management of pain. Education is first among these: little time is spent during medical school or residency training programs studying the assessment and treatment of chronic pain syndromes; still less time is allocated to the appropriate use of opioid analgesics. In a society that is very concerned about addiction, very little time has been given to

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Topical vs Transdermal Medications

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Recently several drugs have become available in the form of patches that can be absorbed into or through the skin. Other similar agents that can be used in topical application are creams, ointments, gels, or lotions. Each of these drugs will have different effects depending on the absorption dynamics of the product.

Thus, the terms topical and transdermal, which are not necessarily new terminology, reflect potentially significant differences.

Two skin patch formulations well illustrate the differences between topical and transdermal delivery: the Duragesic® patch offers transdermal delivery of fentanyl,[1] whereas the Lidoderm® patch offers topical delivery of lidocaine. Each is an adhesive patch applied to the skin.[2]

The critical difference is that the transdermal product (fentanyl) delivers clinically relevant amounts of the drug into the systemic circulation. The topical product (lidocaine patch 5%) delivers clinically relevant doses into the tissue directly below the patch and, at suggested dosages, may have no systemic effects.[2,3] In the case of transdermal fentanyl, the tissue under the patch serves as an entry port

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LETTER FROM THE CO-CHAIRMEN

Dear Colleague,


Dr. Katz


Dr. Dworkin

The inaugural issue of *Pain Management Today*, the Newsletter Series of the National Initiative on Pain Control™ (NIPC™), is one component of the NIPC's educational programs for physicians who treat patients with pain.

This publication was designed to be clinically useful in your day-to-day practice by providing the latest information on novel approaches to assessing and managing pain. The articles, written by the distinguished members of the NIPC's education council and faculty, are timely and relevant in addressing treatment issues such as the controversial use of opioids in noncancer pain, the differences between transdermal and topical medications, and the mechanisms of neuropathic and nociceptive pain.

As described in its mission, the NIPC is dedicated to heightening the knowledge of physicians and other healthcare providers about the serious impact of unresolved pain on patient care. We believe that we can further this goal by increasing clinicians' understanding of the nature and treatment of pain, as well as the impact of chronic pain on their patients' health and psychological well-being. The goals of the NIPC are listed below this letter.

In summary, physicians can make a difference in their patients' quality-of-life. We hope you find our educational newsletter to be a valuable aid in your practice.

On behalf of all the NIPC members, we would like to express my appreciation to Endo Pharmaceuticals Inc. for providing the unrestricted educational grant that made this publication a reality.

Sincerely,

Nathaniel P. Katz, MD
NIPC Co-chairman

Robert H. Dworkin, PhD
NIPC Co-chairman

PROGRAM GOALS

- Elevate the importance of managing the patient with pain, by heightening physician and healthcare provider awareness of the impact of pain on the patient's daily living in terms of quality of life, lost workdays, and societal/familial consequences.
- Expand physicians' basic understanding of pain etiology, to empower physicians to differentiate types of pain, resulting in improved precision in diagnosis and therapeutic decisions.
- Provide physicians with the latest advances and strategies in pain management (medications, delivery systems, compounding, and mechanisms of action), and translate clinical data into clinical practice utility.
- Emphasize importance of tolerability, safety, and nontoxicity in selecting effective pain therapies. Address cost-effective issues.
- Address barriers to achieving pain control and common misconceptions about the use of pain therapies.
- Provide physicians with patient education tools that improve the channels of communication between the physician/healthcare provider and patient.

Mechanisms-based Diagnosis and Treatment of Pain

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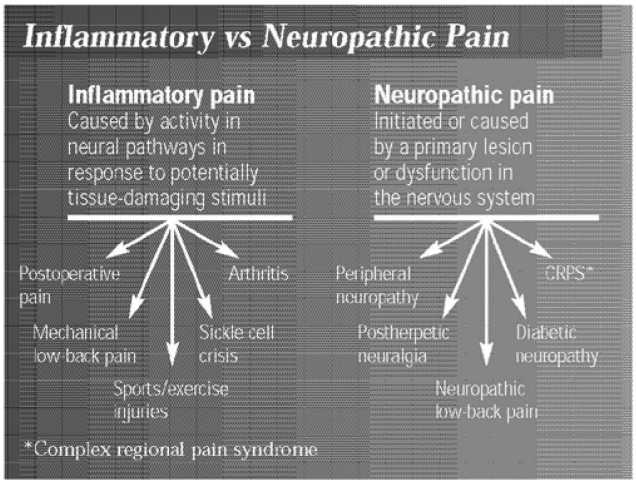
Pain is a complex clinical phenomenon. In most circumstances, pain is a symptom when it happens acutely, but a disease when it presents chronically.

Chronic pain affects the entire body in the same way as conditions such as diabetes and hypertension. The chronic pain affects the whole person. In this sense, chronic pain is attention-grabbing: patients constantly know they are in pain. To diagnose chronic pain, the whole patient must be considered, which can make a difference in how to treat the patient.

In the most general terms, the mechanisms-based diagnostic process starts with establishing the etiology and evaluating the patient for evidence of the mechanism of pain. The next step is assessing the psychological impact of pain on a patient's well-being and overall function.

From a pathophysiological prospective of pain diagnosis, a high degree of certainty is clinically possible when distinguishing between the two major categories of pain: inflammatory pain and neuropathic pain. The figure (upper right) summarizes the differences between inflammatory and neuropathic pain and lists examples of each type of pain. Important diagnostic and therapeutic clinical implications can be drawn from this mechanisms-based distinction. Taking a patient history and conducting a physical examination will show abnormal neurological results in patients with neuropathic pain; however, the results of a neurological examination are normal in cases of inflammatory pain (except for symptoms of hypersensitivity specifically in the area of pain). The therapeutic implication is that inflammatory pain disorders readily respond to opioids, but painful neuropathic disorders are better controlled by adjuvant analgesics, otherwise considered neuromodulators.[1]

The basic science of the pathophysiological mechanisms underlying neuropathic pain were only recently described after the development of animal models of pain. These processes can be characterized as peripheral sensitization and central sensitization depending where on the neuraxis the abnormal physiological and biochemical processes occur.[2]



Abnormalities of Neuropathic Pain

Inflammatory and neuropathic pain share some similarities, such as the release of inflammatory substances in the peripheral nervous system and the activation of N-methyl D-aspartate (NMDA) receptors in the central nervous system. The figure (below) illustrates the similarities. However, major abnormalities related to nerve damage and incomplete repair of the nervous system occur with neuropathic pain. For example, damaged nerves are characterized by:

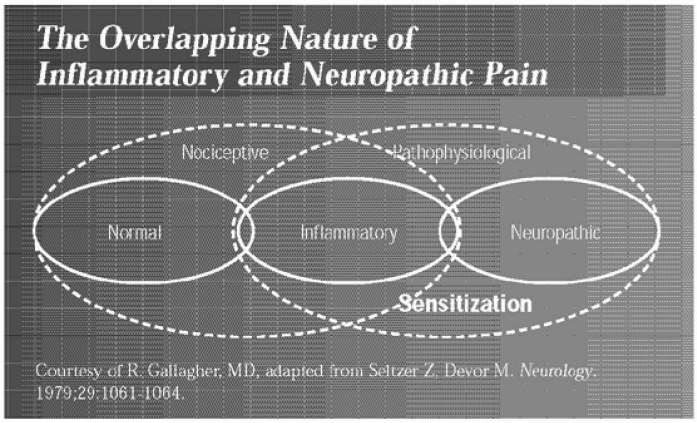
- The formation of neuromas, which are mechanosensitive and chemosensitive
- Ectopic discharges of irritated nociceptors
- Crosstalk or ephaptic transmission between injured and regenerating neurons.

In addition, large fibers, which evoke innocuous sensations such as a tickle when activated under normal circumstances, undergo a phenotypic switch during neuropathic pain and thereby behave like pain fibers and evoke pain. Damage to nerve fibers and pain result in loss of inhibitory interneurons and a loss of inhibition of pain.[2] This loss is one reason why much larger doses of opioids are needed to control neuropathic pain.

Knowing this makes it much easier to understand why patients with neuropathic pain with numbness can simultaneously experience hyperalgesia. We now have more specific treatments and the means for developing them beyond the traditional analgesics.

Physicians can assess patients with neuropathic pain according to standard pain assessment tools such as the Short-Form McGill[3] and Brief Pain questionnaire.[4] In addition, clinicians can use more specific pain questionnaires such as the Neuropathic Pain Scale[5] or LANSS despite their limitations.[6] But fundamental to any pain assessment is taking seriously the patient's pain report. Positive response to a medication with a specific mode of action can further support the postulated mechanism underlying the chronic pain.

With the improvement in the assessment of pain and more specific diagnosis, we will be able to provide our patients with a higher degree of pain relief.



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Opioid Analgesics in Nonmalignant Pain

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the assessment and appropriate management of addiction disorders.[4,6-14] As the JCAHO guidelines take effect, medical schools and residency training programs will be forced to allocate more time to addiction and pain management.

Consequently, it is important to understand some key terms when prescribing opioid analgesics. These terms include addiction, physical dependence, tolerance, and pseudoaddiction. They are defined in the sidebar at the bottom of this page.

Good pain management, like good medical care in general, must be discernable in the medical record. Documenting the physician's thinking in a very clear and readable fashion is important in prescribing opioid medications. Documentation includes the pain history, pain assessment, and physical examination. The pain should be characterized by its qualities (eg, sharp, shooting, lancinating, burning, tingling) in order to discern a presumed pain pathophysiology (ie, nociceptive or neuropathic) and pain etiology. Diagnostic tests should be reviewed and discussed, as must a differential diagnosis, how the ultimate diagnosis was determined and whether the disorder is curable. Previous treatment modalities, including primary treatments, should be reviewed. The prior medical record must also be reviewed and the patient's history and treatment should be discussed with their previous physicians.

The Underutilized Resource

Pharmacists are often an underutilized resource for managing chronic pain. They are often the first healthcare provider to know when a patient may be misusing a medication. So checking with a patient's pharmacy about concerns over aberrant drug use, especially obtaining the same or similar drugs from more than one physician, is a reasonable procedure.[5]

It is also important to determine if the individual is at a high or low risk for addiction.[15-16] One must ask about a personal or family history of alcohol or drug abuse. The medical record should reveal that a discussion of opioid side effects, including the risk of addiction, has occurred.

Part of the decision to use opioid analgesics is demonstrating in the medical record that other modalities were employed and failed to control the pain and that medical evidence exists that the pain syndrome is likely to be opioid responsive. The other modalities should include adjuvant and nonopioid analgesics as well as attempts at primary therapy. Further, the management of chronic pain requires an interdisciplinary approach that includes physical therapy and behavioral and cognitive therapies. Lifestyle changes and education should also be an important part of pain management.

Some pain specialists believe that a written agreement is helpful in making sure that the patient is compliant with medications. These agreements specify rules for treatment and discuss the consequences of aberrant behaviors. Other physicians do not support the use of these agreements. In either case, it is important to make clear to patients and their families that opioid analgesics are controlled substances that should be taken carefully according to specific rules. These rules include:

- The patient will not call in early for prescriptions and not call after the prescribing physician's office hours.
- Patients can receive prescriptions for their analgesic medication from only one physician and get them filled at only one pharmacy.
- Patients should not increase the medication without prior approval from the prescribing physician.
- The medication should only be used for the purposes of pain control.
- The medication cannot be sold or shared.

If the rules are broken the opioid analgesic should be stopped. Patients are then required to make weekly visits to their physician to have a urine toxicology screen, the opioid may be prescribed on a weekly basis, and treatment by an addiction specialist may be necessary.

Dosing Opioid Analgesics

Opioids are indicated for moderate-to-severe pain. Once the decision has been made to start an opioid analgesic, patients should initially be given a low dose. Starting with a low dose and increasing the dose slowly can prevent adverse effects. The dose should be given around-the-clock with extra medication available for breakthrough pain. The dose is increased slowly until analgesia is achieved or dose-limiting side effects occur. Side effects can be treated (eg, nausea with an antiemetic), or the patient can be switched to another

KEY TERMS FOR OPIOID ANALGESICS

Addiction for the purposes of pain management is often defined as using a drug despite the harm it is causing to one's life, use of a drug for other than its intended medical purposes, and loss of control over taking the drug. An important characteristic of addiction is that an alteration occurs in the function of the central nervous system which some individuals find desirable. This change leads to behaviors to obtain the drug and cravings for the drug.

Physical dependence means that suddenly stopping an opioid or reversing an opioid agonist by administering an opioid antagonist will precipitate an abstinence syndrome. Neither physical dependence nor tolerance should be equated with addiction, although both can be part of addiction.

Tolerance means that the dose of a drug needs to be increased to achieve the same effect that was previously obtained at a lower effective dose. Tolerance develops to the changes in central nervous system (CNS) function that drug addicts seek (eg, getting "high"), and the patient now requires increasingly higher doses. But tolerance does not seem to develop as quickly to the analgesic effect of these medications.

Pseudoaddiction refers to behaviors that might seem aberrant, but actually indicate inadequate treatment of pain. The behaviors resolve when the pain medication is increased and appropriate analgesia is obtained.[1-6]

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opioid analgesic. When switching from one opioid to another, it is important to calculate the equianalgesic dose and then cut back by 50% for most opioids and by 75% for methadone.[17-22] The goal is to have around-the-clock dosing with a long-acting opioid supplemented by a short-acting opioid for breakthrough pain.

After opioid analgesic therapy has been initiated, follow-up visits should also be well documented in the medical record.[23] One simple method is called the four A's, which stand for analgesia, adverse events, activity level, and addiction. Pain intensity is one method of assessing analgesia. The intensity of pain can be determined by having the patient state on a zero (no pain) to 10 (worse pain imaginable) scale how bad their pain is at the moment, the worse it has been during the week, the least it has been, and how much pain the patient has had on average. Another measure of analgesia is pain relief that can be indicated on a 0% (no pain relief) to 100% (complete pain relief) scale. Pain control can also be a good measure of analgesia. For example, is the pain under excellent, good, fair, poor, or no control. Because analgesia always exists in a balance with side effects, it is also very important to ask the patient whether they would like better pain control and whether the pain medication needs to be adjusted.

The second A is for adverse effects or side effects. Opioid analgesics have a number of troubling side effects, so it is important to ask the patient about these.

The third A is for activity level, which is a good measure of the success of pain management. It is important to ask whether activity level has increased, decreased, or stayed the same.

The last A is for addiction, which can be assessed by the physician's experience of the patient's care. Has the patient followed the rules well or do they consistently test the limits? It is reasonable to ask patients if they are addicted to the medication, if they are using it for any other purpose than pain control, whether they find themselves taking rescue doses even when they are not in pain, and whether they are sharing or selling the medication.

Involve the Family

Finally, for assessing the success of pain management and for evidence of aberrant drug use, it is reasonable to have the patient bring a family member, spouse, or friend to an office visit. Individuals often have people who care about them and are willing to confirm the patient's experience or challenge the patient's report. For example, a family member may report that the patient really is not taking the medication as directed and is undermedicating for any reason, including intolerable side effects. Or a husband might state that he is concerned that his wife sleeps all the time. Sometimes these people wrongly assume that any use of an opioid analgesic means that the patient is addicted. Educating the patient's support system can be very helpful in improving compliance and limiting stress.

It is reasonable to ask patients if they are addicted to the medication, if they are using it for any other purpose than pain control, whether they find themselves taking rescue doses even when they are not in pain, and whether they are sharing or selling the medication.

The following question is central to pain management: how can one safely prescribe strong analgesics to patients who could benefit from these agents and also satisfy a cardinal moral and ethical imperative to relieve suffering while not being duped by individuals seeking these medications for aberrant purposes? The answer is to develop good practice habits and make sure that these habits are reflected in the medical record.

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REVIEW OF RECENT MEDICAL LITERATURE:

Developments in Managing Chronic Pain

This summary of recently published articles in peer-reviewed medical journals focuses on information that could affect the practices of physicians who treat patients with chronic pain. These articles discuss the treatment, diagnosis, and assessment of several types of chronic pain. The topics reviewed in these articles include the use of long-term opioids for chronic pain, other options in chronic pain therapy, the diagnosis of diabetic neuropathy, and pain-management scales.

Physicians who are interested in these subjects are advised to consult the full articles. Inclusion of an article in this summary should not be construed as a recommendation by the National Initiative on Pain Control™.

Treatment of Chronic Pain

Recent articles reviewed the use of long-acting opioids for chronic pain and advances in treating neuropathic pain.

McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther.* 2001;8:181-186.

The authors discuss the treatment of chronic pain with opioid agonists, which they describe as controversial even though these agents are considered to be "among the most effective analgesics available for reducing pain perception." The article states that, "Short-acting opioids provide effective analgesia for acute pain but should be avoided as primary analgesics for chronic pain management. Long-acting opioids have greater utility than short-acting opioids in treating chronic pain in patients with consistent pain levels. Results of studies show that improved quality of life is directly related to the use of long-acting opioids in patients with chronic pain of both cancer and noncancer etiology."

Carter GT, Galer BS. Advances in the management of neuropathic pain. *Phys Med Rehabil Clin N Am.* 2001;12:447-459.

The authors reviewed the research, patient assessment, and treatment progress achieved during the past 5 years for neuropathic pain. They focused on the use of new treatments, especially the anticonvulsant gabapentin and the topical lidocaine patch 5%, for neuropathic pain. They conclude that, "The available clinical trial data indicate that newer antiepileptic drugs, most notably gabapentin, are better alternatives to older medications such as carbamazepine or phenytoin in the treatment of neuropathic pain."

In addition, the authors contend that, "With the advent of the topical lidocaine patch, the first drug with an FDA-approved indication for postherpetic neuralgia, a revolutionary new agent is now available for the treatment of neuropathic pain that does not have any systemic side effects."

Two nonpharmaceutical methods for treating chronic pain are implanted, continuous flow infusion pumps and spinal cord stimulation with electricity or a pulse generator. The successful use of both methods has been discussed in a number of articles. A summary of one article on spinal cord stimulation follows.

Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med.* 2000;343:654-656

The authors conducted a randomized trial in 36 patients who received either spinal cord stimulation or physical therapy for complex regional pain syndrome, which is a painful, disabling disorder that does not have a proven treatment. Stimulation was successful in 24 patients, and a statistically significant number of the patients were much improved (P=0.01). The authors concluded that "electrical stimulation of the spinal cord can reduce pain and improve the health-related quality of life."

Diagnosing Neuropathic Pain

Several diagnostic tests and procedures have recently been evaluated in the clinical literature. One evaluation attempted to develop recommendations for screening tests for diabetic neuropathy.

Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care.* 2001;24:250-256.

According to the authors, clinical practice guidelines lack the clinical evidence to recommend screening tests for diabetic neuropathy. The authors, therefore, sought to evaluate four "rapid and reliable sensory tests" that would be "appropriate for the diagnosis of neuropathy in the diabetes clinic." The four tests are the 10-g Semmes-Weinstein monofilament examination (SWME), superficial pain sensation, vibration testing by the on-off method, and vibration testing by the timed method. The tests were independent blinded evaluations and were administered to 478 subjects and compared with the standard of nerve conduction studies. Based on the results of their evaluation, the authors concluded that, "Annual screening for diabetic neuropathy should be conducted using superficial pain sensation testing, SWME, or vibration testing by the on-off method."

Pain Assessment Scales

Pain scales that assess the extent and degree of patients' pain have become a tool of patient management. The current standard scale for neuropathic pain is the Neuropathic Pain Scale (Galer BS, Jensen MP. *Neurology.* 1997;48:332-338). The scale relies on patients' descriptions of their pain. The descriptions include "intense," "sharp," "itchy," and "deep." A new scale that was evaluated recently in a clinical trial is the Amsterdam Pain Management Index. Another clinical study compared the effectiveness of diagnosing pain by asking patients about their pain or using pain scales.

de Wit R, van Dam F, Loonstra S, et al. The Amsterdam Pain Management Index compared to eight frequently used outcome measures to evaluate the adequacy of pain treatment in cancer patients with chronic pain. *Pain.* 2001;91:339-349.

The recently developed Amsterdam Pain Management Index evaluates the effectiveness of cancer pain treatment by comparing patients' present pain intensity, average pain intensity, and worst pain intensity with a composite score of analgesics used. The index then corrects for what a patient considers as a tolerable level of pain.

This trial compared the Amsterdam index with eight frequently used outcome measures. The randomized controlled trial involved 313 cancer patients with pain for at least 1 month and questioned the patients three times during the 2 months after their hospital discharge. The researchers concluded, "The test of known-groups comparisons and equivalence between groups indicated that the Amsterdam Pain Management Index showed promising results."

Kamel HK, Phlavan M, Malekgoudarzi B, et al. Utilizing pain assessment scales increases the frequency of diagnosing pain among elderly nursing home residents. *J Pain Symptom Manage.* 2001;21:450-455.

The researchers studied the effectiveness of two types of pain assessment: asking residents of nursing homes, "Do you have pain?" or assessing pain according to three pain scales: the visual analog scale, the behavior (faces) scale, and the pain descriptive scale. A total of 305 residents in skilled nursing facilities in New York and Missouri participated in the study.

A significantly greater number of patients were diagnosed with pain in the group evaluated by the pain scales (P<0.01) than among patients who were asked if they had pain.

Topical vs Transdermal Medications

Continued from page 1

into the body allowing fentanyl to pass through the dermis and into subcutaneous tissues. Fentanyl's lipophilic nature allows it to be selectively absorbed into subcutaneous fat, which then serves as a conduit for slow release into the general circulation. The area to which the patch is applied does not need to be the same as the targets that the drug seeks to affect.[1]

In contrast, topical delivery systems such as the lidocaine patch 5% are geographically targeted so that the area of application on the skin directly corresponds to the tissue needing treatment. The drug is formulated to allow lidocaine to penetrate through the epidermis and into the dermis with minimal further passage into the subcutaneous tissues. Therefore, the systemic absorption of lidocaine patch 5% is approximately 1% to 5% of the dose. With the use of three or fewer patches for no more than 12 hours per day, systemic levels have been found to be minimal, even after repeated applications and maximum daily dosing.[2]

Topical vs Transdermal: Opposite Profiles

In summary, the topical application can offer concentrated effects on a local area related to the skin without clinically relevant systemic effects, whereas transdermal delivery can offer the opposite profile of relevant systemic levels without significant local effects. The table summarizes the differences between the two types of delivery systems.[2,3]

Although the analgesic products Duragesic® and Lidoderm® exemplify the differences between topical and transdermal drug delivery, other agents are currently being used for similar purposes. Clonidine, which is available as a topical patch, offers transdermal delivery but also may have topical effects. Thus, patients using the patch* for pain relief may place it on the skin near the area of pain, whereas patients using it for hypertension may place it anywhere.[4,5] Capsaicin cream, a derivative of chili peppers that can deplete substance P from nerve terminals in the skin, can be an effective topical analgesic agent. However, application can be problematic for some patients because of capsaicin's initial burning effects on certain affected skin or other tissues.[6] There is also a trend in pain medicine towards compounding special combinations of analgesic agents in creams, lotions, or gels that can be applied to the skin near symptoms. Compounded preparations have included almost any combination of drugs, including nonsteroidal anti inflammatory drugs, amitriptyline, gabapentin, ketamine, clonidine*, and many others.[5,7-9] Anecdotal reports suggest efficacy; however, the systemic absorption of these drugs may be possible and is potentially difficult to quantify and modulate. Nonetheless, compounded preparations represent an important area of drug delivery.

Topical and transdermal drug delivery systems can be effective routes of drug administration. Understanding the different and sometimes overlapping properties of these systems will help clinicians maintain efficacy and safety.

Topical vs Transdermal Drug Delivery Systems

Characteristic	Topical (eg, lidocaine patch 5%)	Transdermal (eg, fentanyl patch)
Site of activity	Peripheral tissue	Systemic
Placement	Directly over painful site	Arbitrary
Serum level	Insignificant	Necessary
Systemic side effects	Unlikely	Possible

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*Not approved by FDA for this use.

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