Tricyclic antidepressants (TCAs) have been used systemically for chronic pain treatment for more than 40 years and have been shown to produce analgesia in a wide variety of animal models, including nociceptive, inflammatory, and more recently, neuropathic pain models. Traditionally, TCAs have been considered to act with a central mode of action, within the spinal cord and at supraspinal sites, but recent evidence indicates that TCAs also work peripherally to produce analgesia.

Our investigations in 1999 were among the first to demonstrate that local peripheral administration of antidepressants produces analgesia in the formalin model of tonic pain, a preclinical model involving inflammation and central sensitization. Following formalin injection in animals, there is a characteristic biphasic expression of behaviors, including flinching, shaking, biting, and licking of the injected hind paw. The initial studies showed that coadministration of amitriptyline with the formalin suppressed these behaviors. The drugs were found to exert a local rather than systemic action; no effect was observed with injections into the opposite hind paw. These findings suggest these agents could be developed as topical formulations (eg, cream or gel formulations) to recruit peripheral antinociceptive actions in chronic pain states. Subsequent investigations have shown that several antidepressants are active in the formalin test, including desipramine, nortriptyline, doxepin, and fluoxetine—with all agents acting locally rather than systemically. All agents showed a similar potency and efficacy in suppressing formalin-evoked responses (Figure 1).

In addition to this inflammatory model, we have also administered antidepressants peripherally, using...
neuropathic pain models. Following the ligation of spinal nerves, applying a noxious thermal stimulus to the rat hind paw produces a hyperalgesic response; when a mild mechanical stimulus is applied, an allodynic response is indicated. The thermal hyperalgesia response is mediated by C-fibers. This model demonstrated a complete reversal of hyperalgesia, which was long-lasting and entirely peripherally mediated, following local administration of amitriptyline. Similar results have been observed in a model of diabetic neuropathy.

PERIPHERAL MODE OF ACTION

Antidepressants block the reuptake of noradrenaline and 5-hydroxytryptamine (5-HT); have direct and indirect actions on opioid receptors; inhibit histamine, cholinergic, 5-HT, and N-methyl-D-aspartate glutamate receptors; inhibit ion channel activity; and block adenosine uptake (Table). The contributions of these different actions have been appreciated over time. A variety of adverse events result from this broad range of pharmacologic actions: sedation is due to blockade of central histamine receptors, whereas orthostatic hypotension results from blockade of peripheral alpha-adrenergic receptors; dry mouth, blurred vision, and constipation result from blockade of muscarinic receptors.

Following the demonstration of peripheral analgesic efficacy with TCAs, the question of mechanism arose, because this class of drugs produces multiple pharmacologic actions. A blockade of opioid receptors produced no role in these actions. Further investigation compared the effect of amitriptyline to mepyramine (a histamine H1 receptor blocker), to mecamylamine (a nicotinic cholinergic receptor blocker), to atropine (a muscarinic cholinergic receptor blocker), to phentolamine (an alpha-adrenergic receptor blocker), and to a range of compounds that block multiple 5-HT receptors. These agents generally produced some peripheral analgesic activity against formalin-evoked behavior, but amitriptyline was significantly more potent than these other agents. Although mimicry of the action of amitriptyline by these agents is necessary to consider causality, it is not sufficient to establish that a particular mechanism is involved in the action of amitriptyline.

| Table. Mechanisms of Action of Antidepressants: A Timeline of Appreciation of Pharmacologic Actions |
| 1960-1980 | Block of uptake of noradrenaline/5-HT Receptor upregulation/downregulation |
| 1980s | Mu-opioid receptor interactions Block of H1, alpha, 5-HT, muscarinic/nicotinic cholinergic receptors Block of NMDA receptors |
| 1990s | Block of Na+ channels Interactions with adenosine |

5-HT = 5-hydroxytryptamine; NMDA = N-methyl-D-aspartate.
Investigations of the local anesthetic properties of antidepressants have used a model in which amitriptyline or bupivacaine, a long-lasting local anesthetic, was injected adjacent to the sciatic nerve. Motor, proprioceptive, and nociceptive functions were then measured, and findings for the 2 drugs were compared. At 0.5% bupivacaine (approximately 15 mM), all functions were blocked for approximately 2 hours, with full recovery occurring by 3 hours. Amitriptyline also demonstrated blockade of all functions, with nociceptive blockade being somewhat delayed in onset, lasting longer at the lower dose (5 mM), and showing a time course similar to the other functions at the higher dose (10 mM; Figure 2). The investigators concluded that amitriptyline was acting as a local anesthetic, with greater potency than even bupivacaine.

Multiple adenosine receptors exert peripheral influences on pain signaling. Inhibitory adenosine A1 receptors on sensory nerve terminals cause analgesia, while A2 receptors on the nerve terminal actually facilitate the pain signal. Thus, 2 different adenosine receptors produce opposite effects on pain signaling, yet the affinity of adenosine for these 2 receptor systems is similar. Activation of A3 receptors on mast cells adjacent to the sensory nerve terminal exerts indirect effects on pain transmission.

Our research attempted to determine whether peripheral adenosine systems are involved in the action of amitriptyline. We applied adenosine receptor antagonists to determine whether they modified the activity of amitriptyline. Using the formalin model, caffeine (a nonselective adenosine A1 and A2 receptor antagonist) administered with amitriptyline blocked the analgesic effect of amitriptyline. Similar results were observed using cyclopentyltheophylline, a selective adenosine A1 receptor antagonist, in combination with amitriptyline (Figure 3). Comparable results were obtained using neuropathic pain models. These observations support other reports demonstrating that caffeine can block the action of TCAs when both drugs are given systemically.

Figure 2. Impact of Amitriptyline on Motor, Proprioceptive, and Nociceptive Functions

Figure 3. Suppression of Local Analgesia by Amitriptyline with Adenosine Receptor Antagonists Using the Rat Formalin Model
Clinical investigations suggest that antidepressants may be useful as analgesics following topical application and, perhaps, other methods of local delivery. Thus, doxepin produces a peripheral analgesia following local application in neuropathic pain in human trials. The antidepressant doxepin is available as a cream for treatment of eczema but has not been approved for use as an analgesic. Current investigations into the topical use of antidepressants show great promise. The multimodal action of this drug class may recruit multiple mechanisms that act to suppress pain, creating a peripheral autosynergistic drug effect. We are exploring additional mechanisms of action within this drug class to allow for optimal analgesia and to minimize drug dosages and adverse effects.

**Other Topical Analgesics**

**Nonsteroidal Anti-inflammatory Drugs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) act peripherally to reduce the production of prostaglandins that sensitize nerve endings at the site of injury, generating analgesic effects. A newer strategy has been the development of topical formulations of NSAIDs to minimize systemic absorption and consequent adverse drug effects. Bioavailability and plasma concentrations following topical application are 5% to 15% of those achieved by systemic delivery. Relatively high concentrations occur in the dermis, whereas levels in the muscle are at least equivalent to those following systemic administration.

The efficacy of topical NSAIDs as analgesics has been the subject of several recent reviews. One study reported the efficacy of NSAIDs in musculoskeletal and soft-tissue injuries as well as rheumatic diseases, another accessed a database of more than 10,000 patients, and a third review examined efficacy in chronic rheumatic diseases. These reports suggest clear evidence that topical NSAIDs are effective analgesics and may be given by gel, spray, or patch in soft-tissue injury conditions. In arthritis, however, the effects of topical NSAIDs are modest and highly variable, possibly related to the patient's use of rescue medications as well as variability in percutaneous absorption rates. Topical NSAIDs are associated with both cutaneous and systemic adverse reactions. Cutaneous reactions are more common and include rash and pruritus at the site of application; systemic effects include gastrointestinal reactions.

**Opioids**

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

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

**Capsaicin**

Capsaicin, derived from red chili peppers, is analgesic following topical application and is commercially available. Depending on the concentration used and the mode of application, capsaicin can selectively activate or desensitize sensory afferent nerves. At a molecular level, capsaicin activates vanilloid-1 ligand-gated cation channels and allows for Ca2+ entry, neuronal activation, and peptide release from both peripheral and central terminals of sensory neurons. Desensitization occurs with repeated administration of capsaicin. This desensitization involves Ca2+ and calmodulin-dependent processes and phosphorylation of the cation channel.

Randomized, placebo-controlled studies, open-label trials, and clinical reviews all report capsaicin-induced analgesia. However, even placebo-controlled trials of capsaicin have been impossible to blind due to the burning sensation caused by this agent. Capsaicin typically results in modest pain relief in the treatment of a variety of pain conditions, including postherpetic neuralgia, diabetic neuropathy and trigeminal neuralgia, osteoarthritis, and cutaneous conditions. Although some patients experience greater benefits compared with other patients, capsaicin is usually considered as an adjuvant to other pain therapies. The most frequently reported adverse event is burning pain at the site of application.
which contributes to patient nonadherence. Delayed onset of efficacy (1 or more weeks) has also impaired adherence, but administration of higher capsaicin concentrations applied under regional anesthesia has been reported as an effective option.40

**Local Anesthetics**

Local anesthetics that block voltage-gated sodium channels have long been used during surgical procedures to abolish pain temporarily by blocking nerve conduction, but local anesthetics are now being used as an effective treatment for many chronic pain conditions. Topical formulations of local anesthetics, which do not reach clinically significant blood levels, provide an alternative to systemic medications and reduce the risk of drug-drug interactions and adverse systemic drug events. Recently, clinical attention has focused on topical formulations of lidocaine as a 5% gel or patch. Both have been reported to provide effective pain relief in postherpetic neuralgia with no systemic adverse effects.41,42 A time-to-study-exit trial showed the lidocaine patch produced a significantly prolonged time to exit without systemic adverse effects.43 A later open-label study noted clinically meaningful pain relief in a variety of neuropathic pain conditions.44 This therapy has been proposed as a first-line agent for postherpetic neuralgia, particularly in elderly patients, who are more susceptible to drug-drug interactions and systemic adverse effects.

**Alpha-Adrenoceptor Agonists**

Clonidine, an alpha-adrenoceptor agonist used in the treatment of hypertension, is available as a patch for transdermal administration and has been used in patients with chronic pain conditions. The efficacy of local clonidine in sympathetically maintained pain may result from presynaptic inhibition of noradrenaline release from sympathetic nerves, as well as actions directly on primary afferent nerve terminals. Acting systemically, transdermal clonidine relieved symptoms of neuropathic pain in patients with diabetic neuropathy.45 Applied as a cream for local effects, it provides some relief from orofacial neuralgia-like pain.46

**Possibilities for the Future**

**Adenosine**

Intravenous infusion of adenosine has produced analgesia in experimental pain models as well as in acute perioperative pain and chronic neuropathic pain.47 Local peripheral administration of inhibitors of adenosine kinase also produces analgesia in models of inflammatory pain and neuropathic pain.10,48,49 These reports of adenosine producing a peripherally mediated analgesia suggest that topical formulations of either adenosine A1 receptor agonists or inhibitors of adenosine kinase may be worth further investigation. Peripheral adenosine kinase inhibitors may produce a direct effect on pain by actions on the sensory nerve terminal via A1 receptors as well as an indirect effect on the inflammatory process itself via A2 receptors.

**Glutamate Receptor Antagonists**

The systemic and spinal administration of glutamate receptor antagonists has been reported to produce analgesia in several chronic pain models, raising the possibility of developing these substances as a new class of analgesics. However, these agents have been associated with adverse motor and other effects,50,51 slowing the process of further clinical investigations. Preclinical laboratory investigations suggest the involvement of local release of glutamate and activation of both inotropic and metabotropic glutamate receptors in inflammatory pain in particular, suggesting that topical formulations of these agents may be worth investigating further.52

**Conclusion**

As we learn more about the biochemical and pathophysiologic mechanisms of pain, highly targeted strategies for specific conditions may soon be possible. The degree of involvement of inflammatory versus neurogenic components of pain may form the foundation for selecting an appropriate plan for pain management. For example, NSAIDs, or other therapies that primarily target inflammation, may be less effective in treating nerve injury pain, which may be more responsive to drugs that act directly on the sensory nerve to mitigate sensory afferent nerve activity. 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.
REFERENCES


