Therapeutic Class Overview
Topical Analgesics and Anesthetics

Therapeutic Class

- **Overview/Summary:** The topical analgesics and anesthetics are approved by the Food and Drug Administration (FDA) for a variety of indications. The anesthetic agents included within this review are lidocaine (AneCream®, Lidoderm®, LidoRx®, LMX 4®, LMX 5®,LTA 360 Kit®*, RectiCare®, Solarcaine®*, Xylocaine®), lidocaine/hydrocortisone , lidocaine/prilocaine (EMLA®), and lidocaine/tetracaine (Pliaglis®, Synera®).[1-8] These agents are indicated to alleviate itching and pain caused by insect bites, minor burns, sunburns, atopic dermatitis, hemorrhoids, or eczema. Lidocaine transdermal patch is indicated for the relief of pain due to post herpetic neuralgia and is the only topical anesthetic in the class to carry this indication.[1-8] The combination lidocaine/prilocaine is FDA-approved to provide analgesia on genital mucosal membranes for superficial minor surgery as well as pre-treatment for infiltration anesthesia (EMLA®).[6] Lidocaine/tetracaine is FDA-approved for analgesia for superficial venous access and superficial dermatological procedures, with Synera® being indicated for children three years of age or older.[7,8] Lidocaine and prilocaine are amide-type local anesthetic and tetracaine is an ester-type anesthetic. Theyare believed to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.[1-8] Hydrocortisone acetate provides relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.[3] The absorption of lidocaine following topical application is sufficient to produce analgesia, but less than the amount necessary to produce a complete sensory block.[1-8]

  Nonsteroidal antiinflammatory drugs (NSAIDs) primary act via inhibition of cyclooxygenase (COX), thereby preventing the transformation of arachidonic acid to inflammatory prostaglandins, prostacyclin, and thromboxanes.[9-11] The COX enzyme exists as two isoforms, COX-1 and COX-2. The antiinflammatory properties of NSAIDs are associated with the inhibition of COX-2, which is primarily expressed during states of inflammation. COX-1 is expressed in most tissues and regulates normal cellular processes including gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function. The inhibition of COX-1 is believed to be associated with the adverse event profile of NSAIDs, including an increased risk of gastroduodenal erosions, bleeding, development of colon cancer and bronchoconstriction.[9-11] Oral NSAIDs are effective in the treatment of moderate to severe pain, but are associated with an increased risk of several gastrointestinal and cardiovascular adverse events. The NSAID products as a class carry a Black Box Warning regarding the risk of cardiovascular and gastrointestinal adverse events associated with their use.[9-11] The use of topical NSAIDs applied directly to the affected area reduces overall systemic absorption and minimizes the risk of severe adverse events.[14] The topical NSAIDs include diclofenac epolamine (Flector®) and diclofenac sodium (Pennsaid®, Voltaren®). Topical diclofenac sodium come as different formulations and all have different indications. Pennsaid® is a topical solution that is indicated to treat the symptoms of osteoarthritis of the knee, while Solaraze® and Voltaren® are gels that are approved for the treatment of osteoarthritis on areas for which topical therapy is appropriate (knees and hands)[9,10] Pennsaid® is formulated in a dimethyl sulfoxide vehicle, which may enhance its absorption into joints.[12] Flector® patch is approved for the treatment of acute pain due to minor strains, sprains, and contusions.[11] The adverse events associated with the topical NSAIDs are typically dermatologic in nature and are self-limiting in most cases.[9-11] There are no topical diclofenac formulations available generically; however, various oral NSAIDs are available generically.

Table 1. Current Medications Available in the Therapeutic Class[1-13]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Diclofenac epolamine (Flector®)	Treatment of acute pain due to minor strains, sprains and contusions		-
Diclofenac sodium (Pennsaid®, Voltaren®)	Treatment of osteoarthritis pain of joints amenable to topical treatment,		-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	such as the knees hands[†], treatment of signs and symptoms of osteoarthritis of the knee(s)[‡]		
Lidocaine (AneCream®, Lidoderm®*, LidoRx®*, LMX 4®*, LMX 5®*,LTA 360 Kit®*, RectiCare®, Solarcaine®*, Xylocaine®*)	For prevention and control of pain in procedures involving the male and female urethra[§], lubricant for endotracheal intubation[§], relief of pain associated with postherpetic neuralgia[‖], temporary relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures and similar conditions of the skin and mucous membranes[¶,#], topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract**, topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx[††,#]		✔
Combination Products			
Lidocaine/ hydrocortisone (LidoCort®)	Relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area		✔
Lidocaine/prilocaine (EMLA®*)	Provide local analgesia on intact skin, provide local analgesia on genital mucosal membranes for superficial minor surgery, pretreatment for infiltration anesthesia		✔
Lidocaine/tetracaine (Pliaglis®, Synera®)	local dermal analgesia for superficial venous access and superficial dermatological procedures[‡‡], local analgesia for superficial dermatological procedures[§§]		-

* Generic available in at least one dosage form or strength.
†Voltaren®.
‡Pennsaid®.
§Lidocaine jelly.
‖Lidoderm®.
¶Lidocaine cream.
#Lidocaine ointment.
**Lidocaine topical solution.
††Lidocaine viscous solution.
‡‡ Synera® only.
§§ Pliaglis® only.

Evidence-based Medicine

- In clinical studies comparing treatment with lidocaine/prilocaine, lidocaine and placebo, the lidocaine products did not consistently demonstrate significant improvements in pain scores compared to placebo.[21,22,31,32]

- The results of head-to-head studies comparing lidocaine/prilocaine cream to various lidocaine formulations have generally indicated a similar anesthetic effect between the treatments.[20,24,33] Lidocaine may reduce pain intensity compared to ethyl chloride vapocoolant spray and placebo in patients undergoing cannulation for dialysis (*P*=0.00 for both).[19]
- In patients with postherpetic neuralgia, treatment with lidocaine patches resulted in significant pain relief, higher rates of patient preference, less use of rescue medication and decreases in allodynia and neuropathic symptoms compared to treatment with placebo.[26,27]
- In patients who had experienced a sports-related sprain, strain, or contusion, there was a statistically significantly improvement in scores for pain and functioning following application of the diclofenac epolamine patch over 14 days (*P*=0.036 and *P*=0.048 respectively).[34] In a second study by Kuehl et al, patients with a minor soft tissue injury experienced an 18.2% reduction in visual analog scale pain scores following twice-daily application of the diclofenac epolamine patch compared to those receiving placebo for 14 days (*P*=0.002).[35]
- The efficacy and safety of the diclofenac gel has been evaluated in patients with osteoarthritis of the hands and knees. Study results consistently demonstrated a greater pain relief with diclofenac sodium gel compared to placebo.[28-32,34-36]
- In a study by Simon et al, patients treated with the topical diclofenac sodium solution achieved statistically significant reductions in pain scores compared to patients treated with placebo (-6.0 vs -4.7; *P*=0.015) and dimethyl sulfoxide alone (-6.0 vs -4.7; *P*=0.009); however, there was no statistically significant difference in pain scores compared to patients receiving diclofenac tablets (-6.0 vs -7.0; *P*=0.429).[37]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - For the initial management of osteoarthritis pain of the hand, topical capsaicin, oral or topical nonsteroidal antiinflammatory drugs (NSAIDs) or tramadol may be used. In patients >75 years of age, topical NSAIDs are preferred over oral formulations.[15]
    - For the initial management of osteoarthritis pain of the knee, acetaminophen, NSAIDs (oral or topical), tramadol or intraarticular corticosteroid injections may be used. In patients >75 years of age, topical NSAIDs are preferred over oral formulations.[15]
    - For the treatment of hemorrhoids, over-the-counter topical agents are recommended despite the lack of supportive data regarding their efficacy. Topical analgesics are useful for symptomatic relief of pain and itching.[13]
    - Corticosteroid creams may decrease local inflammation but long-term use of high potency corticosteroids should be avoided. There is no data to show that corticosteroids reduce hemorrhoid swelling, bleeding, or protrusion. More recent guidelines do not make a recommendation for pharmacotherapy.[13,14]
    - Tricyclic antidepressants, gabapentin and pregabalin are recommended as initial treatment options for postherpetic neuralgia. Topical lidocaine may be considered first-line for elderly patients, especially if there are concerns of adverse events with oral medications.[17]
- Other Key Facts:
    - Currently, most lidocaine products are available generically, including lidocaine patches; however, generic products are not available for certain lidocaine formulations and some combination products.
    - Pennsaid® is formulated in a dimethyl sulfoxide vehicle, which may enhance its absorption into joints; however, the clinical significance of this suggestion has not been established.
    - No comparative studies evaluating pain intensity with topical NSAID products are available.

References

1. Lidocaine ointment 5% [package insert]. Amityville (NY): Hi-Tech Pharmacal Co.; 2011 Sep.
2. AneCream® [package insert]. Knoxville (TN): Focus Health Group; 2011 Dec.
3. Lidocaine HCl 3% - Hydrocortisone Acetate 0.5% Creame [package insert]. San Fernado (CA): PharmaPure RX; 2011 Jun.
4. Lidoderm® [package insert]. Malvern (PA): Endo Pharmaceuticals Inc.; 2014 Jul.
5. Xylocaine® [package insert]. Lake Forest (IL): Oak Pharmaceuticals, Inc.; 2012 Jun.
6. EMLA® [package insert]. Lake Forest (IL): Oak Pharmaceuticals, Inc.; 2012 Nov.
7. Synera ® [package insert]. Souderton (PA): Galen US, Inc.; 2014 Mar.

8. Pliaglis® [package insert]. Fort Worth (TX): Galderma Laboratories, L.P.; 2010 Oct.
9. Voltaren® [package insert]. Chadds Ford (PA): Endo Pharmaceuticals Inc.; 2009 Oct.
10. Pennsaid® [package insert]. Hazelwood (MO): Mallinckrodt Brand Pharmaceuticals Inc.; 2014 Jan.
11. Flector Patch® [package insert]. Sanbonmatsu, Kagawa, Japan: Teikoku Seiyaku Co., Ltd.; 2011 Aug.
12. Galer BS. A comparative subjective assessment study of PENNSAID® and Voltaren Gel®, two topical formulations of diclofenac sodium. Pain Pract. 2011 May-Jun;11(3):252-60.
13. American Gastroenterological Association. Technical review on the diagnosis and treatment of hemorrhoids. Gastroenterology. 2004;126:1463-73.
14. Rivadeneira DE, Steele SR, Ternent C, Chalasani S, Buie WD, Rafferty JL, et al. Practice parameters for the management of hemorrhoids (revised 2010). Dis Colon Rectum. 2011 Sep;54(9):1059-64.
15. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):455-74.
16. American Academy of Orthopedic Surgeons: Clinical practice guideline on the treatment of osteoarthritis of the knee (non-arthroplasty). Rosemont (IL): 2013 [Guideline on the internet] [cited 2014 July 25] Available from: http://www.aaos.org/research/guidelines.
17. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010 Sep;17(9):1113-e88.
18. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2014 [cited 2014 Aug 14]. Available from: http://www.thomsonhc.com/.
19. Çelik G, Özbek O, Yılmaz M, Duman I, Özbek S, Apiliogullari S. Vapocoolant spray vs lidocaine/prilocaine cream for reducing the pain of venipuncture in hemodialysis patients: a randomized, placebo-controlled, crossover study. Int J Med Sci. 2011;8(7):623-7.
20. Koh J, Harrison D, Myers R, et al. A randomized, double-blind comparison study of EMLA® and ELA-Max® for topical anesthesia in children undergoing intravenous insertion. Pediatric Anesthesia. 2004;14:977-82.
21. Dutta A, Puri G, Wig J. Piroxicam gel, compared to EMLA cream is associated with less pain after venous cannulation in volunteers. Can J Anesth. 2003;50(8):775-8.
22. McCluskey A, Currer B, Sayeed I. The efficacy of 5% lidocaine-prilocaine (EMLA) cream on pain during intravenous injection of propofol. Anesth Analg. 2003;97:713-4.
23. Moppett I, Szypula K, Yoeman P. Comparison of EMLA and lidocaine iontophoresis for cannulation analgesia. Eur J Anaesthesiol. 2004;21:210-3.
24. Kuvaki B, Gokmen N, Gunenc F, et al. EMLA® does not permit pain-free retrobulbar injection. Acta Anaesthesiol Scand. 2003;47:739-41.
25. Herberger K, Krause K, Maier K, Zschocke I, Radtke M, Augustin M. Local anesthetic effects of Lidocaine cream: randomized controlled trial using a standardized prick pain. J Dermatolog Treat. 2012 Dec;23(6):437-42. doi: 10.3109/09546634.2011.593486. Epub 2011 Jul 31.
26. Devers A, Galer B. Topical lidocaine patch relieves a variety of neuropathic pain conditions: and open-label study. Clin J Pain. 2000;16(3):205-8.
27. Katz N, Gammaitoni A, Davis M, et al. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. Pain Medicine. 2002;3(4):324-32.
28. Galer B, Jensen M, Ma T, Davies P, Rowbotham M. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, three-week efficacy study with use of the neuropathic pain scale. Clin J Pain. 2002;18(5):297-301.
29. Galer B, Rowbotham M, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain. 1999;80:533-8.
30. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain. 2003;106:151-8.
31. Corkill A, Lavender T, Walkinshaw S, Alfirevic Z. Reducing postnatal pain from perineal tears by using lidocaine gel: a double-blind randomized trial. Birth. 2001;28(1):22-7.
32. Minassian V, Jazayeri A, Prien S, Timmons R, Stumbo K. Randomized trial of lidocaine ointment vs placebo for the treatment of postpartum perineal pain. Obstetrics and Gynecology. 2002;100(6):1239-43.
33. Hopper SM, McCarthy M, Tancharoen C, Lee KJ, Davidson A, Babl FE. Topical lidocaine to improve oral intake in children with painful infectious mouth ulcers: a blinded, randomized, placebo-controlled trial. Ann Emerg Med. 2014 Mar;63(3):292-9. doi: 10.1016/j.annemergmed.2013.08.022. Epub 2013 Nov 7.
34. Galer B, Rowbotham M, Perander J, Devers A, Friedman E. Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. Journal of Pain Symptom Management. 2000;19:287-94.
35. Kuehl K, Carr W, Yanchick J, Magelli M, Rovati S. Analgesic efficacy and safety of the diclofenac epolamine topical patch 1.3% (DETP) in minor soft tissue injury. Int J Sports Med. 2011 Aug;32(8):635-43.
36. Predel HG, Koll R, Pabst H, et al. Diclofenac patch for topical treatment of acute impact injuries: a randomized, double blind, placebo controlled, multicenter study. British Journal of Sports Medicine. 2004;38:318-23.
37. A 12-week, randomized, double-blind, multi-center, vehicle-controlled, parallel group study to assess the efficacy and safety of diclofenac sodium gel (DSG) 1% for the relief of signs and symptoms in patients with osteoarthritis of the knee. Novartis unpublished clinical trial. Study Number VOSG-PN-310. Available at: http://www.novartis.com.
38. An eight-week, multi-center, randomized, double-blind, placebo-controlled, parallel group trial of diclofenac sodium 1% gel in patients with primary osteoarthritis of the hand. Novartis unpublished clinical trial. Study Number VOSG-PE-315. Available at: http://www.novartis.com.

39. An eight-week, multi-center, randomized, double-blind, placebo-controlled, parallel group trial of diclofenac sodium gel 1% in patients with primary osteoarthritis of the hand. Novartis unpublished clinical trial. Study Number VOSG-PE-314. Available at: http://www.novartis.com.
40. A 12-week, randomized, double-blind, multi-center, vehicle-controlled, parallel group study to assess the efficacy and safety of diclofenac sodium gel 1% for the relief of signs and symptoms in patients with osteoarthritis of the knee. Novartis unpublished clinical trial. Study Number VOSG-PN-304. Available at: http://www.novartis.com.
41. Peniston JH, Gold MS, Alwine LK. An open-label, long-term safety and tolerability trial of diclofenac sodium 1% gel in patients with knee osteoarthritis. Phys Sports Med. 2011 Sep;39(3):31-8.
42. Hsieh LF, Hong CZ, Chern SH, Chen CC. Efficacy and side effects of diclofenac patch in treatment of patients with myofascial pain syndrome of the upper trapezius. J Pain Symptom Manage. 2010 Jan;39(1):116-25.
43. Altman RD, Dreiser RL, Fisher CL, Chase WF, Dreher DS, Zacher J. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. J Rheumatol. 2009 Sep;36(9):1991-9.
44. Simon LS, Grierson LM, Naseer Z, Bookman AA, Zev Shainhouse J. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared to those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. Pain. 2009 Jun;143(3):238-45.
45. Zacher J, Altman R, Bellamy N, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin. 2008 Apr;24(4):925-50.
46. Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomized placebo-controlled trials. Eur J Pain. 2007 Feb;11(2):125-38.
47. Green S, Buchbinder R, Barnsley L, et al. Nonsteroidal anti-inflammatory drugs for treating lateral elbow pain in adults. Cochrane Database Syst Rev. 2002;(2):CD003686.
48. Peniston JH, Gold MS, Wieman MS, Alwine LK. Long-term tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. Clin Interv Aging. 2012;7:517-23. doi: 10.2147/CIA.S35416. Epub 2012 Nov 20.
49. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17:76(20):1758-65.
50. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract. 2007 May-Jun;13(Suppl 1):S1-68.
51. Boulton AJ, Vinkik AL, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-62.
52. Dubinsky RM, Kabbani H, El-Chami, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2004;63:959.
53. Kalunian KC. Pharmacologic therapy of osteoarthritis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sep 8]. Available from: http://www.utdol.com/utd/index.do.

Therapeutic Class Review
Topical Analgesics and Anesthetics

Overview/Summary

The topical analgesics and anesthetics are approved by the Food and Drug Administration (FDA) for a variety of indications. The anesthetic agents included within this review are lidocaine (AneCream®, Lidoderm®, LidoRx®, LMX 4®, LMX 5®,LTA 360 Kit®, RectiCare®, Solarcaine®, Xylocaine®), lidocaine/hydrocortisone (LidoCort®), lidocaine/prilocaine (EMLA®), and lidocaine/tetracaine (Pliaglis®, Synera®).[1-8] These agents are indicated to alleviate itching and pain caused by insect bites, minor burns, sunburns, atopic dermatitis, hemorrhoids, or eczema. Lidocaine transdermal patch is indicated for the relief of pain due to post herpetic neuralgia and is the only topical anesthetic in the class to carry this indication.[1-8] The combination lidocaine/prilocaine is FDA-approved to provide analgesia on genital mucosal membranes for superficial minor surgery as well as pre-treatment for infiltration anesthesia (EMLA®).[6] Lidocaine/tetracaine is FDA-approved for analgesia for superficial venous access and superficial dermatological procedures, with Synera® being indicated for children three years of age or older.[7,8] Lidocaine and prilocaine are amide-type local anesthetic and tetracaine is an ester-type anesthetic. Theyare believed to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.[1-8] Hydrocortisone acetate provides relief of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.[3] The absorption of lidocaine following topical application is sufficient to produce analgesia, but less than the amount necessary to produce a complete sensory block.[1-8] Currently, most lidocaine products are available generically, including lidocaine patches; however, generic products are not available for certain lidocaine formulations and some combination products.

Nonsteroidal antiinflammatory drugs (NSAIDs) primary act via inhibition of cyclooxygenase (COX), thereby preventing the transformation of arachidonic acid to inflammatory prostaglandins, prostacyclin, and thromboxanes.[9-11] The COX enzyme exists as two isoforms, COX-1 and COX-2. The antiinflammatory properties of NSAIDs are associated with the inhibition of COX-2, which is primarily expressed during states of inflammation. COX-1 is expressed in most tissues and regulates normal cellular processes including gastric cytoprotection, vascular homeostasis, platelet aggregation and kidney function. The inhibition of COX-1 is believed to be associated with the adverse event profile of NSAIDs, including an increased risk of gastroduodenal erosions, bleeding, development of colon cancer and bronchoconstriction.[9-11] Oral NSAIDs are effective in the treatment of moderate to severe pain, but are associated with an increased risk of several gastrointestinal and cardiovascular adverse events. The NSAID products as a class carry a Black Box Warning regarding the risk of cardiovascular and gastrointestinal adverse events associated with their use..[9-11] The use of topical NSAIDs applied directly to the affected area reduces overall systemic absorption and minimizes the risk of severe adverse events.[12] The topical NSAIDs include diclofenac epolamine (Flector®) and diclofenac sodium (Pennsaid® Voltaren®). Topical diclofenac sodium come as different formulations and all have different indications. Pennsaid® is a topical solution that is indicated to treat the symptoms of osteoarthritis of the knee, while Voltaren® is a gel that is approved for the treatment of osteoarthritis on areas for which topical therapy is appropriate (knees and hands).[8-10] Pennsaid® is formulated in a dimethyl sulfoxide vehicle, which may enhance its absorption into joints.[12] Flector® patch is approved for the treatment of acute pain due to minor strains, sprains, and contusions.[11] The adverse events associated with the topical NSAIDs are typically dermatologic in nature and are self-limiting in most cases.[8-11] There are no topical diclofenac formulations available generically; however, various oral NSAIDs are available generically.

Consensus guidelines for the use of topical anesthetics are lacking, therefore, decision making regarding the use of these agents is based on patient-specific factors and available comparative efficacy data. Recent guidelines for the management of hemorrhoids do not make recommendations regarding pharmacotherapy; however, previously published guidelines note that topical analgesics are useful for symptomatic relief of pain and itching and corticosteroid creams may decrease local inflammation. There is no data to demonstrate that corticosteroids reduce hemorrhoidal swelling, bleeding, or protrusion.[13,14]

For the initial management of osteoarthritis of the hand, guidelines suggest topical capsaicin, NSAIDs (topical or oral) or tramadol be used, with topical NSAIDs preferred over oral NSAIDs in patients >75 years of age. Acetaminophen and intraarticular steroid injections may also be used as initial treatment in patients with osteoarthritis of the knee; however, topical capsaicin should not be use in these patients.[15] Guidelines by the American Academy of Orthopedic Surgeons recommend topical or oral NSAIDs or tramadol with symptomatic osteoarthritis of the knee, with a statement neither for nor against the use of acetaminophen, opioids, intraarticular corticosteroids, and other treatments.[16] In the elderly patient with postherpetic neuralgia topical lidocaine may be considered first-line, especially if there are concerns of adverse events with the use of oral medications.[17]

Medications

Table 1. Medications Included Within Class Review[1-11]

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Diclofenac epolamine (Flector®)	Nonsteroidal anti-inflammatory drugs	-
Diclofenac sodium (Pennsaid®, Voltaren®)	Nonsteroidal anti-inflammatory drug	-
Lidocaine (AneCream®, Lidoderm®*, LidoRx®*, LMX 4®*, LMX 5®*,LTA 360 Kit®*, RectiCare®, Solarcaine®*, Xylocaine®*)	Topical anesthetics	✔
Combination Products		
Lidocaine/hydrocortisone	Topical anesthetic/ corticosteroid	✔
Lidocaine/prilocaine (EMLA®*)	Topical anesthetics	✔
Lidocaine/tetracaine (Pliaglis®, Synera®)	Topical anesthetics	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-11]

Indication	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
For prevention and control of pain in procedures involving the male and female urethra			✔ (jelly)			
Lubricant for endotracheal intubation			✔ (jelly)			
Provide local analgesia on intact skin					✔	
Provide local analgesia on genital mucosal membranes for superficial minor surgery					✔	
Pretreatment for infiltration anesthesia					✔	
Relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area				✔		
Relief of pain associated with postherpetic neuralgia			✔ (topical patch)			
Temporary relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures and similar conditions of the skin and mucous membranes			✔ (cream and ointment)			
Topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract			✔ (topical solution)			
Topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx			✔ (viscous solution, ointment)			
Treatment of acute pain due to minor strains, sprains and contusions	✔					
Treatment of osteoarthritis pain of joints amenable to topical treatment, such as the knees hands		✔ (Voltaren®)				
Treatment of signs and symptoms of osteoarthritis of the knee(s)		✔ (Pennsaid®)				
Indicated for use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision,						✔ (Synera®)

Indication	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
electrodessication and shave biopsy of skin lesions						
Indicated for use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal						✔ (Pliaglis®)

In addition to their respective Food and Drug Administration-approved indications, the topical anesthetics may also be effective in the treatment of several other conditions. Lidocaine is used for the treatment of anal fissures and partial-thickness burns. The lidocaine transdermal patch may be effective in the treatment of diabetic neuropathy, burns or intractable hiccoughs. The combination of lidocaine/prilocaine may be used for the treatment of anal fissures in addition to postoperative pain and debridement of leg ulcers. Lidocaine/tetracaine has been used off label as a topical local anesthetic for arterial puncture. The topical nonsteroidal antiinflammatory drugs have been used off-label in the treatment of postherpetic neuralgia, gout, migraine, and many other types of pain.[18]

Pharmacokinetics

Table 3. Pharmacokinetics[1-11,18]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents					
Diclofenac epolamine	Not reported	Not reported	65	Not reported	12
Diclofenac sodium	~6	Not reported	65	4'-hydroxydicofenac	2
Lidocaine	3 (patch)	Not reported	>98	Monoethylglycine xylidide and glycinexylidide	0.12 to 0.50
Combination Products					
Lidocaine/ hydrocortisone	Not reported	Not reported	Not reported	Not reported	Not reported
Lidocaine/ prilocaine	Minimal	Minimal	>98/not reported	Not reported	1.0 to 2.5/ 0.16 to 2.50
Lidocaine/ tetracaine	Not reported	Minimal	>98/not reported	Not reported	1.8/not reported

Clinical Trials

The clinical studies evaluating the safety and efficacy of the topical analgesic and anesthetic agents in their respective Food and Drug Administration-approved indications are described in Table 4.[19-49]

Lidocaine/prilocaine has been evaluated as an anesthetic agent in several settings. Treatment with lidocaine/prilocaine and lidocaine formulations have not consistently demonstrated significant improvements in pain scores compared to treatment with placebo.[23,32,33] The results of head-to-head studies comparing lidocaine/prilocaine cream to various lidocaine formulations have generally indicated a similar anesthetic effect.[20,25] In one study, pain scores were significantly lower in patients treated with lidocaine/prilocaine compared to patients treated with piroxicam during cannulation and during cannula advancement ($P<0.01$ and $P<0.05$ respectively). However, pain scores were significantly higher in the lidocaine/prilocaine group compared to the piroxicam group at six, 12, 24, and 48-hour intervals following cannula removal ($P<0.01$).[21] In a single-dose study of patients undergoing cannulation for dialysis, treatment with lidocaine/prilocaine was associated with a significantly lower visual analog score for pain compared to treatment with ethyl chloride spray and placebo ($P=0.00$ for both).[19]

In patients with postherpetic neuralgia, treatment with lidocaine patches results in significant pain relief compared to treatment with placebo. In addition, treatment with lidocaine patches has been associated with higher rates of patient preference, less use of rescue medication and decreases in allodynia and neuropathic symptoms compared to treatment with placebo.[22-25] A noncomparative, open-label study evaluating lidocaine patches for the management of postherpetic neuralgia supports the findings of placebo-controlled studies.[29]

A head-to-head study compared lidocaine 4% and lidocaine/prilocaine 2.5% in local anesthesia for a superficial minor injury. Lidocaine showed significantly reduced pain compared to placebo at all assessment points. Pain reduction was achieved significantly earlier using lidocaine occlusively (30 minutes). No significant differences were found concerning the anesthetic efficacy of lidocaine and lidocaine-prilocaine cream (P not reported).[25]

In patients who had experienced a sports-related sprain, strain, or contusion, there was a statistically significantly improvement in scores for pain and functioning following application of the diclofenac epolamine patch over 14 days ($P=0.036$ and $P=0.048$ respectively).[34] In a second study by Kuehl et al,

patients with a minor soft tissue injury experienced an 18.2% reduction in visual analog scale (VAS) pain scores following twice-daily application of the diclofenac epolamine patch compared to those receiving placebo for 14 days (*P*=0.002).[35] The efficacy and safety of the diclofenac gel has been evaluated in patients with osteoarthritis of the hands and knees. Study results consistently demonstrate a greater pain relief with diclofenac sodium gel compared to placebo.[36-43] In a study by Simon et al, patients treated with the topical diclofenac sodium solution achieved statistically significant reductions in pain scores compared to patients treated with placebo (-6.0 vs -4.7; *P*=0.015) and dimethyl sulfoxide alone (-6.0 vs -4.7; *P*=0.009); however, there was no statistically significant difference in pain scores compared to patients receiving diclofenac tablets (-6.0 vs -7.0; *P*=0.429).[44] Peniston et al evaluated diclofenac topical gel for osteoarthritis in seniors and patients with comormidities. These results suggest that long-term DSG treatment is safe in patient subpopulations with an elevated risk of NSAID-related adverse events, such as the elderly and those with the comorbidities of hypertension, type 2 diabetes mellitus, and cerebrovascular or cardiovascular disease.[48]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pretreatment for Infiltration Anesthesia				
Çelik et al[19] Lidocaine/prilocaine 2.5%/2/5% applied one hour prior to venipuncture vs ethyl chloride vapocoolant spray applied prior to venipuncture vs placebo	AC, PC, RCT, XO Patients ≥18 years of age who were undergoing hemodialysis three times per week	N=41 1 week	Primary: Pain score following cannulation (VAS) and safety Secondary: Not reported	Primary: Following cannulation, the mean VAS score was significantly lower in the lidocaine/prilocaine group (10.7±10.6) compared to patients receiving ethyl chloride (14.0±12.4; P=0.00) and placebo (33.4±19.5; P=0.00). Furthermore, patients treated with lidocaine/prilocaine experienced a statistically significant reduction in VAS scores compared to baseline values (10.7±10.6 vs 28.8±17.9; P=0.00). All treatments were considered to be well tolerated. A rash was reported in one patient who was treated with lidocaine/prilocaine. Secondary; Not reported
Koh et al[20] Lidocaine/prilocaine cream applied to the skin for one hour vs lidocaine 4% cream applied to the skin for 30 minutes	DB, RCT Patients 8 to 17 years of age undergoing IV insertion prior to surgery	N=60 1 day	Primary: Pain scores (VAS), investigator-assessed difficulty of IV placement Secondary: Not reported	Primary: There was no significant difference in pain ratings according to the VAS between the two groups (P=0.87). There was no statistically significant difference between the groups with regard to the investigator ratings of procedure difficulty (P=0.73). There was significantly more blanching in the lidocaine/prilocaine group compared to the lidocaine group (P=0.04). Secondary: Not reported
Dutta et al[21] Lidocaine/prilocaine cream applied to the skin one hour prior to cannulation	DB, PRO, RCT Healthy patients 20 to 60 years of age	N=10 48 hours	Primary: Pain scores (VAS) on cannulation, during cannula advancement,	Primary: Pain scores were significantly higher in the piroxicam group compared to the lidocaine/prilocaine group on cannulation and during cannula advancement (P<0.01 and P<0.05 respectively). Pain scores were significantly higher in the lidocaine/prilocaine group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs piroxicam gel* applied to the skin one hour prior to cannulation			and at regular intervals over 48 hours after cannula removal and local skin condition (blanching, erythema, induration, edema) Secondary: Not reported	compared to the piroxicam group at six, 12, 24 and 48-hour intervals after cannula removal (P<0.01). All patients in the lidocaine/prilocaine group experienced blanching at the time of cannulation compared to zero patients in the piroxicam group (P<0.05). Significant differences were observed up to hour six. No statistically significant differences in erythema and edema were observed between the treatment groups (P value not reported). Induration was significantly higher in the lidocaine/prilocaine group compared to the piroxicam group at the six-hour time interval (P<0.05). Secondary: Not reported
Local Analgesia for Superficial Minor Surgery				
McCluskey et al[22] Lidocaine/prilocaine cream applied over a wide area of skin on the hand one hour prior to cannulation and induction of anesthesia with propofol mixed with saline vs placebo cream applied over a wide area of skin on the hand one hour prior to cannulation and induction of anesthesia with propofol mixed with saline vs	DB, PC, RCT Patients 18 to 70 years of age presenting for gynecological day surgery	N=90 1 day	Primary: Pain severity scores for insertion of cannula and pain severity scores during injection of propofol Secondary: Not reported	Primary: There was a statistically significant reduction in the incidence of pain associated cannula insertion in the lidocaine/prilocaine group compared to the other treatment groups (P=0.015). There was no significant difference in the frequency of pain associated with injection of propofol between the lidocaine/prilocaine group and the placebo group (P value not reported). Significantly greater pain frequency was seen in the lidocaine/prilocaine group compared to the lidocaine and propofol mixed injection group (P=0.002). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo cream applied over a wide area of skin on the hand one hour prior to cannulation and induction of anesthesia with propofol mixed with lidocaine				
Moppett et al[23] Lidocaine/epinephrine patch* delivered via iontophoresis vs lidocaine/prilocaine cream One product was applied to one hand of the patient with a placebo version of the other product and vice versa.	DB, PC, RCT Patients 19 to 77 years of age undergoing elective ears, nose and throat surgery (patients were to undergo cannulation in the hand)	N=28 1 day	Primary: Pain scores after cannulation on a 10-point verbal rating scale Secondary: Not reported	Primary: Pain scores after cannulation were significantly lower in the hand treated with lidocaine/prilocaine compared to the hand treated with lidocaine/epinephrine iontophoresis (P=0.023). Secondary: Not reported
Kuvaki et al[24] Lidocaine/prilocaine cream applied to the outer half of the inferior orbital margin at least 45 minutes prior to retrobulbar injection vs lidocaine 5% ointment applied to the outer half of the inferior orbital margin at least 45 minutes prior to retrobulbar injection	DB, RCT Patients presenting for day case cataract surgery under local anesthesia	N=103 1 day	Primary: Subjective pain intensity on a 10-point scale Secondary: Not reported	Primary: There were no statistically significant differences in pain scores between the patients treated with lidocaine/prilocaine or lidocaine ointment (P=0.67). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Herberger et al (abstract)[25] Lidocaine 4% cream vs lidocaine/prilocaine 2.5% cream vs placebo	AC, DB, PC, RCT, XO Healthy volunteers	N=40 One assessment	Primary: To evaluate the analgesic efficacy of lidocaine cream compared with lidocaine-prilocaine cream and placebo Secondary: To assess the safety and tolerability	Primary: Lidocaine showed significantly reduced pain compared to placebo at all assessment points. Pain reduction was achieved significantly earlier using lidocaine occlusively (30 minutes). No significant differences were found concerning the anesthetic efficacy of lidocaine and lidocaine-prilocaine cream (P value not reported). Secondary: There were no relevant adverse events.
Relief of Pain Associated with Postherpetic Neuralgia				
Devers et al[26] Lidocaine 5% transdermal patch applied for 12 hours daily (up to three patches could be applied at once)	OL Patients 23 to 85 years of age diagnosed with peripheral neuropathic pain	N=16 12 weeks	Primary: Degree of pain relief using a verbal five-point scale Secondary: Not reported	Primary: Thirteen patients (81%) reported either “moderate relief”, “a lot of relief” or “complete relief” from the lidocaine patch. Of these 13 patients, all noted a reduction in brush-evoked mechanical allodynia. All patients who responded to medication continued to experience relief throughout the duration of the study. Secondary: Not reported
Katz et al[27] Lidocaine 5% transdermal patch applied for 12 hours daily (up to three patches could be applied at once)	OL Patients 20 to 99 years of age diagnosed with postherpetic neuralgia	N=332 28 days	Primary: Changes in pain intensity, pain interference in quality of life, pain relief, patient and physician global assessments	Primary: Mean scores for all measures of pain intensity were significantly lower following treatment compared to baseline scores at all evaluations (P=0.0001). At the end of the study 40% of patients experienced a ≥50% reduction in average daily pain intensity. Mean pain interference with quality of life scores were significantly lower with treatment compared to baseline at all evaluations (P=0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	The majority of patients responded to lidocaine treatment within the first week. There was a significant improvement from baseline in pain relief at all evaluations (P=0.0001). Overall, 58% of patients reported moderate to complete pain relief at day 28. The results of the physician global assessments and patient global assessments were similar. Approximately 60% of patients were judged to have complete improvement or moderate ("a lot of") improvement at day 28, slight improvement was reported in approximately 15% of patients and no change was reported in 20% of patients. Secondary: Not reported
Galer et al[28] Lidocaine 5% transdermal patch vs placebo patch	DB, PC, PG, RCT Adults with postherpetic neuralgia involving the torso area for ≥1 month and in whom allodynia was observed on physical examination	N=150 3 weeks	Primary: Change from baseline to week three in neuropathic pain scale and four sub-items of this scale (composite score, total descriptor score, nonallodynic score, and 4 Score [sum of the scores of the four descriptors "sharp," "hot," "dull," and "deep"]) Secondary: Not reported	Primary: The reduction in pain scores for all four composite endpoints was consistently larger in the lidocaine patch group compared to the placebo group (P=0.043, P=0.042, P=0.022 and P=0.013 respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Galer et al[29] Lidocaine 5% transdermal patch for 12 hours daily (up to four patches could be applied at once) vs placebo	PC, RCT, XO Patients 62 to 96 years of age with postherpetic neuralgia already enrolled in the OL protocol and using lidocaine patches on a regular basis for ≥1 month	N=33 28 days	Primary: Time to exit the study (patients exited the study when their verbal pain relief rating decreased by ≥2 categories for any two consecutive days when compared to pre-study OL pain report) Secondary: Not reported	Primary: The median time to exit was >14 days in the lidocaine group compared to 3.8 days in the placebo group (P<0.001). Significantly more patients (78.1%) preferred treatment with lidocaine compared to 9.4% of patients who preferred treatment with placebo (P<0.001). The number of subjects reporting moderate or greater pain relief was 29 in the lidocaine group compared to 13 in the placebo group (P values not reported). Seven subjects used rescue pain relief medications throughout the study (three in the lidocaine group and four in the placebo group; P value not reported). Secondary: Not reported
Meir et al[30] Lidocaine 5% transdermal patch applied for 12 hours daily (up to four patches could be applied at once) vs placebo	DB, PC, PRO, RCT, XO Patients ≥21 years of age suffering from chronic painful peripheral focal neuropathic syndromes that were superficial and localized to a limited skin zone	N=58 28 days	Primary: Ongoing pain intensity (during the first eight hours, every two hours after patch application on day one, and one hour after daily removal of the patch) allodynia, quality of neuropathic symptoms and quality of sleep Secondary: Not reported	Primary: At all time points, ongoing pain intensity decreased compared to pretreatment values in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at two hours (P=0.003), four hours (P=0.004), four days (P=0.03), five days (P=0.02), and seven days (P=0.002). The AUC values show that lidocaine was more effective during the first eight hours and over the course of the treatment week compared to placebo (P=0.017 and P=0.018 respectively). At all time points, allodynia decreased compared to pretreatment values in both the lidocaine and placebo groups (P<0.001 and P<0.05). The differences between groups were significant at two hours (P=0.005), four hours (P=0.009) and six hours (P=0.017) after the first patch application and at day five (P=0.035). Adjusted AUC values show better allodynia relief compared to placebo during

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the first eight hours (P=0.023) and for the remainder of the treatment period (P=0.03). There was a significant reduction in neuropathic symptoms in the lidocaine group compared to baseline (P=0.032), but no significant differences were observed between the lidocaine and placebo groups at any time. No significant differences were observed between the lidocaine and placebo groups in quality of sleep. Secondary: Not reported
Relief of Pain From Minor Cuts, Burns and Abrasions				
Corkill et al[31] Lidocaine 2% gel applied up to every four hours vs placebo gel applied up to every four hours	DB, PC, RCT Female patients who had a normal delivery of a healthy baby and sustained a first or second degree perineal tear	N=149 2 days	Primary: Perineal pain at 24 hours post-delivery (measured on the NRS-101) Secondary: Perineal pain 48 hours post-delivery, the consumption of additional analgesia and maternal satisfaction	Primary: There were no significant differences between the lidocaine and placebo groups at 24 hours according to the NRS-101 (P=0.5). Secondary: At 48 hours, the lidocaine group reported significantly less pain compared to the placebo group according to the NRS-101 (P=0.023). There was no statistically significant difference observed for the amount of additional analgesia used between the two treatment groups (P≤0.227). Women in the placebo group applied significantly more study drug compared to women in the lidocaine group (P=0.015). There were no significant differences between groups in the satisfaction with analgesia received (P value not reported).
Minassian et al[32] Lidocaine ointment 5% applied up to every four hours	DB, PC, RCT Female patients 21 to 23 years of	N=200 2 days	Primary: Amount of pain relief obtained (measured by	Primary: There was no significant difference in the amount of lidocaine or placebo used on postpartum day one (P=0.13) or day two (P=0.08).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo ointment applied up to every four hours	age with an episiotomy or a first, second, third, or fourth degree perineal laceration during their peripartum period		amount of ointment used and total number of pain pills taken by the patient) Secondary: Results of a pain questionnaire administered on the first and second day postpartum	There was no significant difference in the amount of pain pills taken in the lidocaine group compared to the placebo group (P=0.53). There was no statistically significant difference in the satisfaction in the lidocaine group compared to the placebo group (P=0.99). Patients who received an episiotomy used more pain medications compared to those with lacerations (P=0.003). Patients with minor lacerations used fewer pain pills and less ointment on the first postpartum day (P<0.001 and P=0.02, respectively). Secondary: There was no statistically significant difference in subjective pain parameters from the pain questionnaire between patients receiving lidocaine or placebo (P=0.36).
Hopper et al[33] Lidocaine viscous 2% 0.15 mL/kg vs placebo	DB, PC, RCT. Patients age 6 months to 8 years who presented with gingivostomatitis (herpetic or nonherpetic), ulcerative pharyngitis, herpangina, or hand, foot, and mouth disease as clinically diagnosed by the treating clinician and had a history of poor	N=100 single treatment (60 minutes)	Primary: Amount of fluid ingested within 60 minutes of administration Secondary: Difference in the proportions of children ingesting 5, 10, or 20 mL/kg of fluid within 0 to 30 and 0 to 60 minutes from the time of administration of the study drug, the proportion	Primary: The amount of fluid ingested at 60 minutes was similar in both groups. The median amount of fluid ingested in the lidocaine group was 8.49 mL/kg (interquartile range 4.07 to 13.84); in the placebo group, 9.31 mL/kg (interquartile range 3.06 to 15.18) (difference in medians 0.82 mL/kg; 95% CI, –2.52 to 3.26; P=0.9). The mean amount of fluid ingested in the lidocaine group was 9.48 mL/kg (SD 7.02 mL/kg); in the placebo group, 9.32 mL/kg (SD 7.39 mL/kg). The mean difference between groups was 0.15 mL/kg (95% CI, –2.7 to 3.0 mL/kg; P=0.9). Secondary: Short-term secondary outcomes were similar between the groups (no significant differences). Overall, 10 (10%) patients required nasogastric or intravenous fluids and were admitted for fluid administration, seven (14%) in the lidocaine group and three (6%) in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	oral fluid intake		deemed to have an adequate fluid intake	
Treatment of Osteoarthritis and Acute Pain Due to Minor Strains, Sprains, and Contusions				
Galer et al[34] Diclofenac epolamine 1.3% patch applied twice daily vs placebo patch applied twice daily	DB, MC, PC, RCT Patients 18 to 78 years of age who had experienced a sports-related sprain, strain, or contusion less than 72 hours prior to study entry and reported ≥5 out of 10 on a pain scale or ≥50 mm out of 100 mm on a VAS	N=222 2 weeks	Primary: Pain experienced in the course of normal activities as measured by VAS, five-item scale rating functionality, four-item scale for skin irritation, swelling, and joint active range of motion and pain in daily diary outcomes as measured by 100 mm VAS, five- item scale for pain and five-item scale for functional improvement Secondary: Adverse events	Primary: There was a statistically significantly difference favoring diclofenac epolamine over placebo seen at day three (P=0.036) and day 14 (P=0.048) for pain and functioning variables. Diclofenac epolamine was associated with significant greater improvement in "summed pain intensity" on days three, seven and 14 (P≤0.044) as measured by daily diary assessments. Treatment tolerability as assessed by the investigator favored diclofenac epolamine over placebo on day three (P=0.021), day seven (P=0.034) and day 14 (P=0.014) of the study period. Secondary There was no difference in adverse events between the two treatment groups.
Kuehl et al[35] Diclofenac epolamine 1.3% patch applied twice daily	DB, MC, PC, RCT Outpatients aged 18 to 65 years of	N=418 14 days	Primary: Post-treatment pain (VAS) caused by normal activity	Primary: Compared to placebo, patients treated with diclofenac experienced an 18.2% reduction in VAS score over 14 days of treatment (P=0.002). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo patch applied twice daily	age, with minor soft tissue injury (mild or moderate sprain, strain, or contusion) occurring within seven days of study entry, if upon assessment, the patient had a spontaneous pain score ≥5 on a VAS 0 to 10		Secondary: Investigator assessment of global response to therapy, range of motion, time to pain resolution (post hoc) and safety	Patients treated with the diclofenac patch were deemed to have significant improvements on the investigator global assessment of efficacy compared to patients treated with placebo (P=0.008). Investigators rated the effect of treatment as "good" or "excellent" for 58% of patients who received the diclofenac patch compared to 49% of patients receiving placebo. Diclofenac was associated with a statistically significant improvement in range of motion in patients with joint injury compared to placebo (P=0.058). Sustained pain resolution occurred significantly sooner with the diclofenac patch compared to placebo (10 vs 13.5 days; P=0.01). The overall incidence of adverse events was low in both treatment groups. Skin reactions at the application site were the most common events in both treatment groups (7.9 and 5.8% for diclofenac- and placebo-treated patients). The most common skin reactions were pruritus and dermatitis in diclofenac-treated patients and patients (3.4 and 2.5%, respectively) and burning (1.4%) in placebo-treated patients.
Predel et al[36] Diclofenac sodium 140 mg patch (Olfen® patch*) applied twice daily vs placebo patch applied twice daily	DB, MC, PC, PG, RCT Patients18 to 60 years of age were enrolled within three hours of an impact injury	N=120 7 days	Primary: AUC of tenderness over first three days Secondary: AUC of tenderness over seven days, time to resolution of pain, efficacy assessment by patient and investigator on four-point scale and adverse events, including hematological	Primary: Diclofenac sodium patch was found to be significantly more effective compared to placebo with regard to tenderness at day three and day seven (P<0.0001 for both time points). Secondary: More patients receiving diclofenac sodium achieved pain resolution at seven days compared to patients receiving placebo (73.3 vs 6.7%; P<0.0001). Significantly more patients in the diclofenac sodium group compared to the placebo group had a score of "excellent" or "good" on the efficacy scale, as rated by investigators and patients (P<0.0001). The most frequently reported adverse events were localized cutaneous reactions (pruritus and rash) and occurred with a similar incidence between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			markers and vital signs	
Novartis[37] Diclofenac gel 4 g applied to target knee four times daily vs placebo applied to target knee four times daily	DB, MC, PC, PG, RCT Patient's ≥35 years of age with a history of clinical osteoarthritis of the knee for ≥6 months per ACR criteria and X-ray, able to tolerate rescue medication and had a baseline VAS score ≥50 mm measuring POM and a baseline WOMAC score ≥9	N=480 12 weeks	Primary: WOMAC pain score and physical function score and global rating of disease at week 12 Secondary: Incidence of adverse events	Primary: At week 12, the mean change from baseline score for WOMAC pain measures were 5.85 for diclofenac patients and 4.68 for placebo patients (P=0.023). The least squares mean for the differences in change from baseline to endpoint for WOMAC was 1.3 (95% CI, 0.2 to 2.5; P=0.023). The WOMAC physical function score significantly decreased from baseline in the diclofenac group compared to the placebo group (17.5 vs 11.8, respectively; P=0.003). The least squares mean for the differences in change from baseline to endpoint for WOMAC physical function score was 5.7 (95% CI, 2.0 to 9.4; P=0.003). The global rating of disease score was significantly reduced in the diclofenac group compared to the placebo group (P=0.018). The least squares mean for the differences in change from baseline to endpoint for WOMAC physical function score was 8.5 mm (95% CI, 1.5 to 15.6; P=0.003). Secondary: Treatment-related adverse events occurred in 60.2% of patients treated with diclofenac and 53.8% in the placebo group. The most common adverse events were headache (13.8 vs 14.3%, respectively), arthralgia (13.4 vs 8.8%, respectively), and back pain (9.1 vs 6.7%, respectively). Application site dermatitis was more common in the diclofenac group (4.3 vs 1.7%, respectively), while gastrointestinal-related adverse events were similar among the groups (5.9 vs 5.0%). Four serious adverse events were observed (two patients per group); however, none was determined to be drug related.
Novartis[38] Diclofenac gel 2 g applied to target hand four times daily vs	DB, MC, PC, PG, RCT Patients ≥40 years of age with primary osteoarthritis of	N=385 8 weeks	Primary: Osteoarthritis pain intensity score, AUSCAN and global rating of disease activity assessed	Primary: At week four, the mean change from baseline in pain intensity score was 31.1 for diclofenac and 23.9 for placebo (P=0.018). At week six the mean change from baseline in pain intensity was 33.7 with diclofenac compared to 26.7 for placebo (P=0.023). At week four, the mean reduction from baseline in AUSCAN total score was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo applied to target hand four times daily	the hand via ACR criteria and X-ray verification		at weeks four and six using 100 mm VAS Secondary: Incidence of adverse events	significantly greater for patients treated with diclofenac compared to patients treated with placebo (23.5 vs 16.8; P=0.011). The AUSCAN total score at week six was reduced by 25.9 for the diclofenac group compared to 18.6 for the placebo group (P=0.006). There was no statistically significant difference in the global rating of disease score at week four between the diclofenac and placebo groups (P=0.06). By week six the mean change from baseline in global rating of disease scores was significantly lower with diclofenac compared to placebo (23.1 vs 16.3; P=0.023). Secondary: Adverse events occurred in 52.0% of patients treated with diclofenac and 43.9% of patients in the placebo group. The most frequently reported adverse events were musculoskeletal and connective tissue disorders (13.6 vs 17.6%, respectively), nervous system disorders (13.6 vs 12.3%, respectively) and infections/infestations (12.6 vs 7.0%, respectively). Headaches were the most common adverse events reported in patients receiving diclofenac or placebo (11.1 vs 10.2%, respectively). The overall incidence of gastrointestinal adverse events was 7.6% for diclofenac patients and 3.7% for placebo patients.
Novartis[39] Diclofenac gel 2 g applied to target hand four times daily vs placebo applied to target hand four times daily	DB, MC, PC, PG, RCT Patients ≥40 years of age with a diagnosis of primary osteoarthritis via ACR criteria and X-ray	N=not specified 8 weeks	Primary: Osteoarthritis pain intensity score, total AUSCAN index, and global rating of disease activity assessed on 100 mm VAS Secondary: Incidence of adverse events	Primary: There were no differences between groups in any of the primary endpoints. At week four the mean change from baseline in osteoarthritis pain intensity scores was 22.2 for the diclofenac group compared to 19.5 for the placebo group, with a least squares mean difference of 2.0 mm (95% CI, -2.1 to 6.2; P=0.33). There was no statistically significant difference in total AUSCAN scores between the diclofenac and placebo groups (16.4 vs 13.1 mm; P=0.16). Similarly, the global ratings of disease score was not significantly different between patients receiving diclofenac or placebo following treatment (14.4 vs 13.5 mm; P=0.89).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Treatment-related adverse events occurred in 29.7% of diclofenac-treated patients and 29.1% of placebo-treated patients. The most common adverse event categories were nervous system disorders (7.9 vs 11.7%, respectively), musculoskeletal and connective tissue disorders (7.9 vs 6.6%, respectively) and infections/infestations (5.4 vs 8.7%, respectively). Headaches were the most common adverse event reported in the diclofenac and placebo groups (6.9 vs 9.7%, respectively). Application site dermatitis was not reported in patients receiving placebo, but occurred in 2.5% of diclofenac patients. Gastrointestinal adverse events occurred in 4.0% of diclofenac patients and 5.1% of placebo patients.
Novartis[40] Diclofenac gel 4 g applied to target knee four times daily vs placebo applied to target knee four times daily	DB, MC, PC, PG, RCT Patients ≥35 years of age with a history of clinical osteoarthritis of the knee for ≥6 months per ACR criteria and X-ray, able to tolerate rescue medication and had a baseline VAS score ≥50 mm measuring POM and a baseline WOMAC score ≥9	N=not specified 12 weeks	Primary: WOMAC index and physical function scores, global rating of disease scores at week 12 Secondary: Incidence of adverse events	Primary: At week 12, the mean change from baseline in WOMAC pain score was 4.8 for diclofenac patients compared to 4.4 for placebo patients (P=0.31). The WOMAC physical function score reduction from baseline favored the diclofenac group compared to the placebo group (14.4 vs 12.8; P=0.17); however, the difference was not statistically significant. The reduction global rating of disease score was numerically greater with diclofenac compared to placebo; however the difference was not statistically significant (25.1 vs 22.4 mm; P=0.23). Secondary: Treatment-related adverse events occurred in 53.7% of the diclofenac group and 47.1% in the placebo group. The most common adverse events in the diclofenac and placebo groups were headache (16.6 vs 16.5%, respectively), arthralgia (6.9 vs 5.9%, respectively), and back pain (6.9 vs 7.5%, respectively). Nasopharyngitis was more common in the diclofenac group (6.2 vs 2.4%, respectively), while gastrointestinal-related adverse events were lower among the diclofenac group (3.1 vs 3.9%).
Peniston et al[42]	ES, MC, OL	N=583	Primary: WOMAC index,	Primary: At month 12, mean WOMAC scale scores for pain were improved following

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Diclofenac sodium gel 4 g applied to target knee(s) four times daily	Patients completing a previous 12-week study who were ≥35 years of age with a ≥6-month history of symptomatic mild-to-moderate knee osteoarthritis (ACR criteria) and radiographic evidence of Kellgren-Lawrence grades 1 to 3 disease and had experienced knee pain for ≥15 days during the preceding month	Up to 12 months	stiffness and physical function scores and safety Secondary: Not reported	treatment with diclofenac compared to baseline values (-4; P value not reported). Similarly, diclofenac treatment was associated with reduced scores for stiffness and physical functioning (-1.5 and -12.8, respectively) following 12 months of continued treatment. At one year, improvement from baseline was 39.8% for WOMAC pain scale score, 33.4% for stiffness scale score and 36.9% for physical function scale score. Improvements from baseline appeared to be greater in patients receiving treatment for one knee vs both knees, although this difference was not statistically evaluated. One or more treatment-related adverse events were reported in 75.3% of patients applying treatment to one knee and 75.0% of patients treating both knees. The most frequently reported adverse events were headache, arthralgia, back pain and application-site dermatitis. Secondary: Not reported
Hsieh et al[42] Diclofenac sodium 60 mg patch applied three times daily to upper trapezius vs placebo patch applied three times daily to upper trapezius	DB, PC, RCT Patients ≥18 years of age who presented with clinically active myofascial trigger point (an active trigger point with spontaneous pain at rest, or	N=153 8 days	Primary: Change in pain score (VAS) Secondary: Cervical active range of motion, pressure pain threshold of the myofascial trigger point, patient global	Primary: Following eight days of treatment, patients randomized to receive treatment with the diclofenac sodium patch experienced significantly lower VAS scores for pain compared to patients treated with placebo (-26.90 vs -21.21%; P<0.01). Secondary: The cervical range of motion was significantly improved (as determined by the angle between the neutral head position and maximally tilted position) with topical diclofenac sodium compared to placebo (18.4 vs 6.6%; P<0.01). There was no statistically significant difference between topical diclofenac

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pain in response to contraction or stretching of the involved muscle)		assessment, and Neck Disability Index	sodium and placebo with regard to pressure pain threshold of the myofascial trigger point (4.93 vs 4.77 kg; P=0.23) Scores on the Neck Disability Index were significantly improved in patients treated with diclofenac sodium compared to patients treated with placebo over eight days (32.4 vs -25.6%; P=0.04). Patient global assessment of improvement significantly favored treatment with diclofenac sodium over placebo following eight days of treatment (P<0.05).
Altman et al[43] Diclofenac sodium gel 1% applied four times daily vs placebo applied four times daily	DB, MC, PC, PG, RCT Patients ≥40 years of age with osteoarthritis in their dominant hand, (defined by ACR criteria) and pain in the dominant hand for ≥12 months with use of an NSAID for ≥1 episode of pain and pain in the dominant hand during the 24 hours before the baseline visit (rated as ≥40 mm on a 100-mm VAS and pain in the dominant hand had to exceed	N=385 8 weeks	Primary: Pain intensity in the dominant hand during the previous 24 hours (VAS), AUSCAN score for the dominant hand; and global rating of disease activity (VAS) at four and six weeks Secondary: Pain intensity in the dominant hand during the previous 24 hours (VAS), AUSCAN score for the dominant hand; and global rating of disease	Primary: There was a statistically significant reduction in VAS pain score at week four with diclofenac sodium compared to placebo (-42.3 vs -32.5%; P=0.018). Total AUSCAN score was also significantly reduced in patients receiving diclofenac sodium compared to patients receiving placebo (-35.0 vs -25.2%; P=0.011); however, there was no statistically significant difference between the groups with regard to global rating of disease (-36.1 vs -26.2%; P=0.06). At week six, patients treated with diclofenac sodium experienced a statistically significant improvement in VAS pain score compared to patients randomized to receive placebo (-45.8 vs -36.3%; P=0.023). Similarly, there were statistically significant improvements in total AUSCAN (-38.5 vs -27.9%; P=0.006) and global rating of disease (-40.1 vs -28.8%; P=0.023) scores for patients treated with diclofenac sodium compared to patients treated with placebo. Secondary: The VAS score for pain intensity was significantly lower with diclofenac sodium compared to placebo at week one (P<0.05), week two (P<0.05); however, no statistically significant difference between groups occurred at week eight. Total AUSCAN score was significantly improved at weeks one, two and eight for patients treated with diclofenac sodium compared to patients receiving placebo (P<0.05 for all). No statistically significant differences were reported between the diclofenac

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pain in the nondominant hand by ≥20 mm)		activity (VAS) at weeks one, two and eight, pain, stiffness, and physical function subscales within the AUSCAN index and OARSI response (improvement ≥50% and an absolute change ≥20 mm in either pain or physical function, or as an improvement ≥20% and an absolute change ≥10 mm in ≥2 of the following: pain, patient global rating of disease, and physical function)	sodium and placebo groups with regard to global rating of disease at weeks one, two or eight. Statistically significant improvements in AUSCAN pain scores occurred in the diclofenac sodium group compared to the placebo group at weeks one, two, four and six (P<0.05 for all). Patients treated with diclofenac sodium experience statistically significant improvements in AUSCAN function scores compared to patients treated with placebo at weeks one, four, six and eight (P<0.05 for all). Statistically significant improvements in AUSCAN stiffness scores occurred in the diclofenac sodium group compared to the placebo group at weeks one, two, four, six and eight (P<0.05 for all). The OARSI responder rate was significantly higher in patients treated with diclofenac sodium compared to placebo at week one (P=0.008) and week four (P=0.013); however, there was no statistically significant difference between groups at the other time points evaluated.
Galer et al[12] Diclofenac sodium 1.5% solution with dimethyl sulfoxide 40 drops applied to the knee as a single dose vs diclofenac sodium gel 4 g	RCT Non-smoking adults 40 to 75 years of age with a BMI of 19 to 36 kg/m^2	N=24 1 day	Primary: Questionnaire scores, patient preference and safety Secondary: Not reported	Primary: The mean satisfaction scores for topical diclofenac sodium solution were higher compared to scores for the diclofenac sodium gel on nine of ten (90%) questions, indicating a more favorable overall rating for topical diclofenac sodium solution. Seven of the ten questions (70%) for topical diclofenac sodium solution were scored as a four or higher (of a maximum of five) compared to three of ten (30%) questions scored as a four or higher with diclofenac sodium gel. Rating scores were significantly higher for topical diclofenac sodium solution

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied as a single dose				compared to diclofenac sodium gel with regard to "odor/smell" (4.54 vs 3.79; P=0.004), "oiliness/greasiness" (3.67 vs 2.92; P=0.047) and "stickiness/tackiness" (4.63 vs 2.83; P<0.0001). There were no statistically significant differences between the diclofenac sodium solution and gel formulations on the remaining questionnaire components. No adverse events occurred during the evaluation period. Secondary: Not reported
Simon et al[44] Diclofenac sodium 1.5% solution with dimethyl sulfoxide 40 drops applied to the knee four times daily plus oral placebo tablet once-daily vs dimethyl sulfoxide vehicle 40 drops applied to the knee four times daily plus oral placebo tablet once-daily vs placebo solution 40 drops applied to the knee four times daily plus oral placebo tablet once-daily vs placebo solution 40 drops	DB, DD, MC, PC, RCT Patients 40 to 85 years of age with primary osteoarthritis of the knee based on standard radiological criteria, regular use of an NSAID or other analgesic medication (≥3 days a week in the previous month) and a flare of pain with a minimum Likert pain score of 8/20 (40 on a scale normalized to 0 to 100)	N=775 12 weeks	Primary: Change from baseline in WOMAC pain and physical function scores and patient overall health assessment Secondary: WOMAC stiffness scores and patient global assessment	Primary: After 12 weeks of treatment, patients receiving the topical diclofenac sodium solution achieved statistically significant reductions in WOMAC pain scores compared to patients treated with placebo (-6.0 vs -4.7; P=0.015) and dimethyl sulfoxide (-6.0 vs -4.7; P=0.009). There was no statistically significant difference in pain scores compared to patients receiving diclofenac sodium tablets (-6.0 vs -7.0; P=0.429). Treatment with topical diclofenac sodium was associated with statistically significant improvements in WOMAC physical function scores at 12 weeks compared to patients receiving placebo (-15.8 vs -12.3; P=0.034) and dimethyl sulfoxide (-15.8 vs -12.1; P=0.026); however, there was no statistically significant difference compared to diclofenac sodium tablets (P=0.319). Patients receiving topical diclofenac sodium experienced significant improvements in their overall health assessment compared to patients receiving treatment with placebo or dimethyl sulfoxide (P≤0.016 for both). There was no statistically significant difference between the topical diclofenac sodium and oral diclofenac sodium tablet groups with regard to patient health assessment (P=0.956). Secondary: Topical diclofenac sodium therapy was associated with statistically significant improvements in WOMAC stiffness scores compared to dimethyl sulfoxide (P=0.035); however, no difference was reported compared to patients treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
applied to the knee four times daily plus oral diclofenac extended-release tablet once-daily vs diclofenac sodium 1.5% solution with dimethyl sulfoxide 40 drops applied to the knee four times daily plus oral diclofenac extended-release tablet once-daily				with placebo or diclofenac sodium oral tablets (P=0.112 and P=0.596, respectively). Patient global assessment scores were significantly reduced from baseline in the topical diclofenac sodium group compared to those treated with placebo (-1.36 vs -1.01; P=0.016) and dimethyl sulfoxide (-1.36 vs -1.07; P=0.018). There was no statistically significant differences compared to the diclofenac sodium tablet group (-1.53; P=0.439).
Zacher et al[45] Diclofenac topical preparations (treatment regimen varied)	MA (19 trials) DB, PC, RCTs in soft-tissue injuries, soft-tissue rheumatic disorders and osteoarthritis	N=3,000 Duration varied in the 19 trials	Primary: Pharmacokinetic and Pharmaco-dynamic parameters, efficacy and safety endpoints Secondary: Not reported	Primary: Topical diclofenac demonstrated good skin penetration and a localized effect based upon characteristics including a low volume of distribution, short half-life and mild acidity. Onset of action was shown to be relatively rapid in acute pain studies, with differences in onset between topical formulations. Various topical diclofenac products were generally well tolerated, with minor application site irritation being the most commonly reported adverse event. Secondary: Not reported
Bjordal et al[46] Paracetamol vs oral NSAIDs (diclofenac, diflunisal, etodolac, nabumetone, naproxen,	MA (63 trials) RCTs comparing patients (median, 63.2 years of age) treated with specified interventions for	N=14,060 Duration varied in the 63 trials	Primary: Reduction in pain intensity from baseline, as measured on the WOMAC index or on a 100 mm VAS for global or walking pain	Primary: The mean baseline pain intensities on 100 mm VAS were 72.8 mm for opioid therapy, 64.3 mm for oral NSAIDs, 57.4 mm for steroid injections, 54.9 mm for paracetamol, 54.7 mm for topical NSAIDs, 53.8 mm for glucosamine sulfate and 50.7 mm for chondroitin sulfate. The maximum pain-relieving effect seen with oral NSAIDs as measured by a decrease from baseline on 100 mm VAS was observed at 2.3 weeks (10.2 mm; 95% CI, 8.8 to 11.6). The values dropped slightly at four weeks (9.0 mm;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
oxaprozin, tiaprofenic acid*, valdecoxib*, celecoxib, meloxicam, lumiracoxib*) vs topical NSAIDs (diclofenac, eltenac gel*, and ibuprofen gel*) vs steroid injection (triamcinolone, methylprednisolone, cortivazol) vs glucosamine sulfate vs chondroitin sulfate vs opioids (codeine, oxymorphone, oxycodone, morphine sulfate, tramadol) The dosage regimens varied between the trials.	clinically or radiologically confirmed knee osteoarthritis lasting for ≥3 months		within four weeks of treatment start Secondary: Reduction in pain intensity from baseline, as measured on the WOMAC index or 100 mm VAS scale for global or walking pain at eight to 12 weeks, heterogeneity of primary and secondary outcome measure and corresponding subgroup analysis	95% CI, 4.9 to 13.1). The maximum pain relief for topical NSAIDs as measured by a decrease from baseline on 100 mm VAS appeared after a mean of 1.6 weeks (11.6 mm; 95% CI, 7.4 to 15.7), while pain relief dropped at four weeks (7.0 mm; 95% CI, 5.5 to 8.6). The maximum pain relief for steroid injection efficacy as measured by a decrease from baseline on 100 mm VAS was at the first post injection evaluation at 1.5 weeks (14.5 mm; 95% CI, 9.7 to 19.2) decreasing by week four (6.7 mm; 95% CI, 0.4 to 13.0). There was not enough data to identify a time point for maximum pain relief with paracetamol, glucosamine and chondroitin sulfate. There was a 3.0 mm (95% CI, 1.4 to 4.7), 4.7 mm (95% CI, –0.3 to 9.1) and a 3.7 mm (95% CI, 0.3 to 7.0) decrease from baseline on 100 mm VAS identified within the four-week period, respectively. The pain relief associated with opioids as measured by a decrease from baseline on 100 mm VAS scale was 12.9 mm (95% CI, 8.4 to 17.4) at two to four weeks. Withdrawal rates were high and intention-to-treat analyses were only presented in last value carried forward scenarios. Secondary: The efficacy as measured by decrease from baseline on 100 mm VAS of paracetamol did not change at week 12 during the follow-up period (4.0 mm; 95% CI, 1.1 to 6.9). Efficacy, as measured by decrease from baseline on 100 mm VAS, gradually declined at week 12 during follow-up for oral NSAIDs (9.8 mm; 95% CI, 6.9 to 12.8), topical NSAIDs (7.0 mm; 95% CI, 1.0 to 13.0) and intraarticular steroid injections (5.7 mm; 95% CI, 1.4 to 10.1). For topical NSAIDs, there was a decrease from baseline on 100 mm VAS scale at four weeks (one trial, 7.0 mm; 95% CI, 1.0 to 13.0) and at 12 weeks

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(one trial, 6.2 mm; 95% CI, 1.0 to 10.9). For intraarticular steroid injections, there were decreases from baseline on 100 mm VAS scale at six weeks (two trials, 5.6 mm; 95% CI, 4.4 to 15.6) and after eight to 12 weeks (four trials, 5.5 mm; 95% CI, 0.8 to 10.2). For glucosamine sulfate, there was a decrease from baseline on 100 mm VAS scale at week eight (3.8 mm; 95% CI, 1.4 to 9.0) and at week 12 (5.6 mm; 95% CI, 1.1 to 12.2). Based on the results of six trials with chondroitin sulfate, there was a larger decrease from baseline on 100 mm VAS at week eight (7.1 mm; 95% CI, 3.3–10.8) and at week 12 (10.6 mm; 95% CI, 6.0 to 15.2) compared to week four weeks. Based on the results of one trial with opioids, there was a decrease from baseline on 100 mm VAS scale at 12 weeks (10.2 mm; 95% CI, 4.1 to 16.3). Heterogeneity in trial samples for the primary outcomes for oral NSAIDs (Q-value 58.9; P=0.001, decrease of 10.2 mm from baseline on VAS; 95% CI, 9.0 to 11.9) was assumed to result from patient selection bias in trials which excluded patients who did not experience a flare of symptoms after being taken off their NSAID prior to treatment allocation (non responders). Subgroup analyses demonstrated a reduction of heterogeneity to non-significance for pain data in both subgroups (P≥0.3; Q-value, 13.8 and 10.8 for biased and unbiased trials, respectively). There was a significantly greater maximum decrease from baseline on VAS scale (P<0.001) for the subgroup of 14 trials which excluded non-responders compared to the 12 trials that included non-responders (11.8 mm; 95% CI, 10.5 to 13.1 vs 7.9 mm; 95% CI, 6.9 to 8.9). The results for secondary outcomes were consistent with these findings (P<0.001). Heterogeneity in trial samples for the primary outcomes topical NSAIDs (Q-value 23.2; P=0.002; decrease of 11.6 mm on VAS; 95% CI, 6.1 to 16.5) was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				assumed to be caused by inefficacy of one of the three different gels (eltenac) and use beyond two weeks. There was no heterogeneity in outcome measures during the first four weeks of treatment for glucosamine sulfate, chondroitin sulfate and paracetamol (Q-values of 1.3, 1.8 and 2.3, respectively).
Green et al[47] (Cochrane Musculoskeletal Group 2002) Topical NSAIDs (lecithin liposomal organo gel*, diflam cream*, iontophoresis of sodium diclofenac*, iontophoresis of sodium salicylate*, proglumetacin*, diclofenac tissugel patch*, diclofenac diethylamine salt*) or oral NSAIDs (diflunisal, naproxen, diclofenac sodium) vs placebo or a second NSAID	MA (14 trials) RCTs of NSAIDs compared to placebo or another NSAID in patients ≥16 years of age with lateral elbow pain ≥3 weeks in duration	N=not reported 1 to 12 weeks	Primary: Pain as measured on VAS scale Secondary: Patient satisfaction, adverse effects, strength, tenderness, range of motion and doctor's opinion's on response	Primary: Topical NSAIDs were associated with a significantly greater reduction in pain as measured by VAS scale compared to placebo (WMD, -1.88; 95% CI, -2.54 to -1.21). Two trials assessed the effect of oral NSAIDs; however, these could not be pooled. One trial demonstrated significant short-term decrease from baseline on 100 mm VAS scale with diclofenac compared to placebo (WMD, -13.9; 95% CI, -23.21 to -4.59). The second trial showed no difference in median pain score after four weeks of naproxen compared to placebo. One trial compared two types of oral NSAIDs, demonstrating no differences between diflunisal and naproxen with regard to improvement of symptoms (WMD, 0.24; 95% CI, 0.03 to 1.89) or pain relief (WMD, 0.10; 95% CI, 0.01 to 1.61). Secondary: Topical NSAIDs performed better in measures of patient satisfaction compared to placebo (RR, 0.39; 95% CI, 0.23 to 0.66). There was a significant difference demonstrated between groups with regard to adverse events (RR, 2.26; 95% CI, 1.04 to 4.94). When considered individually, the frequency of the two reported adverse effects (foul breath and minor skin irritation) were not significantly different between the treatment and placebo groups. Topical NSAIDs and placebo did not significantly differ in the effects on strength, tenderness, range of motion or doctor's opinion regarding effect.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Based on the results of one trial, there was significantly more abdominal pain (RR, 3.17; 95% CI, 1.35 to 7.41) and diarrhea (RR, 1.92; 95% CI, 1.08 to 3.14) reported by those taking oral NSAIDs.
Peniston et al[48] Diclofenac sodium 1% gel 4 grams applied to one or both knees Rescue medication (acetaminophen, maximum 4 g daily) was allowed.	MC, OL Patients ≥35 years of age with mild to moderate osteoarthritis of the knee for ≥6 months	N=947 12 months	Primary: Adverse events Secondary: Not reported	Primary: The safety population consisted of 575 patients <65 years of age and 372 patients ≥65 years of age. The percentage of patients who experienced any adverse event was similar for patients in both subgroups. 68.2% of patients <65 years of age experience an adverse effect and 67.2% of patients ≥65 years of age. Other adverse reactions were similar in the <65 years of age and ≥65 years of age groups: application-site reactions (8.7% and 13.2%, respectively), gastrointestinal adverse effects (9.4% and 6.7% respectively) and cardiovascular adverse effects (3.3% and 3.2%) for any adverse effect. Patients aged < 65 years were more likely to experience gastrointestinal adverse events and less likely to experience application site dermatitis compared with patients aged ≥ 65 years (P value not reported). Other adverse effects that occurred in ≥3% of either age group included headache (19.1% and 15.3%), arthralgia (13.4% and 14.8%), back pain (11.1% and 12.6%), nasopharyngitis (8.0% and 5.6%), upper respiratory tract infection (7.5% and 3.0%), pain in extremity (5.7% and 7.0%), pain (4.7% and 2.2%), influenza (4.7% and 1.9%), sinusitis (4.5% and 2.4%), toothache (3.1% and 1.1%), sinus congestion (3.1% and 0.3%), myalgia (3.0% and 2.4%) and neck pain (1.7% and 3.5%). Almost half the patients (438/947; 46.3%) had hypertension. However, just slightly more than 10% had type 2 diabetes mellitus (100/947; 10.6%) and cerebrovascular or cardiovascular disease (97/947; 10.2%). The percentage of patients who experienced any adverse event was similar between patients with the comorbidities of hypertension, type 2 diabetes mellitus, or cerebrovascular or cardiovascular disease (61.9 to 65.5%) and slightly lower than the adverse event rates of patients without these comorbidities (68.2 to 69.7%). The percentage of patients experiencing gastrointestinal adverse events was similar among patients with comorbid conditions of hypertension,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				type 2 diabetes mellitus, or cerebrovascular or cardiovascular disease (7.0 to 12.4%) and generally similar to gastrointestinal adverse event rates in patients without these conditions (7.9 to 8.5%). Patients with hypertension, type 2 diabetes mellitus, or cardiovascular disease experienced similar rates of cardiovascular adverse events (5.0 to 8.0%). Slightly lower cardiovascular adverse event rates (1.8 to 2.9%) were observed in patients without these comorbid conditions. Application site dermatitis occurred at rates of 8.2 to 12.4% among the comorbidity subgroups and the three corresponding groups without comorbidities. Secondary: Not reported

*Agent not available in the United States.
Study abbreviations: AC=active control, DB=double-blind, DD=double-dummy, ES=extension study, MC=multicenter, MA=meta-analysis, OL=open-label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, XO=crossover
Other abbreviations: ACR=American College of Rheumatology, AUC=area under the curve, AUSCAN=Australian/Canadian Osteoarthritis Hand Index, CI=confidence interval, IV=intravenous, NRS-101=101-point Numerical Rating, NSAID=nonsteroidal anti-inflammatory drug, OARSI=osteoarthritis research society international, POM=pain on movement, RR=relative risk, VAS=visual analogue scale, WMD=weighted mean difference, WOMAC=Western Ontario and McMaster Universities

Special Populations

Table 5. Special Populations[1-11]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Diclofenac epolamine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction; use caution.	Not studied in hepatic dysfunction; use with caution.	C	Unknown; use caution.
Diclofenac sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction; use is not recommended in advanced renal disease.	Not studied in hepatic dysfunction; use with caution.	C	Unknown; use caution.
Lidocaine	No dosage adjustment required in the elderly. Dosage adjustment required in the pediatric population.	No dosage adjustment required.	Reduce dose by 50% in acute hepatitis and decompensa-ted cirrhosis.	B	Yes (percent not reported).
Combination Products					
Lidocaine/ hydrocortisone	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and effectiveness in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes (percent not reported).
Lidocaine/ prilocaine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Studies have shown less overall benefit in children <7 years of age than in older children and adults.	Smaller areas of treatment are reco-mmended.	Smaller areas of treatment are reco-mmended.	B	Probably (percent not reported).

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Care must be taken to insure the dose and area of application is limited in infants <3 months of age. The area of application and duration should be limited in neonates and children weighing <20 kg.				
Lidocaine/ Tetracaine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy of Synera® has not been established in pediatric patients >3 years of age and older. Application time is the same as for adult patients and should not exceed two patches applied at once. Safety and effectiveness for Pliaglis® use in children has not been established.	Not studied in renal dysfunction; no specific dosing guidelines are available.	Not studied in hepatic dysfunction; use caution in patients with severe hepatic disease.	B	Lidocaine: Yes (percent not reported). Tetracaine: unknown.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-1]

Adverse Event(s)	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
Cardiovascular						
Arrhythmia	-	-	✔	-	-	
Arterial spasms	-	-	✔	-	-	
Asystole	-	-	✔	-	-	
Bradycardia	-	-	✔	-	✔	
Cardiovascular arrest	-	-	-	-	✔	
Cardiovascular collapse	-	-	✔	-	✔	
Defibrillator threshold increases	-	-	✔	-	-	-
Heart block	-	-	✔	-	-	-
Hypotension	-	-	✔	-	✔	✔
Shock	-	-	✔	-	-	-
Sinus node suppression	-	-	✔	-	-	-
Vascular insufficiency	-	-	✔	-	-	-
Central Nervous System						
Agitation	-	-	✔	-	-	-
Anxiety	-	-	✔	-	-	-
Apprehension	-	-	✔	-	-	-
Asthenia	-	-	✔	-	-	-
Central nervous system depression	-	-	✔	-	✔ *	✔
Central nervous system excitation	-	-	✔	-	✔ *	✔
Coma	-	-	✔	-	-	-
Confusion	-	-	✔	-	-	≤1
Disorientation	-	-	✔	-	-	-
Dizziness	-	-	✔	-	-	<1
Drowsiness	-	-	✔	-	-	-
Euphoria	-	-	✔	-	-	-
Hallucinations	-	-	✔	-	-	-
Headache	7	-	✔	-	-	<1
Hyperesthesia	-	-	✔	-	-	-
Hypoesthesia	-	-	✔	-	-	-
Lethargy	-	-	✔	-	-	-
Lightheadedness	-	-	✔	-	-	-

Adverse Event(s)	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
Nervousness	-	-	✔	-	-	≤1
Paresthesia	6	1	✔	-	-	≤1
Psychosis	-	-	✔	-	-	-
Seizure	-	-	✔	-	-	-
Slurred speech	-	-	✔	-	-	-
Somnolence	4	-	✔	-	-	-
Unconsciousness	-	-	✔	-	-	-
Dermatological						
Abnormal sensation	-	-	-	-	✔	-
Acne	-	-	-	-	-	≤1
Application site irritation	-	1	-	-	-	-
Application site reaction	-	7	-	-	41	-
Blanching	-	-	-	✔	37	12 to 16
Blistering of neonatal foreskin	-	-	-	-	✔	-
Blisters	-	-	✔	-	-	-
Bruising	-	-	✔	-	-	-
Burning	2	-	✔	✔	17	-
Contact dermatitis	-	-	✔	-	-	≤1
Depigmentation	-	-	✔	-	-	-
Dermatitis	9	4	-	-	-	-
Edema of the skin	-	-	✔	-	10	14
Erythema	-	1	-	✔	30 to 41	47 to 71
Exfoliation	-	-	✔	-	-	-
Hyperpigmentation	-	-	-	-	✔	-
Itching	-	-	✔	-	2	-
Papules	-	1	✔	-	-	-
Petechia	-	-	✔	-	✔	-
Pruritus	31	-	✔	-	-	≤1
Purpuric reactions	-	-	-	-	✔	-
Rash	-	-	✔	-	<1	≤1
Skin dryness	-	1	-	-	-	≤1
Skin irritation	-	-	✔	-	-	-
Skin reaction	-	-	✔	-	-	-
Stinging	-	-	-	✔	-	-
Thrombophlebitis	-	-	✔	-	-	-

Adverse Event(s)	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
Urticaria	-	-	✔	-	-	-
Vesicles	-	1	✔	-	-	-
Endocrine and Metabolic						
Edema	-	-	✔	-	6	-
Gastrointestinal						
Dysgeusia	10	-	-	-	-	-
Dyspepsia	7	-	-	-	-	-
Metallic taste	-	-	✔	-	-	-
Nausea	17	-	✔	-	-	≤1
Vomiting	-	-	✔	-	-	<1
Laboratory Test Abnormalities						
Methemoglobinemia	-	-	✔	-	-	-
Musculoskeletal						
Tremor	-	-	✔	-	-	-
Twitching	-	-	✔	-	-	-
Weakness	-	-	✔	-	-	-
Respiratory						
Adult respiratory distress syndrome	-	-	✔	-	-	-
Bronchospasm	-	-	✔	-	✔	-
Dyspnea	-	-	✔	-	-	-
Laryngospasm	-	-	✔	-	-	-
Respiratory arrest	-	-	✔	-	-	-
Respiratory depression	-	-	✔	-	✔ *	-
Other						
Allergic reaction	-	-	✔	-	-	-
Alterations in temperature	-	-	✔	-	7	-
Anaphylactic reaction	-	-	✔	-	-	-
Angioedema	-	-	✔	-	✔	-
Blurred vision	-	-	✔	-	-	-
Convulsions	-	-	✔	-	-	-
Dehydration	-	-	-	-	-	≤1
Diplopia	-	-	✔	-	-	-
Fever			-			<1
Flushing	-	-	✔	-	-	-
Pain exacerbation	-	-	✔	-	-	-

Adverse Event(s)	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
Tinnitus	-	-	✔	-	-	-
Urticaria	-	-	-	-	✔	-
Visual changes	-	-	✔	-	-	-

*With systemic absorption.
✔ Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[1-11]

Contraindication	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
Hypersensitivity to corticosteroids or to other components of the preparation	-	-	-	✔	-	-
Hypersensitivity to diclofenac	✔	✔	-	-	-	-
Hypersensitivity to local anesthetics of the amide type or to other components of the preparation	-	-	✔	✔	✔	✔
Hypersensitivity to local anesthetics of the ester type or to other components of the preparation						✔
Hypersensitivity to para-aminobenzoic acid (PAPA)						✔
Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs	✔	✔	-	-	-	-
Patients with tuberculosis or fungal lesions of skin vaccinia, varicella and acute herpes simplex	-	-	-	✔	-	-
Treatment of perioperative pain in the setting of coronary artery bypass graft surgery	✔	✔	-	-	-	-
Use on non-intact or damaged skin resulting from any etiology, including exudative dermatitis, eczema, infection lesions, burns or wounds	✔	-	-	-	-	-
Use on traumatized mucosa or secondary bacterial infection of the proposed application area	-	-	✔	-	-	-

Black Box Warning for Flector®, Pennsaid® and Voltaren®[9-11]

WARNING
Cardiovascular risk: Nonsteroidal antiinflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. Diclofenac is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery. Gastrointestinal risk: NSAIDs cause an increased risk of serious gastrointestinal adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Warnings/Precautions

Table 8. Warnings and Precautions[1-11]

Warning/Precaution	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
Anaphylactic reactions may occur in patients with the aspirin triad and in patients without known sensitivity or prior exposure to nonsteroidal anti-inflammatory drugs (NSAIDs)	✔	✔	-	-	-	-
Anemia; check hemoglobin or hematocrit in patients on long-term NSAID therapy with signs or symptoms of anemia	✔	-	-	-	-	-
Avoid accidental exposure in children	✔	-	-	-	-	✔
Avoid contact of topical diclofenac and eyes and mucosa	✔	-	-	-	-	✔
Class III antiarrhythmic drugs; use with caution as coadministration may result in additive cardiac effects	-	-	-	-	✔	-
Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective NSAIDs have shown an increased risk of serious cardiovascular events	✔	✔	-	-	-	-
Closely monitor renal function in patients with impaired renal function	✔	✔	-	-	-	-
Corticosteroid monitoring; slowly taper patients on prolonged corticosteroid therapy if a decision is made to discontinue	✔	✔	-	-	-	-

Warning/Precaution	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
corticosteroids; NSAIDs are not a substitute for corticosteroids						
Excessive dosing or short intervals between doses may result in high plasma levels and serious adverse events	-	-	-	-	-	✔
Factors that increase the risk for gastrointestinal bleeding in patients treated with NSAIDs include use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status	✔	✔	-	-	-	-
For external use only	✔	✔	✔	✔	✔	✔
Heart failure; use with caution as NSAIDs use may result in fluid retention and edema	✔	✔	-	-	-	-
Hepatic disease; inability to normally metabolize lidocaine may result in the development of toxic blood concentrations of lidocaine	-	-	✔	-	-	✔
Hepatotoxicity; measure transaminases (alanine aminotransferase and aspartate aminotransferase) periodically in patients receiving therapy with diclofenac	✔	✔	-	-	-	-
Hypertension; use, with caution as NSAIDs may lead to new onset or worsening of hypertension	✔	✔	-	-	-	-
If abnormal liver tests persist or worsen or clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur discontinue diclofenac immediately	✔	✔	-	-	-	-
Inflammation; NSAIDS may mask the diagnostic signs of detecting infectious, or painful conditions	✔	✔	-	-	-	-
Laboratory monitoring; check complete blood count and a chemistry profile periodically in patients on long-term treatment as gastrointestinal events may occur without warning symptoms	✔	✔	-	-	✔	-
Methemoglobinemia: avoid use in patients with congenital or idiopathic methemoglobinemia or in infants under 12 months of age who are receiving treatment with methemoglobin-inducing agents (e.g., acetaminophen, nitrates, phenytoin, sulfonamides)	-	-	-	-	✔	✔
Not for ophthalmic use	-	-	-	✔	-	-
Magnetic Resonance Imaging	-	-	-	-	-	✔*
NSAIDs should be used with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding	✔	✔	-	-	-	-
NSAIDs; oral and topical use may result in a higher rate of hemorrhage, more frequent abnormal creatinine, urea and	✔	-	-	-	-	-

Warning/Precaution	Single Entity Agents			Combination Products		
	Diclofenac Epolamine	Diclofenac Sodium	Lidocaine	Lidocaine/ Hydrocortisone	Lidocaine/ Prilocaine	Lidocaine/ Tetracaine
hemoglobin						
Ototoxicity; avoid use in any clinical situation where penetration past the tympanic membrane is possible	-	-	-	✔	✔	-
Patients taking angiotensin converting enzyme inhibitors, thiazides or loop diuretics may have impaired response to these therapies while taking NSAIDs	✔	✔	-	-	-	-
Preexisting asthma; do not administer diclofenac to patients with aspirin sensitivity and use with caution in patients with preexisting asthma	✔	✔	-	-	-	-
Pregnancy; starting at 30 weeks gestation, NSAIDs should be avoided as premature closure of the ductus arteriosus in the fetus may occur	✔	✔	-	-	-	-
Prolonged application time may result in increased absorption and adverse events	-	-	-	✔	✔	✔
Risk for cardiovascular or gastrointestinal event; use the lowest effective dose for the shortest duration possible	✔	✔	-	-	-	-
Risk of severe adverse events; management may require resuscitative equipment, oxygen and other resuscitative drugs	-	-	-	-	-	-
Serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis may occur	✔	✔	-	-	-	-
Severe shock or heart block; use with caution	-	-	✔	-	-	-
Skin irritation; application to irritated skin should be done with caution	-	-	✔	✔	-	-
Sun exposure; minimize exposure on treated areas	-	✔	-	-	-	-
Traumatized mucosa; use caution with application as there is potential for rapid systemic absorption	-	-	✔	✔	-	✔
Use caution when initiating treatment in patients with considerable dehydration	✔	-	-	-	-	-

*Synera® patches only

Drug Interactions

Table 8. Drug Interactions[1-11]

Generic Name	Interacting Medication or Disease	Potential Result
Lidocaine, lidocaine/ hydrocortisone, Lidocaine/prilocaine, Lidocaine/tetracaine	Antiarrhythmic dugs	When topical anesthetics and antiarrhythmic drugs are used concomitantly, the toxic effects are additive and potentially synergistic.
Lidocaine, lidocaine/ hydrocortisone, lidocaine/prilocaine, Lidocaine/tetracaine	Local anesthetics	When anesthetics are used concomitantly, the amount absorbed from all formulations must be considered.
Diclofenac	Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs)	Diclofenac may decrease the antihypertensive effect of ACE inhibitors and ARBs potentially precipitating renal failure. Monitor blood pressure, hyperkalemia and renal function.
Diclofenac	Anticoagulants (e.g., warfarin)	Diclofenac used concurrently with anticoagulant medications may result in an increased risk of bleeding. Monitor closely for bleeding, particularly gastrointestinal bleeding, which may be serious.
Diclofenac	Aspirin	Diclofenac may reduce the cardioprotective effect of low-dose uncoated aspirin and may cause a higher risk of gastric irritation.
Diclofenac	Cyclosporine	Diclofenac used concurrently with cyclosporine may lead to additive nephrotoxicity. Monitor renal function.
Diclofenac	Diuretics (loop diuretics, potassium sparing diuretics and thiazide diuretics)	Diclofenac may reduce the effectiveness of diuretics and cause hyperkalemia or nephrotoxicity. Monitor blood pressure, weight changes, urine output, potassium levels, and creatinine levels.
Diclofenac	Methotrexate	Diclofenac used with methotrexate may result in methotrexate toxicity. Avoid diclofenac administration within 10 days of high-dose methotrexate. If concomitant administration is necessary, monitor for toxicity, especially myelosuppression and gastrointestinal toxicity. Lower doses have been tolerated with nonsteroidal anti-inflammatory drug therapy; however, caution is advised.
Diclofenac	Lithium	Concurrent use of diclofenac and lithium may result in an increased risk of lithium toxicity. Monitor serum lithium levels for any symptoms of lithium toxicity.
Lidocaine/prilocaine, Lidocaine/tetracaine	Drugs associated with drug-induced methemoglobinemia (e.g., sulfonamides, acetaminophen, benzocaine, chloroquine, dapsone, nitrates, nitrites, nitrofurantoin, phenobarbital, phenytoin)	Prilocaine may contribute to the formation of methemoglobin when used concomitantly with drugs associated with inducing methemoglobin.

Dosage and Administration

Table 9. Dosing and Administration[1-11]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
Diclofenac epolamine	Treatment of acute pain due to minor strains, sprains, and contusions: Transdermal patch: apply one patch to the most painful area twice daily Max: two patches/day	Safety and efficacy in children have not been established.	Transdermal patch: 1.3%
Diclofenac sodium	Treatment of osteoarthritis pain of joints amenable to topical treatment, such as the knees hands: Topical gel: apply 4 g to the affected foot, knee or ankle four times daily; apply 2 g to the affected hand, elbow or wrist four times daily; maximum, 8 g daily to any single joint of the upper extremities and 16 g daily to any single joint of the lower extremities and 32 g daily, over all affected joints Treatment of signs and symptoms of osteoarthritis of the knee(s): Topical solution: apply 40 drops to the affected knee(s) four times daily	Safety and efficacy in children have not been established.	Topical gel: 1% Topical solution: 2% (20 mg/pump)
Lidocaine	Lubricant for endotracheal intubation: Jelly: apply a moderate amount to the external surface of the endotracheal tube shortly before use Topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx, topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract: Ointment: apply up to 5 g to dried oral mucosa Viscous solution: apply 15 mL no more frequently than every three hours; maximum, eight doses per 24 hours	Lubricant for endotracheal intubation: Jelly: dose varies with age and weight; maximum, 4.5 mg/kg Topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx Ointment: apply to previously dried oral mucosa; maximum, 4.5 mg/kg Viscous solution (<3 years of age): up to 1.25 mL applied with cotton tip applicator no more than every three hours; maximum, four doses in	Cream: 0.5% 3% 4% Gel: 2% Lotion: 3% (Ointment: 5% Solution: 4% Transdermal patch: 5% Viscous solution: 2%

Generic Name	Adult Dose	Pediatric Dose	Availability
	Relief of pain associated with postherpetic neuralgia: Transdermal patch: apply up to three patches to intact skin to cover the most painful area once for up to 12 hours within a 24-hour period Temporary relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes: Cream: apply a thin film to affected area two to three times daily Ointment: apply topically for adequate control of symptoms; a single application should not exceed 5 g For prevention and control of pain in procedures involving the male and female urethra: Jelly: instill 15 mL (males) or 3 to 15 mL (females) into the urethra; several minutes should be allowed before beginning urological procedures	12 hours Viscous solution (≥3 years of age): up to 4.5 mg/kg applied orally no more than every three hours; maximum, four doses in 12 hours Relief of pain associated with post-herpetic neuralgia: Safety and effectiveness in children have not been established. Temporary relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes: Cream (≥2 years of age): apply thin film to affected area two to three times daily Cream (≥12 years of age): apply a thick layer to intact skin; a single application in a child weighing between 10 kg and 20 kg should not be applied to an area larger than 600 cm^2 For prevention and control of pain in procedures involving the male and female urethra: Jelly: instill 15 mL (males) or 3 to 15 mL (females) into the urethra; several minutes should be allowed before beginning	Rectal Cream: 5%

Generic Name	Adult Dose	Pediatric Dose	Availability
		urological procedures	
Combination Products			
Lidocaine/ hydrocortisone	Relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area: Cream, lotion, pad: apply to affected area twice daily or as directed	Safety and effectiveness in children have not been established.	Cream: 3%/0.5% Rectal Cream: 2%/2% 3%/0.5% 3%/1% Rectal Gel: 3%/2.5% 2.8%/0.55% 3%/2.5%
Lidocaine/ prilocaine	Providing local analgesia on intact skin: Cream: apply 2 g of cream per 10 cm^2 of skin surface and allow to remain in contact with skin for at least two hours (major procedures) or apply 2.5 g of cream over 20 to 25 cm^2 of skin surface for at least one hour (minor procedure) Providing local analgesia on genital mucosal membranes for superficial minor surgery: Cream: apply 1 g per 10 cm^2 for 15 minutes (males) or apply 5 to 10 g for five to 10 minutes (females) Pretreatment for infiltration anesthesia: Cream: apply 2.5 g over 20 to 25 cm of skin surface area for at least one hour	Providing local analgesia on intact skin: Cream: dosage varies based on age and weight of child	Cream: 2.5%/2.5%
Lidocaine/ Tetracaine	Local Anesthesia: Apply one patch 20 – 30 (60) minutes before the procedure, remove patch before procedure Max: 1 patch at on the body at any time; area of application of cream should not exceed 400 cm^2	Topical Patch: same as adult Safety and effectiveness in children have not been established for cream use.	Patch 70 mg/70 mg Cream: 7%/7%

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
The American Gastroenterological Association: **Technical Review on the Diagnosis and Treatment of Hemorrhoids (2004)**[13]	• Universal recommendations include adding fiber to the diet and avoiding straining at defecation. • Over-the-counter topical agents are recommended despite the lack of supportive data regarding their efficacy. • Topical analgesics are useful for symptomatic relief of pain and itching. • Corticosteroid creams may decrease local inflammation but long-term use of high potency corticosteroids should be avoided. • There is no data to show that corticosteroids reduce hemorrhoidal swelling, bleeding, or protrusion. • Topical nitroglycerin may relieve pain associated with hemorrhoids by decreasing anal tone. • Flavonoids may be of benefit since they may increase venous tone, lymphatic drainage, capillary resistance, and may normalize capillary permeability. Nonoperative treatment such as banding and sclerotherapy, and operative procedures such as hemorrhoidectomy, may be useful in patients with more severe hemorrhoids and in those not responding to other treatments.
American Society of Colon and Rectal Surgeons: **Practice Parameters for the Management of Hemorrhoids, 2010 Update (2010)**[14]	• The evaluation of patients with hemorrhoids should include a direct history and physical examination. • In select patients with hemorrhoids and rectal bleeding, a complete endoscopic evaluation of the colon is warranted. • First line non-pharmacologic therapy for patients with symptomatic hemorrhoids includes adequate fluid and fiber intake. • Office-based procedures such as banding, sclerotherapy and infared coagulation may be effective in patients with grade I, II or III hemorrhoids in whom medical therapy has failed. • A majority of patients with thrombosed external hemorrhoids benefit from surgical excision within 72 hours of the symptom onset. Reserve surgical hemorrhoidectomy for patients who are refractory to office procedures, those who cannot tolerate office procedures, who have large external hemorrhoids, or who have combined internal and external hemorrhoids with significant prolapsed (grades III to IV).
American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)**[15]	<u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u> • It is recommended that health professionals should: o Evaluate the ability to perform activities of daily living. o Instruct in joint protection techniques. o Provide assistive devices, as needed, to help patients perform activities of daily living. o Instruct in use of thermal modalities. o Provide splints for patients with trapeziometacarpal joint osteoarthritis. <u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u> • It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical nonsteroidal anti-inflammatory drugs (NSAIDs),

Clinical Guideline	Recommendations
	including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. • It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. • It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. <u>Nonpharmacologic recommendations for the management of knee osteoarthritis</u> • It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis. o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs. o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in

Clinical Guideline	Recommendations
	combination with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> • It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. • It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. • No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> • It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). • It is conditionally recommend that patients with hip osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. • No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. <u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u> • It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections.

Clinical Guideline	Recommendations
	• It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. • No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. o Opioid analgesics.
American Academy of Orthopedic Surgeons: **Clinical Practice Guideline on Osteoarthritis of the Knee (2013)**[16]	Nonpharmacological/surgical therapy • Patients with symptomatic osteoarthritis of the knee should be encouraged to participate in self-management educational programs, lose and maintain weight loss if overweight (body mass index >25), participate in low-impact aerobic fitness exercises and use range of motion/flexibility exercises and quadriceps strengthening. • Patients with symptomatic osteoarthritis of the knee should use patellar taping for short-term relief of pain and improvement in function. Lateral heel wedges should not be prescribed for patients with symptomatic medial compartmental osteoarthritis of the knee. • Needle lavage and arthroscopy with debridement or lavage should not be used for patients with primary symptomatic osteoarthritis of the knee. Arthroscopic partial meniscectomy or loose body removal is an option in patients with symptomatic osteoarthritis of the knee that also have primary signs and symptoms of a torn meniscus and/or a loose body. Pharmacological therapy • Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee. • Patients with symptomatic osteoarthritis of the knee should receive one of the following analgesics for pain unless there are contraindications to this treatment: o o NSAIDs (topical or oral) o Tramadol • Cannot make a recommendation for or against the use of acetaminophen, opioids, pain patches, intraarticular corticosteroids, growth factor injections, and/or platelet rich plasma in symptomatic osteoarthritis of the knee • Hyaluronic acid should not be used in symptomatic osteoarthritis of the knee
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[17]	Painful polyneuropathy • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. • Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine). • Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. • Strong opioids are recommended third-line treatments due to concerns

Clinical Guideline	Recommendations
	regarding long-term safety, including addiction potential and misuse. • In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. Postherpetic neuralgia (PHN) • Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin. • Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. • Strong opioids and capsaicin cream are recommended as second-line therapies.
American Academy of Neurology/ American Association of Neuromuscular and Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[49]	Anticonvulsants • If clinically appropriate, pregabalin should be offered for treatment. • Gabapentin and sodium valproate should be considered for treatment. • There is insufficient evidence to support or refute the use of topiramate for treatment. • Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. Antidepressants • Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. • Venlafaxine may be added to gabapentin for a better response. • There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. Opioids • Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. Other pharmacologic options • Capsaicin and isosorbide dinitrate spray should be considered for treatment. • Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. • Lidocaine patch may be considered for treatment. • There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. Nonpharmacologic options • Percutaneous electrical nerve stimulation should be considered for treatment. • Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. • Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
American Association of	Neuropathy

Clinical Guideline	Recommendations
Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[50]	• All patients with type 2 diabetes should be assessed for neuropathy at the time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients. • Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene. • Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament. • Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes. • Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy. • When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized. • Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities. • Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms. • Maintain a referral network for podiatric and peripheral vascular studies and care.
American Diabetes Association: **Diabetic Neuropathies (2005)**[51]	Algorithm for the management of symptoms diabetic polyneuropathy • Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[52]	• Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN. • There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. • Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. • Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin. • In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN. • Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. • The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN. • There is insufficient evidence to make any recommendations on the long-term effects of these treatments.

Conclusions

The agents within the topical analgesic and anesthetic class include topical nonsteroidal antiinflammatory drugs (NSAIDs) and the single-entity and combination lidocaine products. Lidocaine is available in various formulations including creams, ointments, gels, solutions and a topical patch.[1] The lidocaine-containing products are generally Food and Drug Administration (FDA)-approved as a local anesthetic for oral mucous membrane use in laser/cosmetic surgeries; minor burns, cuts, and abrasions of the skin.[1-4,6] The lidocaine patch (Lidoderm®) is only indicated for the relief of pain associated with postherpetic neuralgia and provides up to 12 hours of analgesia.[5] Currently, all of the lidocaine formulations are available generically with the exception of the lidocaine patch.[1]

The NSAIDs are used for the treatment of moderate to severe pain in patients with osteoarthritis or who have failed to achieve adequate analgesia with acetaminophen.[47] The topical application of NSAIDs may reduce the risk of severe adverse events associated with oral NSAID use. Diclofenac epolamine (Flector®) is available in a 1.3% patch and is indicated for acute pain due to minor strains, sprains, and contusions. Diclofenac sodium is available as a topical 1% gel (Voltaren®) and 1.5% solution (Pennsaid®) that are FDA-approved for the treatment of osteoarthritis.[8,9] None of the topical NSAID products are available generically; however, oral formulations of diclofenac are available. Furthermore, no other NSAID is formulated as a topical preparation.[1]

Several studies have demonstrated the efficacy of various lidocaine preparations for use as a local anesthetic prior to venipuncture, operative procedures, and for the treatment of pain associated with lacerations from episiotomy and postpartum perineal tears. The efficacy of lidocaine in patients suffering from lacerations from episiotomies and patients with postpartum perineal tears was not significantly different from placebo.[26,27] Comparative trials with lidocaine cream 4%, lidocaine ointment 5% and lidocaine/prilocaine cream have not demonstrated significant differences in pain scores among patients.[17,20] In patients with postherpetic neuralgia, treatment with lidocaine patches resulted in significant pain relief compared to treatment with placebo.[21-25] The results of studies evaluating the topical NSAID products for the treatment of osteoarthritis or minor sprains, strain and contusions have consistently shown these products to be more effective with regard to pain intensity compared to placebo. To date, no head-to-head studies have been conducted comparing these agents.[28-41]

Current clinical guidelines addressing the treatment of hemorrhoids recommend the use of topical products for symptomatic relief despite the lack of supportive data.[13,14] There are no controlled trials that are adequate to evaluate the efficacy of this combination for these indications. Recent guidelines do not address the role of pharmacologic management in the treatment of hemorrhoids. In the treatment of postherpetic neuralgia, topical lidocaine may be considered a first-line treatment in the elderly patient, especially if there are concerns of adverse events with the use of oral medications.[17] For the initial management of osteoarthritis of the hand or knee, pharmacologic treatments include NSAIDs (oral or topical) or tramadol. Topical capsaicin may also be an initial treatment option for osteoporosis pain of the hand, and acetaminophen or intraarticular corticosteroids injections may be used in those with knee involvement. No one topical NSAID product is recommended over another within guidelines.[15]

References

1. Lidocaine ointment 5% [package insert]. Amityville (NY): Hi-Tech Pharmacal Co.; 2011 Sep.
2. AneCream® [package insert]. Knoxville (TN): Focus Health Group; 2011 Dec.
3. Lidocaine HCl 3% - Hydrocortisone Acetate 0.5% Creame [package insert]. San Fernado (CA): PharmaPure RX; 2011 Jun.
4. Lidoderm® [package insert]. Malvern (PA): Endo Pharmaceuticals Inc.; 2014 Jul.
5. Xylocaine® [package insert]. Lake Forest (IL): Oak Pharmaceuticals, Inc.; 2012 Jun.
6. EMLA® [package insert]. Lake Forest (IL): Oak Pharmaceuticals, Inc.; 2012 Nov.
7. Synera ® [package insert]. Souderton (PA): Galen US, Inc.; 2014 Mar.
8. Pliaglis ® [package insert]. Fort Worth (TX): Galderma Laboratories, L.P.; 2010 Oct.
9. Voltaren® [package insert]. Chadds Ford (PA): Endo Pharmaceuticals Inc.; 2009 Oct.
10. Pennsaid® [package insert]. Hazelwood (MO): Mallinckrodt Brand Pharmaceuticals Inc.; 2014 Jan.
11. Flector Patch® [package insert]. Sanbonmatsu, Kagawa, Japan: Teikoku Seiyaku Co., Ltd.; 2011 Aug.
12. Galer BS. A comparative subjective assessment study of PENNSAID® and Voltaren Gel®, two topical formulations of diclofenac sodium. Pain Pract. 2011 May-Jun;11(3):252-60.
13. American Gastroenterological Association. Technical review on the diagnosis and treatment of hemorrhoids. Gastroenterology. 2004;126:1463-73.
14. Rivadeneira DE, Steele SR, Ternent C, Chalasani S, Buie WD, Rafferty JL, et al. Practice parameters for the management of hemorrhoids (revised 2010). Dis Colon Rectum. 2011 Sep;54(9):1059-64.
15. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):455-74.
16. American Academy of Orthopedic Surgeons: Clinical practice guideline on the treatment of osteoarthritis of the knee (non-arthroplasty). Rosemont (IL): 2013 [Guideline on the internet] [cited 2014 July 25] Available from: http://www.aaos.org/research/guidelines.
17. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010 Sep;17(9):1113-e88.
18. Micromedex® Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2014 [cited 2014 Aug 14]. Available from: http://www.thomsonhc.com/.
19. Çelik G, Özbek O, Yılmaz M, Duman I, Özbek S, Apiliogullari S. Vapocoolant spray vs lidocaine/prilocaine cream for reducing the pain of venipuncture in hemodialysis patients: a randomized, placebo-controlled, crossover study. Int J Med Sci. 2011;8(7):623-7.
20. Koh J, Harrison D, Myers R, et al. A randomized, double-blind comparison study of EMLA® and ELA-Max® for topical anesthesia in children undergoing intravenous insertion. Pediatric Anesthesia. 2004;14:977-82.
21. Dutta A, Puri G, Wig J. Piroxicam gel, compared to EMLA cream is associated with less pain after venous cannulation in volunteers. Can J Anesth. 2003;50(8):775-8.
22. McCluskey A, Currer B, Sayeed I. The efficacy of 5% lidocaine-prilocaine (EMLA) cream on pain during intravenous injection of propofol. Anesth Analg. 2003;97:713-4.
23. Moppett I, Szypula K, Yoeman P. Comparison of EMLA and lidocaine iontophoresis for cannulation analgesia. Eur J Anaesthesiol. 2004;21:210-3.
24. Kuvaki B, Gokmen N, Gunenc F, et al. EMLA® does not permit pain-free retrobulbar injection. Acta Anaesthesiol Scand. 2003;47:739-41.
25. Herberger K, Krause K, Maier K, Zschocke I, Radtke M, Augustin M. Local anesthetic effects of Lidocaine cream: randomized controlled trial using a standardized prick pain. J Dermatolog Treat. 2012 Dec;23(6):437-42. doi: 10.3109/09546634.2011.593486. Epub 2011 Jul 31.
26. Devers A, Galer B. Topical lidocaine patch relieves a variety of neuropathic pain conditions: and open-label study. Clin J Pain. 2000;16(3):205-8.
27. Katz N, Gammaitoni A, Davis M, et al. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. Pain Medicine. 2002;3(4):324-32.

28. Galer B, Jensen M, Ma T, Davies P, Rowbotham M. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, three-week efficacy study with use of the neuropathic pain scale. Clin J Pain. 2002;18(5):297-301.
29. Galer B, Rowbotham M, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. Pain. 1999;80:533-8.
30. Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain. 2003;106:151-8.
31. Corkill A, Lavender T, Walkinshaw S, Alfirevic Z. Reducing postnatal pain from perineal tears by using lidocaine gel: a double-blind randomized trial. Birth. 2001;28(1):22-7.
32. Minassian V, Jazayeri A, Prien S, Timmons R, Stumbo K. Randomized trial of lidocaine ointment vs placebo for the treatment of postpartum perineal pain. Obstetrics and Gynecology. 2002;100(6):1239-43.
33. Hopper SM, McCarthy M, Tancharoen C, Lee KJ, Davidson A, Babl FE. Topical lidocaine to improve oral intake in children with painful infectious mouth ulcers: a blinded, randomized, placebo-controlled trial. Ann Emerg Med. 2014 Mar;63(3):292-9. doi: 10.1016/j.annemergmed.2013.08.022. Epub 2013 Nov 7.
34. Galer B, Rowbotham M, Perander J, Devers A, Friedman E. Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. Journal of Pain Symptom Management. 2000;19:287-94.
35. Kuehl K, Carr W, Yanchick J, Magelli M, Rovati S. Analgesic efficacy and safety of the diclofenac epolamine topical patch 1.3% (DETP) in minor soft tissue injury. Int J Sports Med. 2011 Aug;32(8):635-43.
36. Predel HG, Koll R, Pabst H, et al. Diclofenac patch for topical treatment of acute impact injuries: a randomized, double blind, placebo controlled, multicenter study. British Journal of Sports Medicine. 2004;38:318-23.
37. A 12-week, randomized, double-blind, multi-center, vehicle-controlled, parallel group study to assess the efficacy and safety of diclofenac sodium gel (DSG) 1% for the relief of signs and symptoms in patients with osteoarthritis of the knee. Novartis unpublished clinical trial. Study Number VOSG-PN-310. Available at: http://www.novartis.com.
38. An eight-week, multi-center, randomized, double-blind, placebo-controlled, parallel group trial of diclofenac sodium 1% gel in patients with primary osteoarthritis of the hand. Novartis unpublished clinical trial. Study Number VOSG-PE-315. Available at: http://www.novartis.com.
39. An eight-week, multi-center, randomized, double-blind, placebo-controlled, parallel group trial of diclofenac sodium gel 1% in patients with primary osteoarthritis of the hand. Novartis unpublished clinical trial. Study Number VOSG-PE-314. Available at: http://www.novartis.com.
40. A 12-week, randomized, double-blind, multi-center, vehicle-controlled, parallel group study to assess the efficacy and safety of diclofenac sodium gel 1% for the relief of signs and symptoms in patients with osteoarthritis of the knee. Novartis unpublished clinical trial. Study Number VOSG-PN-304. Available at: http://www.novartis.com.
41. Peniston JH, Gold MS, Alwine LK. An open-label, long-term safety and tolerability trial of diclofenac sodium 1% gel in patients with knee osteoarthritis. Phys Sports Med. 2011 Sep;39(3):31-8.
42. Hsieh LF, Hong CZ, Chern SH, Chen CC. Efficacy and side effects of diclofenac patch in treatment of patients with myofascial pain syndrome of the upper trapezius. J Pain Symptom Manage. 2010 Jan;39(1):116-25.
43. Altman RD, Dreiser RL, Fisher CL, Chase WF, Dreher DS, Zacher J. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. J Rheumatol. 2009 Sep;36(9):1991-9.
44. Simon LS, Grierson LM, Naseer Z, Bookman AA, Zev Shainhouse J. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared to those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. Pain. 2009 Jun;143(3):238-45.
45. Zacher J, Altman R, Bellamy N, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin. 2008 Apr;24(4):925-50.

46. Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomized placebo-controlled trials. Eur J Pain. 2007 Feb;11(2):125-38.
47. Green S, Buchbinder R, Barnsley L, et al. Nonsteroidal anti-inflammatory drugs for treating lateral elbow pain in adults. Cochrane Database Syst Rev. 2002;(2):CD003686.
48. Peniston JH, Gold MS, Wieman MS, Alwine LK. Long-term tolerability of topical diclofenac sodium 1% gel for osteoarthritis in seniors and patients with comorbidities. Clin Interv Aging. 2012;7:517-23. doi: 10.2147/CIA.S35416. Epub 2012 Nov 20.
49. Bril V, England J, Franklin GM, Backonja M, Cohen J, Del Toro D, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011 May 17:76(20):1758-65.
50. Rodbard HW, Blonde L, Braithwaite SS, Brett EM, Cobin RH, Handelsman Y, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract. 2007 May-Jun;13(Suppl 1):S1-68.
51. Boulton AJ, Vinkik AL, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-62.
52. Dubinsky RM, Kabbani H, El-Chami, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2004;63:959.
53. Kalunian KC. Pharmacologic therapy of osteoarthritis. In: Basow DS (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sep 8]. Available from: http://www.utdol.com/utd/index.do.