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TOPICAL LIDOCAINE PRODUCTS

Drug Regimen Review Center

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Contents

Introduction	3
Indications.....	4
Table 1. Summary of Available Lidocaine Products	5
Mechanism of Action	13
Methods.....	13
Clinical Guidelines	13
Table 2. Summary of Current Clinical Guidelines	14
Clinical Efficacy.....	18
Update (2013-2015).....	19
Unlabeled Uses	19
Topical Lidocaine Patch.....	19
Safety	19
Utah Medicaid Utilization Data.....	21
Summary	22
Factors and limitations to consider when considering the TCI place in therapy.....	27
Recommended Clinical Criteria.....	27
Appendix 1: Evidence Tables	28
Evidence Table: Clinical Evidence Evaluating the Topical Lidocaine Products	28
Appendix 2: Drug Information	32
Table 1. Comparison of the Topical Analgesic and Anesthetic Agents.....	32
Table 2. Summary of Pharmacokinetics of the Topical Analgesic and Anesthetic Agents	35
References	38

Introduction

Topical analgesic and anesthetic agents are indicated in the treatment of pain associated with minor procedures and in the symptomatic relief of pain associated with various localized muscle, joint or skin disorders, including burns, abrasions, sore throat, post-herpetic neuralgia, arthritis and hemorrhoids.^{1,2} Efficacy of the topical agents can vary depending on the disorder being treated. In general, the topical analgesic and anesthetic agents are most effective in the temporary relief of pain associated with minor disorders. Systemic analgesic agents tend to be more effective in the treatment of pain but the topical agents are often preferred as they are associated with fewer systemic adverse effects, including constipation, sedation and respiratory depression. While analgesic and anesthetic agents are effective in treating pain, they are not curative. The cause of the underlying pain should be identified and treated or eliminated in addition to temporary relief of the pain symptoms.^{1,2}

Many topical analgesic and anesthetic agents are currently available for use in the United States: benzocaine, benzyl alcohol, capsaicin, dibucaine, diclofenac, dyclonine, ethyl chloride, hexylresorcinol, lidocaine, pramoxine, proparacaine, tetracaine and trolamine.^{3,4} The analgesic and anesthetic agents are available as aerosols, creams, gels, lotions, lozenges, ointments, patches, solutions and rectal products. Many of the agents are available as over-the-counter products and in mucosal formulations for the treatment of pain associated with mucous membranes and rectal formulations for the treatment or temporary relief of pain associated with hemorrhoids. All of the topical agents are indicated in the treatment or temporary relief of pain and itching associated with minor surgeries, burns, cuts, abrasions, post-herpetic neuralgia, arthritis and other muscle, joint, or skin irritations. A number of combination analgesic and anesthetic products are also available for use in the United States: benzocaine/butamben/tetracaine (Cetacaine[®]), lidocaine/hydrocortisone (various), lidocaine/prilocaine (EMLA[®], Oraqix[®]), lidocaine/tetracaine (Synera[®]), methyl salicylate/menthol (BenGay[®]; Icy Hot[®], others). Tables 1, 2 and 3 in Appendix 2 compare all of the available topical analgesic and anesthetic agents.^{3,4}

This report will focus in the safety and efficacy of the topical lidocaine products. Topical lidocaine is available in a number of over-the-counter and prescription formulations: creams, gels, ointments, patches, solutions and sprays. In general, the lidocaine products are indicated in the treatment or temporary relief of pain and itching associated with minor surgeries, burns, cuts, abrasions, post-herpetic neuralgia, arthritis and other muscle, joint, or skin irritations. Table 1 provides a summary of the available lidocaine products.

Individual topical lidocaine agents may vary in efficacy as a result of differences in potency, vehicle formulation, frequency of application, site of application, disease or pain being treated, individual patient characteristics and whether or not an occlusive dressing is used.¹⁻⁴ For example, occlusive vehicles, like ointments, may increase analgesic activity as they provide increased skin hydration and increased skin permeability. Using a transdermal formulation may also increase analgesic activity. The solubility of the topical agents can affect penetration into the epidermis; propylene glycol is a solvent found in many topical preparations that tends to increase the potency of the agent. Peanut oil is added to some topical agents to form a preparation that is thinner and easier to apply while maintaining the hydrating properties. Creams have increased amounts of petrolatum, are less oily and may be more cosmetically appealing but less hydrating. Lotions, solutions and gels have less penetration but may be more useful in treating diseases in hair-bearing areas. Other formulations, like patches, foams or sprays, may increase convenience.^{1,2}

Indications

Labeled indications may vary between the topical agents. In general, the topical lidocaine creams, gels, ointments, sprays and over-the-counter (OTC) patches are recommended for use on intact skin to provide temporary relief of pain, itching and minor skin irritations. The topical Lidoderm® patch, available by prescription only, is labelled for use in relief of pain associated with postherpetic neuralgia. The topical viscous lidocaine solutions are indicated to produce topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx. Table 1 provides a summary of the labeled indications for the available lidocaine products.

Table 1. Summary of Available Lidocaine Products^{5,6}

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
Topical Patches				
5% lidocaine patch (Lidoderm®) [contains disodium edta, methylparaben, propylene glycol, propylparaben]	RX only, Generic available *Lidoderm® listed as preferred on the PDL; not covered Ntrad or PCN	For relief of pain associated with postherpetic neuralgia.	Apply the prescribed number of patches (max of 3 patches) once for up to 12 hours within a 24 hour period.	When used as recommended, only 1-5% of the lidocaine dose will be absorbed systemically. Peak plasma concentration is about 0.13 ug/mL (or 1/10 of the systemic concentrations used to treat arrhythmias).
4% lidocaine patch (Lidoflex®, Prolida®, others)	OTC *Prolida® listed as non-preferred on the PDL	For the temporary relief of pain.	For adults and children >12 years of age, apply patch for up to 8 up to 3 times daily; do not apply for >12 hours or >3 times daily.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.
70 mg lidocaine 70 mg tetracaine per patch (Synera®)	RX only, No generic available *listed as non-preferred on the PDL	For use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological procedures such as excision, electrodesiccation and shave biopsy of skin lesion.	Apply patch 20-30 minutes before venipuncture or intravenous cannulation and for 30 min before superficial dermatological procedures.	Application of one patch for 30 minutes resulted in peak plasma concentration of <5 ng/mL lidocaine and <0.9 ng/mL tetracaine.
Topical Creams				
2% lidocaine cream (Xolido®, others)	OTC	For temporary relief of pain and itching and minor skin irritations due to minor cuts and scrapes, sunburns and minor burns.	For adults and children two-years or older, apply externally to the affected area. Do not use more than 3-4 times per day.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.
3% lidocaine cream (various)	RX only, Generic available	Anesthetic for 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.	Apply a thin film to the affected area two or three times daily or as directed by a physician.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage. Lidocaine is more readily absorbed through mucous membranes and the GI tract. Following GI absorption, little intact drug reaches circulation because of extensive biotransformation in the liver.

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
3.75% lidocaine cream (Lidozol®)	RX only, No generic available *listed as non-preferred on the PDL	For relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness, pruritus ani, pruritus vulvae, hemorrhoids, anal fissures and similar conditions of skin and mucous membranes.	Apply a thin film to the affected area two or three times daily or as directed by a physician.	Lidocaine may be absorbed following topical administration to mucous membranes, its rate and extent of absorption depending upon the specific site of application, duration of exposure, concentration and total dosage.
3.95% lidocaine cream (Lidovin®)	RX only, No generic available *listed as non-preferred on the PDL	For 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.	Apply a thin film to the affected area two or three times daily or as directed by a physician.	Lidocaine may be absorbed following topical administration to mucous membranes, its rate and extent of absorption depending upon the specific site of application, duration of exposure, concentration and total dosage.
4% lidocaine cream (Anecream®, others)	OTC	For temporary relief of pain and itching and minor skin irritations due to minor cuts and scrapes, sunburns and minor bumps.	For adults and children two-years or older, apply externally to the affected area. Do not use more than 3-4 times per day.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.
5% lidocaine cream (Xolido®, others)	OTC	For temporary relief of pain and itching and minor skin irritations due to minor cuts and scrapes, sunburns and minor bumps.	For adults and children two-years or older, apply externally to the affected area. Do not use more than 3-4 times per day.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.
2% lidocaine HCl 2% hydrocortisone acetate in a 1% Coleus Forskohlii base with cleansing wipes (Ana-Lex® kit; rectal)	RX only, No generic available *listed as non-preferred on the PDL	Used for the anti-inflammatory and anesthetic relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area.	Fill applicator until full. For internal use, insert the applicator tip into the anus and expel its contents to the affected areas. For external use, squeeze the applicator and expel its contents to the affected anal and peri-anal areas. Use as recommended.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage. Lidocaine is more readily absorbed through mucous membranes and the GI tract. Following GI absorption, little intact drug reaches circulation because of extensive biotransformation in the liver.

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
3% lidocaine HCl 1% hydrocortisone (AnaMantle HC® Forte, others; rectal use only)	RX only, Generic available	To decrease swelling, itching, and pain that is caused by minor rectal irritation or hemorrhoids.	Fill applicator until full. For internal use, insert the applicator tip into the anus and expel its contents to the affected areas. For external use, squeeze the applicator and expel its contents to the affected anal and peri-anal areas. Use as recommended.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage. Lidocaine is more readily absorbed through mucous membranes and the GI tract. Following GI absorption, little intact drug reaches circulation because of extensive biotransformation in the liver.
3% lidocaine HCl 0.5% hydrocortisone (AnaMantle HC®, others)	RX only, Generic available	To decrease swelling, itching, and pain that is caused by minor rectal irritation or hemorrhoids.	Fill applicator until full. For internal use, insert the applicator tip into the anus and expel its contents to the affected areas. For external use, squeeze the applicator and expel its contents to the affected anal and peri-anal areas. Use as recommended.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage. Lidocaine is more readily absorbed through mucous membranes and the GI tract. Following GI absorption, little intact drug reaches circulation because of extensive biotransformation in the liver.
2.5% lidocaine 2.5% prilocaine cream (Relador® Pak Plus, EMLA®, others)	RX only, Generic available	For use as a topical anesthetic on normal intact skin for local analgesia and genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.	Adults-Intact Skin: Apply a thick layer and cover with occlusive dressing. Minor dermal procedures: Apply 2.5 gm over 20-25 cm ² of skin for at least 1 hour. Major dermal procedures: Apply 2 gm per 10 cm ² of skin for at least 2 hours. Adult Male genital skin: Apply 1 gm per 10 cm ² of skin for 15 minutes. Adult female genital mucous membranes: Apply 5-10 gm for 5-10 minutes.	Systemic absorption is related to the duration and to the area over which it is applied. When 60 gm was applied over 400 cm ² for 24 hours, peak blood levels of lidocaine were 0.28 ug/ml and 1/20 the systemic toxic level and peak blood levels of prilocaine were 0.14 ug/mL and 1/35 the systemic toxic level. For application to female genital mucous membranes, 10 g applied for 10-60 minutes in the vaginal fornices resulted in peak plasma concentrations of 148- 641 ng/mL for lidocaine and 40-346 ng/mL for prilocaine. Levels which cause systemic toxicity are approximately 5000 ng/mL for lidocaine and prilocaine. Application to broken or inflamed skin or to areas >2,000 cm ² could result in higher plasma levels.

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
7% lidocaine 7% tetracaine Cream (Pliaglis®)	RX only, No generic available *listed as non-preferred on the PDL	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.	For use only on intact skin. For superficial dermatological procedures such as dermal filler injection, non-ablative laser facial resurfacing, or pulsed-dye laser therapy, apply cream for 20-30 minutes before procedure. For superficial dermatological procedures, such as laser-assisted tattoo removal, apply cream 60 minutes prior to the procedure.	The amount of lidocaine and tetracaine absorbed systemically is directly related to the duration and surface area over which it is applied. Application of 59 gm over 400 cm ² for up to 2 hours resulted in peak plasma concentrations of lidocaine of 220 ng/mL and of tetracaine of <0.9 ng/mL. Systemic absorption was proportional to the surface area of application and increased with application time up to 60 minutes.
0.5% lidocaine 0.5% phenol cream (Budpak® First Aid, others)	OTC	To help prevent the risk of skin infection in minor cuts, scrapes, or burns.	Apply an amount equal to the surface area of the tip of a finger to the affected area up to 1-3 times daily. May cover with a sterile bandage.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.
Topical Gels				
3.5% lidocaine gel (Akten®)	RX only, No generic available	For ocular surface anesthesia during ophthalmologic procedures.	Apply 2 drops to the ocular surface. May be reapplied to maintain anesthesia	Lidocaine may be absorbed following topical administration to mucous membranes. The amount of absorption depends upon the dose, site of application, viscosity of the agent, and duration of exposure.
3% Lidocaine gel (Lidocin®, others)	RX only, No generic available *listed as non-preferred on the PDL	For temporary relief of pain associated with minor cuts, scrapes and minor skin irritations.	Apply directly to effected area. Do not use more than four times per day.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
2% lidocaine gel/jelly (Xylocaine®, others)	RX only, Generic available	For the prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal).	<p>The required dosage for anesthesia varies depending on the area to be anesthetized, vascularity of the tissues, individual tolerance, and the technique of anesthesia. The lowest effective dosage to provide anesthesia should be used.</p> <p>Surface anesthesia of the male urethra: Using a sterilized cone attachment, instill 15 mL into the urethra or until the patient has a feeling of tension. Apply a penile clamp at the corona. An additional 15 mL can be applied for adequate anesthesia.</p> <p>Surface anesthesia of the female urethra: Using a sterilized cone attachment, instill 3-5 mL into the urethra.</p> <p>Lubrication for endotracheal intubation: Apply a moderate amount of the jelly onto the external surface of the endotracheal tube shortly before use.</p> <p>No more than 600 mg of lidocaine should be given in a 12 hour period.</p>	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage. Lidocaine is more readily absorbed through mucous membranes and the GI tract. Following GI absorption, little intact drug reaches circulation because of extensive biotransformation in the liver.
3% Lidocaine 2.5% hydrocortisone gel (LidoCort™, others)	RX only, Generic available *Lidocort™ is listed as non-preferred on the PDL	Product is used for the anti-inflammatory and anesthetic relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area.	Apply product to the affected area(s) twice daily or as directed by a physician.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
2.8% Lidocaine 0.55% hydrocortisone gel (Rectagel®; rectal use only)	RX only, Generic available	To decrease swelling, itching, and pain that is caused by minor rectal irritation or hemorrhoids.	Fill applicator until full. For internal use, insert the applicator tip into the anus and expel its contents to the affected areas. For external use, squeeze the applicator and expel its contents to the affected anal and peri-anal areas. Use as recommended.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage. Lidocaine is more readily absorbed through mucous membranes and the GI tract. Following GI absorption, little intact drug reaches circulation because of extensive biotransformation in the liver.
2.5% lidocaine 2.5% prilocaine gel (Oraqix®)	RX only, No generic available	Indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing.	Apply onto the gingival margin around selected teeth using the applicator. Wait 30 seconds. Fill the periodontal pockets with the applicator until the gel becomes visible at the gingival margin. Wait another 30 seconds. Maximum dose is 5 cartridges per treatment session (8.5 g gel).	Lidocaine and prilocaine are absorbed from oral mucous membranes. A single application of 0.9-3.5 g resulted in peak plasma concentrations of 182±53 ng/mL for lidocaine and 77±27 ng/mL for prilocaine. After a total dose of 8-8.5 g, applied as repeated applications over 3 hours, resulted in peak plasma concentrations of 284±122 ng/mL for lidocaine and 106±45 ng/mL for prilocaine. Signs of toxicity with lidocaine occur around 5000 ng/mL, but a small number of patients may show signs of toxicity at 1000 ng/mL. Pharmacological thresholds for prilocaine are not well established.
Topical Sprays				
0.5% lidocaine spray (Solarcaine)	OTC	Temporarily relieves itching and pain due to: sunburn, minor cuts, scrapes, insect bites, minor skin irritations.	Apply to the affected area up to 3-4 times daily. When applying to face, spray into the palm of the hand and gently apply.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.
9.6% w/w lidocaine spray (Male Genital Desensitizer Stud 100)	OTC	Temporarily reduces sensitivity of the penis, which helps to delay ejaculation.	Apply 3 or more sprays to the head and shaft of the penis before intercourse, or as directed by a doctor. Do not exceed 10 sprays during one application or 24 sprays in 24 hours.	Topical lidocaine systemic absorption is dependent upon the specific site of application, duration of exposure, and total dosage.

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
Topical Solutions				
4% lidocaine solution (Laryng-o-jet®)	RX only, No generic available	Indicated for the topical anesthesia of the mucous membranes of the respiratory tract.	For laryngoscopy, bronchoscopy, and endotracheal intubation spray the pharynx with 1-5 mL. The maximum recommended dosage is <300 mg and never to exceed 4.5 mg/kg.	Topical lidocaine is absorbed through mucous membranes. The rate and extent of absorption depends upon the concentration and total dose administered, the site of application, and duration of exposure. The rate of absorption is greatest after intratracheal administration. Peak blood levels occur as early as 5 minutes and as late as 30 minutes following endotracheal administration.
4% lidocaine solution (Lidocaine viscous solution)	RX only, Generic available	For the production of topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract.	When used as a spray, or when applied by means of cotton applicators or packs, as when instilled into a cavity, the suggested dosage of 4% Xylocaine Topical Solution is 1 to 5 mL (40 to 200 mg lidocaine HCl), ie, 0.6 to 3 mg/kg or 0.3 to 1.5 mg/lb body weight. Dosages should be reduced for children and for elderly and debilitated patients. The maximum dose should not exceed 4.5 mg/kg (2 mg/lb) of body weight.	Topical lidocaine is absorbed through mucous membranes. The rate and extent of absorption depends upon the concentration and total dose administered, the site of application, and duration of exposure. Caution should be exercised, particularly when employing large volumes, since the incidence of systemic absorption and adverse effects is directly proportional to the total dose of local anesthetic agent administered.
2% lidocaine solution (Lidocaine viscous solution)	RX only, Generic available	For the production of topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx. It is also useful for reducing gagging during the taking of X-ray pictures and dental impressions.	For symptomatic relief of irritated or inflamed mucous membranes of the oropharynx, use 15 mL, swish around the mouth, and spit out. Wait at least 3 hours between doses. Not to exceed 8 doses in a 24-hour period.	Topical lidocaine is absorbed through mucous membranes. The rate and extent of absorption depends upon the concentration and total dose administered, the site of application, and duration of exposure. The rate of absorption is greatest after intratracheal administration.

Drug	Availability	Indication or uses	Dosing	Systemic Absorption
Topical Ointment				
5% lidocaine ointment (LidoRXKit®, others)	RX only, Generic available	<p>For production of anesthesia of accessible mucous membranes of the oropharynx.</p> <p>It is also useful as an anesthetic lubricant for intubation and for the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites.</p>	A single application should not exceed 5 g of ointment (approximately 300 mg of lidocaine HCl). No more than 17-20 g of ointment should be administered in one day.	Topical lidocaine is absorbed through mucous membranes. The rate and extent of absorption depends upon the concentration and total dose administered, the site of application, and duration of exposure. The rate of absorption is greatest after intratracheal administration.

Key: RX- available by prescription, OTC- available over-the-counter, PDL- Utah Medicaid Preferred Drug List, Ntrad- non-traditional Medicaid coverage, PCN- primary care network Medicaid coverage

Mechanism of Action

Each type of topical anesthetic and analgesic has a distinct mechanism of action. The agents identified broadly as local anesthetics include benzocaine, proparacaine, tetracaine, articaine, dibucaine, lidocaine, prilocaine, pramoxine and dyclonine. This group of agents is further categorized according to molecular type: esters, amides or ethers. While the agents have different molecular makeups, the mechanism of action is the same for each. The local anesthetics work by blocking the permeability of sodium ions to the neuronal membrane, thus stabilizing the electric potential of the neuron.⁷⁻⁹ Stabilizing the neuron effectively blocks the initiation and conduction of nerve impulses, and leads to ‘numbing’ of the affected area. Generally, these agents have little to no systemic absorption through the skin. However, if the skin is broken or damaged or if applied to mucous membranes, the topical anesthetics can be well absorbed systemically. See Table 2 in Appendix 2 for a summary of the pharmacokinetic data available for the topical analgesic and anesthetic agents.

Methods

A Utah Medicaid P&T Drug Class Review on the Topical Analgesic and Anesthetic Agents was published in 2013 (literature search through November 2013).¹⁰ The P&T report includes a summary of the guideline recommendations, systematic reviews and comparative clinical trials available for the topical agents. According to the review, the topical lidocaine products are more effective than placebo and demonstrate similar rates of safety and efficacy in treating or reducing localized pain.

For this report, a PubMed and Cochrane Library literature search for systematic reviews and randomized controlled trials (RCTs) was conducted since November 2013. The Agency for Healthcare Research and Quality (AHRQ), the FDA website (including product labeled information), Micromedex and Lexicomp were also searched for safety information, systematic reviews, clinical trials and guidelines. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first, followed by phase 3 randomized controlled trials, followed by other published phase 3 trials.

Clinical Guidelines

The Institute for Clinical Systems Improvement (2013), American Family Physician (2011), European Federation of Neurological Societies (EFNS, 2010), International Association for the Study of Pain (2007) and American Academy of Neurology (2004) recommend the lidocaine 5% patch (Lidoderm®) as first or second-line treatment options in patients with postherpetic neuralgia. The American Society of Anesthesiologists (2010), American Society of Regional Anesthesia and Pain Medicine (2010) and

American Family Physician (2010) also recommend topical lidocaine for treatment of peripheral neuropathic pain. Topical lidocaine agents, particularly those including hydrocortisone, are effective for temporary relief of pain caused by anorectal disorders. Table 2 provides a summary of the available clinical guidelines and recommendations available for use of the topical lidocaine products.

Table 2. Summary of Current Clinical Guidelines

Clinical Indication or Use (in alphabetical order)	Guideline or Resource	Clinical Recommendation for Use
Intravesical treatment of interstitial cystitis and bladder pain syndrome	2011 – American Urological Association (AUA) Guideline For The Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome	Intravesical lidocaine is recommended as a second-line treatment, after self-care practices and behavioral modifications, for pain related to interstitial cystitis and bladder pain syndrome. Adverse effects are not typically serious but include bladder pain, dysuria, and urethral irritation. Relief is short term and is typically less than 2 weeks. ¹¹
Localized provoked vulvodynia (e.g., vaginal pain during sex, tampon insertion, etc.)	2014 - UK National Guideline on the Management of Vulval Conditions	Topical local anesthetics, e.g. 5% lidocaine ointment or 2% lidocaine gel, should be applied 15-20 prior to penetration and used with caution as they may cause irritation. If used prior to penetrative sex, the lidocaine should be washed off or the partner should use a condom. Oral contact should be avoided. ¹²
Neuropathic pain	<p>2010 - Practice Guidelines for Chronic Pain Management: An Updated Report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine</p> <p>2010 - Treating Diabetic Peripheral Neuropathic Pain by the American Family Physician</p> <p>2010 - Peripheral Neuropathy: Differential Diagnosis and Management by the American Family Physician</p>	<p>May be used in patients with peripheral neuropathic pain: Observational studies have shown that topical agents, including lidocaine, provide relief for peripheral neuropathic pain during assessment periods ranging from 3-6 weeks.¹³</p> <p>Common topical treatments for diabetic peripheral neuropathic pain include capsaicin cream (Zostrix) and lidocaine 5% patches (Lidoderm).¹⁴</p> <p>Several pharmacologic options exist to treat neuropathic pain, including some antiseizure medications (e.g., gabapentin [Neurontin], topiramate [Topamax], carbamazepine [Tegretol], pregabalin [Lyrica]) and antidepressants (e.g., amitriptyline). Topical patches and sprays containing lidocaine (Lidoderm) or capsaicin</p>

Clinical Indication or Use (in alphabetical order)	Guideline or Resource	Clinical Recommendation for Use
		(Zostrix) also may relieve pain in some patients. Other supportive measures, such as foot care, weight reduction, and shoe selection, may also be helpful. Narcotics may have a role in the treatment of chronic neuropathic pain in selected patients; candidates initially should be evaluated for their risk of substance abuse and addiction, and several nonnarcotic regimens should be tried first. ¹⁵
Postherpetic neuralgia	<p>2013 - Institute for Clinical Systems Improvement. Assessment and Management of Chronic Pain.</p> <p>2011 - Herpes Zoster and Postherpetic Neuralgia: Prevention and Management by the American Family Physician</p> <p>2010 - European Federation of Neurological Societies (EFNS) Guidelines on Pharmacological Treatment of Neuropathic Pain</p> <p>2007 - General Guidelines for the Treatment of Neuropathic Pain issued by the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain</p> <p>2004 - Practice Parameter: Treatment of postherpetic neuralgia; An evidence-based report of the Quality Standards Subcommittee of the American</p>	<p>Topical lidocaine 5% patches are FDA approved for postherpetic neuralgia and have shown efficacy in other neuropathic pain syndromes. Systemic absorption of lidocaine is minimal, and the patch has a clean safety profile with the correct dosage schedule.¹⁶</p> <p>Evidence supports treating postherpetic neuralgia with tricyclic antidepressants, gabapentin, pregabalin, long-acting opioids or tramadol; moderate evidence supports the use of capsaicin cream or a lidocaine patch as a second-line agent. Immunization to prevent herpes zoster and postherpetic neuralgia is recommended for most adults 60 years and older.¹⁷</p> <p>Recommended for use in postherpetic neuralgia as a lidocaine patch (up to 3 patches per day). First line treatment in the elderly, particularly with concerns of CNS side effects with other oral agents.¹⁸</p> <p>First-line treatments for postherpetic neuralgia include tricyclic antidepressants, gabapentin and pregabalin, and the topical lidocaine 5% patch.¹⁹</p> <p>Based upon class I evidence, topical lidocaine is effective in reducing the pain of postherpetic neuralgia. Overall, tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and</p>

Clinical Indication or Use (in alphabetical order)	Guideline or Resource	Clinical Recommendation for Use
	Academy of Neurology	maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of postherpetic neuralgia (Level A, class I and II). ²⁰
Preprocedural dermal anesthesia	<p>2012 - Guideline for the Management of Wounds in Patients with Lower-Extremity Venous Disease: An Executive Summary. Wound, Ostomy, and Continence Nurses Society Wound Guidelines Task Force</p> <p>2011 - Emergency Nursing Resource: Needle-Related Procedural Pain in Pediatric Patients in the Emergency Department. Emergency Nursing Association Emergency Nursing Resource</p> <p>2006 – American Society for Dermatologic Surgery Guidelines for Ethical Patient Safety Practices</p>	<p>Lidocaine is recommended as a topical anesthetic agent for consideration for pain relief for venous ulcer debridement, such as in a lidocaine-prilocaine based creams which have been found to reduce pain during debridement.²¹</p> <p>All transdermal formulations of lidocaine are efficacious in reducing pain associated with procedures such as IV cannulation, venipuncture and immunization in children. Creams or patches take longer (e.g., > 60 minutes) to effectively produce sufficient anesthesia.²²</p> <p>Topical lidocaine has been used safely and effectively to help manage the discomfort caused by certain cosmetic procedures. Lidocaine 4% has traditionally been the topical anesthetic of choice.²³</p>
Preprocedural ocular anesthesia	2015 - Lidocaine (Ophthalmic) (Lexi-Drugs; package insert)	Topical lidocaine is used to provide local anesthesia to ocular surface prior to and during ophthalmologic procedures. ^{24,25}
Preprocedural oropharyngeal anesthesia	<p>2008 - Guideline on Appropriate Use of Local Anesthesia for Pediatric Dental Patients. American Academy on Pediatric Dentistry</p> <p>2008 - Sedation and Anesthesia in GI Endoscopy. Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy</p>	<p>Topical lidocaine is recommended as a topical anesthetic to help minimize discomfort that may occur during the administration of local anesthesia during dental procedures. Systemic absorption of topical anesthetics must be considered when determining the total systemic exposure of anesthetics.²⁶</p> <p>Topical pharyngeal sprays with lidocaine are often used for anesthesia during upper endoscopy.²⁷</p>

Clinical Indication or Use (in alphabetical order)	Guideline or Resource	Clinical Recommendation for Use
	<p>2012 - Difficult Airway Society Guidelines for the Management of Tracheal Extubation</p> <p>2006 - A Guidance on the Use of Topical Anesthetics for Naso/Oropharyngeal and Laryngotracheal Procedures. US Dept of Veterans Affairs VHA Pharmacy Benefits Management Strategic Healthcare Group</p>	<p>Topical lidocaine sprayed on the vocal cords has been used to reduce the risk of laryngospasm following short procedures. Topical lidocaine has been used to reduce coughing during intubation. It is administered topically onto the cuff of the tracheal tube.²⁸</p> <p>Topical lidocaine gel or ointment is used as a lubricant for intubation. Topical lidocaine is strongly recommended for anesthesia during bronchoscopy and endoscopy in non-sedated patients. Topical lidocaine may be useful as an anesthetic during bronchoscopy in sedated patients, awake intubation, intubation in sedated patients, insertion of a NG tube, and endoscopy in sedated patients. Lidocaine-induced anesthesia is useful to reduce cough, gag reflex, and airway hyper-reactivity during naso/oropharyngeal and laryngotracheal procedures.²⁹</p>
Preprocedural urogenital anesthesia	<p>2015 – Intrauterine contraceptive device: Insertion and removal</p> <p>2015 - Lidocaine (Topical) (Lexi-Drugs)</p>	<p>Topical lidocaine has been used for cervical anesthesia before intrauterine device insertion. However, in randomized trials, topical cervical lidocaine did not reduce pain during insertion relative to placebo.³⁰</p> <p>Topical lidocaine has been used for the prevention and control of pain during procedures of the male and female urethra and for the treatment of painful urethritis.³¹</p>
Temporary relief of localized pain	<p>2015 - Lidocaine (Topical) (Lexi-Drugs)</p> <p>2010 - Practice Guidelines for Chronic Pain Management: An Updated Report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American</p>	<p>Topical lidocaine has been used as a local anesthetic for oral mucous membranes, cosmetic surgeries, pruritus, insect bites, pain, soreness, minor burns, abrasions, cuts, anorectal discomfort, and similar conditions of the skin and mucous membranes.³¹</p> <p>Randomized, placebo-controlled controlled trials of topical agents (e.g., capsaicin, lidocaine, and ketamine) are equivocal regarding relief of peripheral pain for patients with neuropathic pain (e.g., diabetic neuropathy and</p>

Clinical Indication or Use (in alphabetical order)	Guideline or Resource	Clinical Recommendation for Use
	<p>Society of Regional Anesthesia and Pain Medicine</p> <p>2011 - Carpal tunnel syndrome. Occupational medicine practice guidelines.</p>	<p>postherpetic neuralgia) (Category C2 evidence). Studies with observational findings indicate that topical agents (e.g., capsaicin, lidocaine, and ketamine) provide relief for peripheral neuropathic pain for assessment periods ranging from 3 to 6 weeks (Category B2 evidence).¹³</p> <p>Recommended: Lidocaine patches for select cases of acute, subacute, or chronic CTS with pain (Insufficient evidence).³²</p>
Unprovoked vulvodynia	2014 - UK National Guideline on the Management of Vulval Conditions	Topical local anesthetics, e.g. 5% lidocaine ointment or 2% lidocaine gel as alternative regimens for unprovoked vulvodynia. Use with caution as they may cause irritation. ¹²
Vestibulodynia, vulvodynia, and penile dysesthesia due to lichen sclerosis	2010 - British Association of Dermatologists' Guidelines for the Management of Lichen Sclerosus	If neuropathic pain from lichen sclerosis does not respond to topical corticosteroids, 5% lidocaine ointment is recommended. Oral medication, such as gabapentin or a tricyclic antidepressant, is recommended for unresponsive cases. ³³
Temporary relief of pain caused by anorectal disorders	<p>2015 - Treatment of hemorrhoids</p> <p>2015 - Lidocaine (Topical) (Lexi-Drugs)</p>	<p>Topical ointments, such as those including hydrocortisone and lidocaine, are effective for relieving pain caused by hemorrhoids.³⁴</p> <p>Topical lidocaine has been used for temporary relief of pain caused by anorectal disorders.³¹</p>

Clinical Efficacy

Clinical evidence evaluating the topical analgesic and anesthetic agents is limited. According to the 2013 P&T drug class review¹⁰, the majority of clinical evidence available for the analgesic and anesthetic agents are placebo-controlled trials. Comparative clinical trials evaluating various lidocaine products were identified for evaluation.³⁵⁻⁴⁰ According to the clinical evidence, the topical lidocaine agents are more efficacious than placebo in treating or reducing localized pain. Differences may exist in duration of effect, patient preferences and other secondary outcomes. Comparative clinical evidence comparing lidocaine/prilocaine to lidocaine

demonstrates similar rates of efficacy.^{35,36,39} One clinical trial comparing topical lidocaine/prilocaine, lidocaine and placebo reported no differences in efficacy between treatment groups.^{38,40} A trial comparing topical lidocaine to ethyl chloride spray demonstrated reduced pain intensity in the topical lidocaine treatment group.³⁷ A number of placebo-controlled trials evaluating the efficacy of lidocaine patches in the treatment of post-herpetic neuralgia reported significant pain relief, higher rates of patient preference and less use of rescue medication in patients using the lidocaine patches.^{39,41-43}

Update (2013-2015)

A literature search was conducted to identify articles addressing clinical safety or efficacy of the lidocaine agents, searching the MEDLINE database (1950 – 2015), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE after 12/2013, evaluating efficacy of the agents are included. Trials evaluating the topical lidocaine agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included.⁴⁴⁻⁸³ Four systematic reviews and meta-analyses and 3 comparative clinical trials were identified for evaluation.⁸⁴⁻⁹⁰ Overall, efficacy varies between the individual lidocaine products based on differences in potency, vehicle formulation and disease/pain being treated. Table 1 of Appendix 1 provides a summary of the clinical evidence 2013-2015.

Unlabeled Uses

Topical Lidocaine Patch

The topical lidocaine patch (Lidoderm®) is labeled for relief of pain associated with postherpetic neuralgia.^{5,6} Practice Guidelines for Chronic Pain Management (American Society of Anesthesiologists, 2010¹³) and clinical guidance for diagnosis and management of peripheral neuropathy (American Family Physician, 2010^{14,15}) list the lidocaine patch as a topical treatment option in the relief of peripheral neuropathic pain. One systematic review, published in 2014⁸⁴, evaluated the efficacy of topical lidocaine (patch, cream, gel or spray) in the treatment of neuropathic pain. According to the review, no quality evidence is available to support the use of topical lidocaine in the treatment of chronic neuropathic pain. Another systematic review, published in 2015⁸⁵, evaluated lidocaine patch therapy for acute or postoperative pain management. According to the review, no improvements in outcomes (pain intensity, opioid consumption, length of hospital stay) were demonstrated with lidocaine patch therapy.

Safety

The topical analgesic and anesthetic agents are associated with both local and systemic adverse events.^{5,6} Rate of adverse events tends to increase with increased duration of use. Local adverse effects

are more prevalent than systemic reactions. Local adverse events most frequently reported with topical lidocaine agents include: Burning or stinging at the administration site and allergic reactions. Elements found in topical agents that may cause an allergic reaction include: propylene glycol, sorbitan sesquioleate, methylchloroisothiazolinone or methylisothiazolinone, lanolin, parabens, or formaldehyde releasing preservatives (imidazolidinylurea/diazolidinylurea).^{5,6}

Usually, up to 99% of the topical lidocaine agent is cleared from the skin and only 1% is therapeutically active and only a very small portion of that, if any, is systemically absorbed.^{5,6} Potentially life-threatening systemic adverse effects reported with the topical analgesic and anesthetic agents include: seizure, central nervous system (CNS) depression and cardiovascular toxicity. In general, risk of lidocaine toxicity occurs at serum drug levels above 5 mcg/mL. Systemic absorption can vary depending on striatum thickness, frequency of application and use of an occlusive barrier. To reduce the risk of systemic absorption, topical analgesic and anesthetic agents, including lidocaine, should not be used on ulcerated, atrophic or infected skin.⁹¹ Long-term use and excessive dosing (large application site and applying a topical patch for longer than recommended) of topical lidocaine is not recommended; dosing and administration product label information should be followed exactly. Pediatric and smaller adult patients and those with impaired liver function and/or elimination may be at risk for increased systemic absorption.⁹² Of note, some clinical evidence evaluating the systemic absorption of topical lidocaine creams on skin of patients with partial-thickness burns reports “significant pain relief of long duration without associated systemic side effects.”⁹³

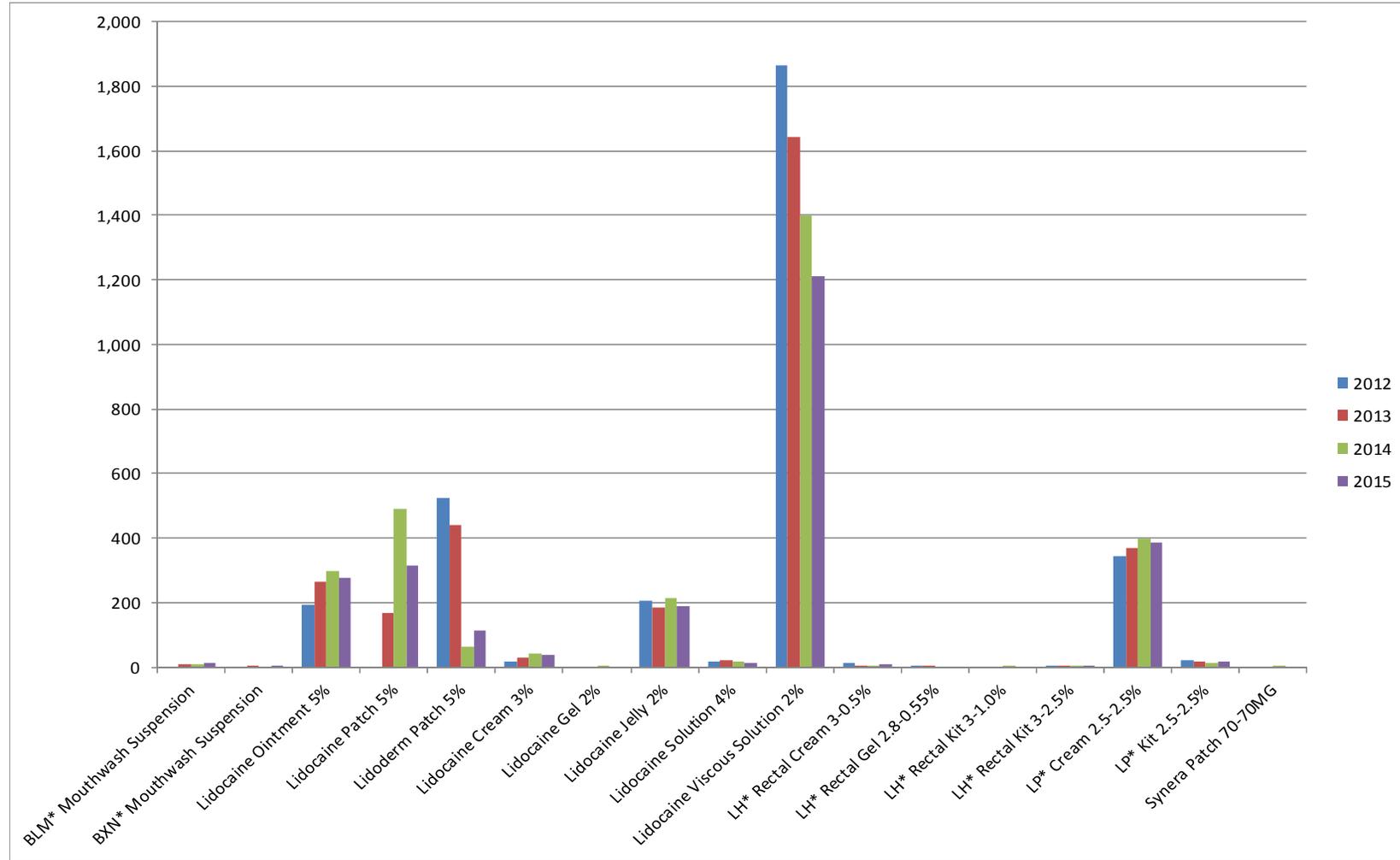
Viscous lidocaine solution agents used in the mouth can cause significant adverse events if swallowed and these agents are not recommended for use in children. All topical lidocaine products have a Food and Drug Administration (FDA) Black Box Warning for life-threatening and fatal events in infants and young children: “Postmarketing cases of seizures, cardiopulmonary arrest, and death in patients under the age of 3 years have been reported with use of lidocaine 2% viscous solution when it was not administered in strict adherence to the dosing and administration recommendations. In the setting of teething pain, lidocaine 2% viscous solution should generally not be used. For other conditions, the use of the product in patients less than 3 years should be limited to those situations where safer alternatives are not available or have been tried but failed.”^{5,6,94,95} Dosage adjustment may be required and some studies have shown less overall benefit in children <7 years of age.⁹⁶

Methemoglobinemia has rarely been reported with topical anesthetic agents^{97,98} but it appears to occur more frequently with topical benzocaine compared to topical lidocaine (FDA adverse event reporting of methemoglobinemia in 2013: lidocaine- 16 reports, benzocaine- 375 reports).⁹⁹

In general, topical lidocaine agents are safe and effective in the geriatric population when a low-potency preparation is used for short periods of time.^{5,6} No evidence of differences in safety or efficacy has been reported between elderly and younger adult patients. Elderly patients may have thin skin, which can lead to increased penetration of topical lidocaine and an increase in both systemic and local adverse events.

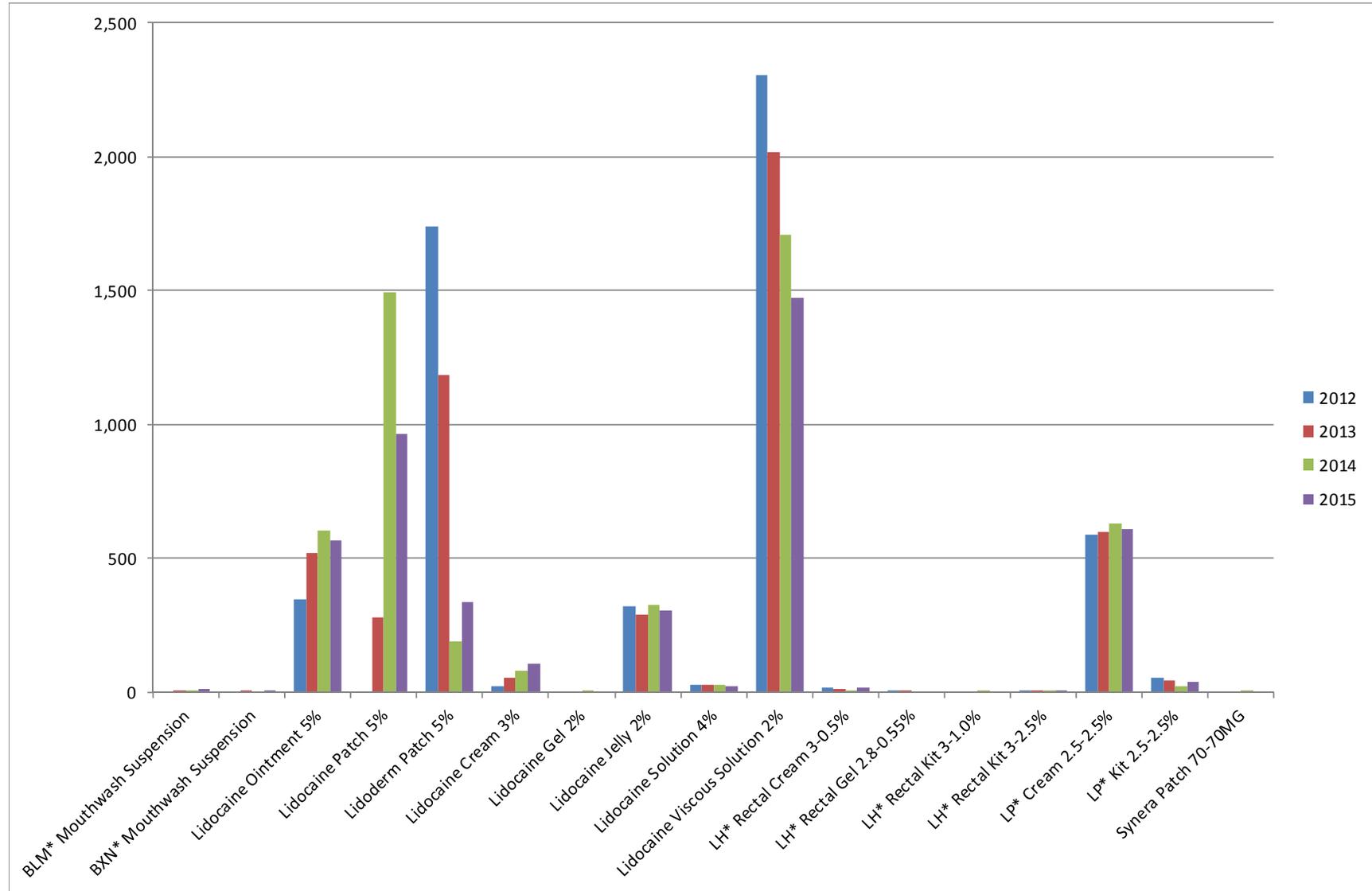
Utah Medicaid Utilization Data

Total number of Patients, by year



Key: BLM- Diphenhydramine-Lidocaine- Alum Hydroxide-Mg Hydroxide-Simethicone; BXN- Diphenhydramine-Lidocaine-Nystatin; LH- Lidocaine/Hydrocortisone; LP- Lidocaine/Prilocaine

Total number of Prescription Claims, by year



Key: BLM- Diphenhydramine-Lidocaine- Alum Hydroxide-Mg Hydroxide-Simethicone; BXN- Diphenhydramine-Lidocaine-Nystatin; LH- Lidocaine/Hydrocortisone; LP- Lidocaine/Prilocaine

Lidocaine Prescription Claims 2012-2015*, pain-related diagnosis code

ICD	Diagnosis	Patients	Percent
462	ACUTE PHARYNGITIS	1849	10.92%
7242	LUMBAGO	849	5.01%
7862	COUGH	751	4.43%
78900	ABDOMINAL PAIN, UNSPECIFIED SITE	698	4.12%
7295	PAIN IN LIMB	696	4.11%
78079	OTHER CHRONIC MALAISE AND FATIGUE	631	3.73%
33829	OTHER CHRONIC PAIN	584	3.45%
7840	HEADACHE	552	3.26%
7245	BACKACHE NOS	540	3.19%
78650	CHEST PAIN NOS	487	2.88%
7291	MYALGIA AND MYOSITIS NOS	444	2.62%
0340	STREP SORE THROAT	417	2.46%
7231	CERVICALGIA	407	2.40%
78909	ABDOMINAL PAIN, OTHER SPECIF SITE,MULTIPLE SITE	379	2.24%
71946	PAIN IN JOINT (PATELLOFEMORAL SYNDROME)	352	2.08%
5282	ORAL APHTHAE	306	1.81%
V5881	FITTING,ADJUST VASCULAR CATHETER,REMOVE.REPLACEMT	300	1.77%
463	ACUTE TONSILLITIS	280	1.65%
V4589	POSTSURGICAL STATES NEC	279	1.65%
72885	SPASM OF MUSCLE	269	1.59%
4660	ACUTE BRONCHITIS	268	1.58%
71941	JOINT PAIN-SHLDER	266	1.57%
52800	STOMATITIS AND MUCOSITIS, UNSPECIFIED	263	1.55%
3384	CHRONIC PAIN SYNDROME	251	1.48%
E8499	ACCIDENT IN PLACE NOS	248	1.46%
71945	JOINT PAIN-PELVIS	247	1.46%
78720	DYSPHAGIA, UNSPECIFIED	239	1.41%
7820	SKIN SENSATION DISTURB	239	1.41%
72252	LUMB/LUMBOSAC DISC DEGEN	234	1.38%
486	PNEUMONIA, ORGANISM NOS	232	1.37%
78907	ABDOMINAL PAIN, GENERALIZED	225	1.33%
34690	MIGRAINE,UNSPECIFIED,W/O INTRACTBLE MIGRAINE	224	1.32%
7244	LUMBOSACRAL NEURITIS NOS	219	1.29%
78906	ABDOMINAL PAIN, EPIGASTRIC	218	1.29%
5289	ORAL SOFT TISSUE DIS NEC	208	1.23%
7213	LUMBOSACRAL SPONDYLOSIS	196	1.16%
E8490	ACCIDENT IN HOME	185	1.09%
47400	CHRONIC TONSILLITIS	185	1.09%
0740	HERPANGINA	184	1.09%
33818	OTHER ACUTE POSTOPERATIVE PAIN	181	1.07%
71947	JOINT PAIN-ANKLE	177	1.05%
7292	ACUTE NEURALGIA, NEURITIS, RADICULITIS NOS	165	0.97%
7241	PAIN IN THORACIC SPINE	157	0.93%
1120	THRUSH	152	0.90%
78659	CHEST PAIN NEC	148	0.87%
38870	OTALGIA NOS	142	0.84%
33819	OTHER ACUTE PAIN	141	0.83%
73390	BONE CARTILAGE DIS NOS	139	0.82%
78096	GENERALIZED PAIN	133	0.79%

*Top 50 pain-related diagnosis codes reported

Topical Lidocaine Patch Prescription Claims 2012-2015*, by pain-related diagnosis code

ICD	Diagnosis	Patients	Percent
7242	LUMBAGO	390	10.56%
7295	PAIN IN LIMB	291	7.88%
33829	OTHER CHRONIC PAIN	268	7.26%
7245	BACKACHE NOS	265	7.17%
7291	MYALGIA AND MYOSITIS NOS	186	5.04%
7231	CERVICALGIA	176	4.76%
78650	CHEST PAIN NOS	176	4.76%
78900	ABDOMINAL PAIN, UNSPECIFIED SITE	169	4.57%
7840	HEADACHE	160	4.33%
71946	PAIN IN JOINT (PATELLOFEMORAL SYNDROME)	158	4.28%
71941	JOINT PAIN-SHLDER	142	3.84%
71945	JOINT PAIN-PELVIS	129	3.49%
72252	LUMB/LUMBOSAC DISC DEGEN	123	3.33%
7820	SKIN SENSATION DISTURB	119	3.22%
7244	LUMBOSACRAL NEURITIS NOS	118	3.19%
3384	CHRONIC PAIN SYNDROME	114	3.09%
78909	ABDOMINAL PAIN, OTHER SPECIF SITE,MULTIPLE SITE	103	2.79%
7213	LUMBOSACRAL SPONDYLOSIS	98	2.65%
72885	SPASM OF MUSCLE	88	2.38%
E8499	ACCIDENT IN PLACE NOS	87	2.36%
V4589	POSTSURGICAL STATES NEC	86	2.33%
7292	ACUTE NEURALGIA, NEURITIS, RADICULITIS NOS	84	2.27%
71947	JOINT PAIN-ANKLE	82	2.22%
72210	LUMBAR DISC DISPLACEMENT	82	2.22%

*Top 25 pain-related diagnosis codes reported

Topical Lidocaine Patch Prescription Claims 2012-2015, by Postherpetic Neuralgia-related Diagnosis Codes

ICD	Diagnosis	Patients
3501	TRIGEMINAL NEURALGIA	4
05312	POSTHERPES TRIGEM NEURAL	2

Topical Lidocaine Patch Prescription Claims, by age and gender

Lidocaine BLM* Mouthwash Suspension 2012-2013

Age**	M	F	Total	Percent
< 03	0	1	1	12.50%
03-07	3	1	4	50.00%
08-18	3	0	3	37.50%
> 18	0	0	0	0.00%
TOTAL	6	2		

*BLM- Diphenhydramine-Lidocaine-Alum Hydroxide-Mg Hydroxide-Simethicone, **Age at first fill

Lidocaine BXN* Mouthwash Suspension 2012-2013

Age**	M	F	Total	Percent
< 03	0	0	0	0.00%
03-07	0	0	0	0.00%
08-18	0	0	0	0.00%
> 18	0	2	2	100.00%
TOTAL	0	2		

*BXN- Diphenhydramine-Lidocaine-Nystatin, **Age at first fill

Lidocaine Solution 4% 2012-2013

Age*	M	F	Total	Percent
< 03	0	0	0	0.00%
03-07	3	1	4	10.81%
08-18	2	3	5	13.51%
> 18	5	23	28	75.68%
TOTAL	10	27		

* Age at first fill.

Lidocaine Viscous Solution 2% 2012-2013

Age*	M	F	Total	Percent
< 03	237	224	461	13.59%
03-07	246	265	511	15.07%
08-18	420	593	1,013	29.87%
> 18	302	1,104	1,406	41.46%
TOTAL	1,205	2,186		

* Age at first fill.

Lidocaine BLM* Mouthwash Suspension 2014-2015

Age**	M	F	Total	Percent
< 03	2	0	2	10.53%
03-07	3	4	7	36.84%
08-18	2	2	4	21.05%
> 18	2	4	6	31.58%
TOTAL	9	10		

*BLM- Diphenhydramine-Lidocaine-Alum Hydroxide-Mg Hydroxide-Simethicone, **Age at first fill

Lidocaine BXN** Mouthwash Suspension 2014-2015

Age*	M	F	Total	Percent
< 03	0	0	0	0.00%
03-07	0	0	0	0.00%
08-18	0	0	0	0.00%
> 18	0	1	1	100.00%
TOTAL	0	1		

*BXN- Diphenhydramine-Lidocaine-Nystatin, **Age at first fill

Lidocaine Solution 4% 2014-2015

Age*	M	F	Total	Percent
< 03	0	0	0	0.00%
03-07	0	1	1	3.45%
08-18	1	6	7	24.14%
> 18	4	17	21	72.41%
TOTAL	5	24		

* Age at first fill.

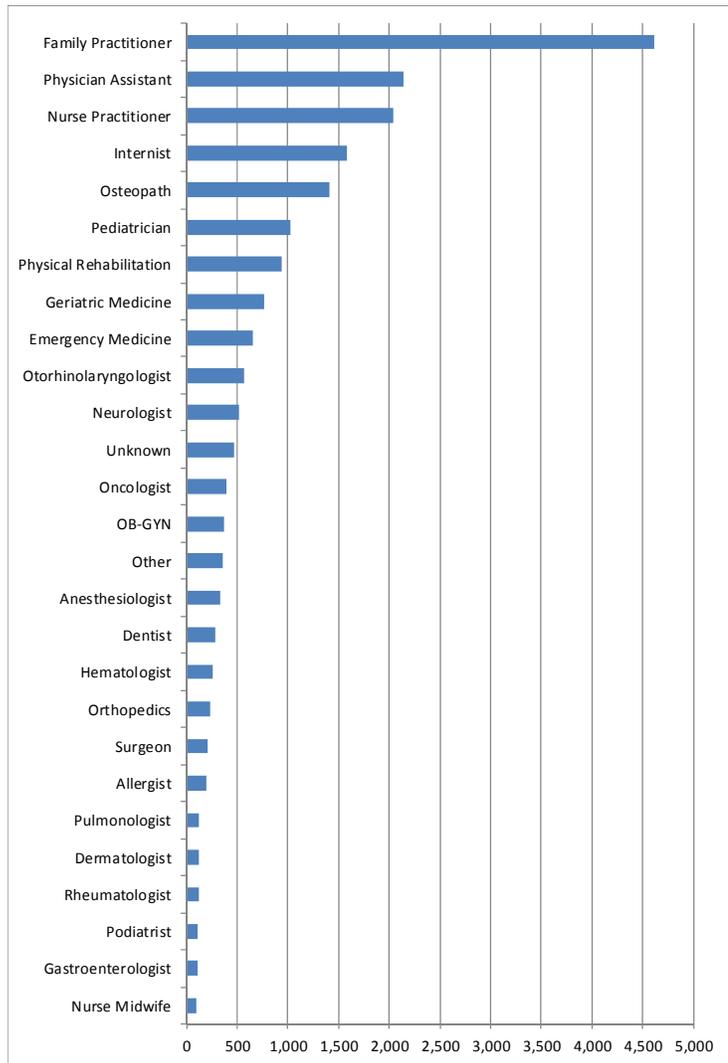
Lidocaine Viscous Solution 2% 2014-2015

Age*	M	F	Total	Percent
< 03	157	144	301	11.80%
03-07	169	173	342	13.41%
08-18	336	449	785	30.77%
> 18	253	870	1,123	44.02%
TOTAL	915	1,636		

* Age at first fill.

Lidocaine Prescription Claims 2012-2015, by prescriber type

PRESCRIBER TYPE	TOTAL CLAIMS	2012-15
Nurse Midwife	95	0.48%
Gastroenterologist	104	0.52%
Podiatrist	107	0.54%
Rheumatologist	116	0.58%
Dermatologist	118	0.59%
Pulmonologist	125	0.63%
Allergist	198	0.99%
Surgeon	209	1.05%
Orthopedics	231	1.16%
Hematologist	254	1.27%
Dentist	285	1.43%
Anesthesiologist	328	1.64%
Other	351	1.76%
OB-GYN	374	1.87%
Oncologist	393	1.97%
Unknown	467	2.34%
Neurologist	514	2.57%
Otorhinolaryngologist	567	2.84%
Emergency Medicine	656	3.28%
Geriatric Medicine	761	3.81%
Physical Rehabilitation	934	4.67%
Pediatrician	1,029	5.15%
Osteopath	1,404	7.03%
Internist	1,579	7.90%
Nurse Practitioner	2,036	10.19%
Physician Assistant	2,135	10.69%
Family Practitioner	4,610	23.07%



Summary

The topical lidocaine agents are available in different formulations, have varying potencies and may have different indications and uses. In general, the topical products exhibit minimal absorption and serious systemic adverse effects; including seizure, respiratory depression, cardiovascular toxicity and death; are uncommon. Some factors may increase the risk of systemic absorption including: excessive dosing (large application site, frequent administration and applying a topical patch for longer than recommended), long-term use, use of more than one lidocaine product at a time, use of topical lidocaine on ulcerated/atrophic/infected skin, use of an occlusive barrier and use of viscous lidocaine solutions in the pediatric population. In general, treatment with topical lidocaine is determined by clinical judgment based upon location of procedure/pain, prior treatment and other complicating conditions (infection, age of patient, duration of action).

Factors and limitations to consider when considering the TCI place in therapy

- Labeled indication and treatment options: Patients should have a diagnosis code for postherpetic neuralgia if receiving the lidocaine patch (Lidoderm®)
- Efficacy: Refer to guideline and efficacy sections
- Administration (e.g. ease of administration or fill quantity): Refer to table 1. A reasonable amount to be filled could be the equivalent of one large tube size of topical lidocaine cream/ointment/solution per 30 day time period.
- Adverse effects: Refer to safety section. Pediatric patients under the age of 3 should not receive viscous lidocaine solutions.
- Duplication of therapy: Concurrent administration of two or more topical lidocaine agents is not recommended and may result in increased risk of potentially life-threatening systemic adverse effects.

Recommended Clinical Criteria

You may wish to consider the following criteria:

- Diagnosis code: Postherpetic Neuralgia required for all transdermal lidocaine patch (Lidoderm®) claims
- Age criteria: Patients must be ≥ 3 years of age to receive viscous lidocaine solutions.
- Quantity limitations: One large tube size of topical lidocaine cream/ointment/solution per 30 day time period
- Limitation to prevent concurrent use of topical lidocaine agents: One fill for a topical lidocaine agent per 30 day time period

Appendix 1: Evidence Tables

Evidence Table: Clinical Evidence Evaluating the Topical Lidocaine Products

Reference	Abstract
Bai et al, Lidocaine patch for acute pain management: a meta-analysis of prospective controlled trials (2015) ⁸⁵	<p>BACKGROUND: Local anesthetic is one of the cornerstones of multimodal analgesia. We investigated the efficacy of the lidocaine patch for acute pain management.</p> <p>METHODS: We searched MEDLINE, CINAHL, Scopus, and the Cochrane Controlled Trials Register for published prospective controlled clinical trials that evaluated the analgesic effect of the lidocaine patch for acute or postoperative pain management (1966--2014). The outcomes were postoperative opioid consumption, pain intensity and length of hospital stay.</p> <p>RESULTS: Five trials comparing the lidocaine patch with control (no treatment/placebo) for acute or postoperative pain treatment/management were included in this meta-analysis. Data was analyzed on 251 patients. Between the lidocaine patch group and the control group, no significant difference was found for all three outcomes (all $p > 0.05$). For postoperative opioid consumption, mean difference (MD) was -8.2 mg morphine equivalent (95% CI -28.68, 12.24). For postoperative pain intensity, MD was -9.1 mm visual analog scale or equivalent (95% CI -23.31, 5.20). For length of hospital stay, MD was -0.2 days (95% CI -0.80, 0.43).</p> <p>CONCLUSION: Application of a lidocaine patch may not be an effective adjunct for acute and postoperative pain management, in terms of pain intensity, opioid consumption and length of hospital stay.</p> <p>LIMITATIONS: The limitations were a small number of included studies, potential biases from some unblinded studies, clinical heterogeneity between studies, and incomplete reported data for adjunct analgesics."</p>

Reference	Abstract
<p>Derry et al, Topical lidocaine for neuropathic pain in adults (2014)⁸⁴</p>	<p>“BACKGROUND: Lidocaine is a local anaesthetic that is sometimes used on the skin to treat neuropathic pain.</p> <p>OBJECTIVES: To assess the analgesic efficacy of topical lidocaine for chronic neuropathic pain in adults, and to assess the associated adverse events.</p> <p>SEARCH METHODS: We searched CENTRAL, MEDLINE, and EMBASE from inception to 1 July 2014, together with the reference lists of retrieved papers and other reviews. We also searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal to identify additional published or unpublished data.</p> <p>SELECTION CRITERIA: We included randomised, double-blind studies of at least two weeks' duration comparing any formulation of topical lidocaine with placebo or another active treatment in chronic neuropathic pain. Participants were adults aged 18 and over. We included only full journal publication articles.</p> <p>DATA COLLECTION AND ANALYSIS: Two review authors independently extracted efficacy and adverse event data, and examined issues of study quality. We performed analysis using three tiers of evidence. First tier evidence derived from data meeting current best standards and subject to minimal risk of bias (outcome equivalent to substantial pain intensity reduction, intention-to-treat analysis without imputation for dropouts; at least 200 participants in the comparison, 8 to 12 weeks' duration, parallel design); second tier evidence from data that failed to meet one or more of these criteria and that we considered at some risk of bias but with adequate numbers in the comparison; and third tier evidence from data involving small numbers of participants that we considered very likely to be biased or used outcomes of limited clinical utility, or both.</p> <p>MAIN RESULTS: We included 12 studies (508 participants) in comparisons with placebo or an active control. Six studies enrolled participants with moderate or severe postherpetic neuralgia, and the remaining studies enrolled different, or mixed, neuropathic pain conditions, including trigeminal neuralgia and postsurgical or post-traumatic neuralgia. Four different formulations were used: 5% medicated patch, 5% cream, 5% gel, and 8% spray. Most studies used a cross-over design, and two used a parallel-group design. Two studies used enriched enrolment with randomised withdrawal. Seven studies used multiple doses, with one to four-week treatment periods, and five used single applications. We judged all of the studies at high risk of bias because of small size or incomplete outcome assessment, or both. There was no first or second tier evidence, and no pooling of data was possible for efficacy outcomes. Only one multiple-dose study reported our primary outcome of participants with $\geq 50\%$ or $\geq 30\%$ pain intensity reduction. Three single-dose studies reported participants who were pain-free at a particular time point, or had a 2-point (of 10) reduction in pain intensity. The two enriched enrolment, randomised withdrawal studies reported time to loss of efficacy. In all but one study, third tier (very low quality) evidence indicated that lidocaine was better than placebo for some measure of pain relief. Pooling multiple-dose studies across conditions demonstrated no clear evidence of an effect of lidocaine on the incidence of adverse events or withdrawals, but there were few events and the withdrawal phase of enriched enrolment designs is not suitable to assess the true impact of adverse events (very low quality evidence).</p> <p>AUTHORS' CONCLUSIONS: This review found no evidence from good quality randomised controlled studies to support the use of topical lidocaine to treat neuropathic pain, although individual studies indicated that it was effective for relief of pain. Clinical experience also supports efficacy in some patients. Several large ongoing studies, of adequate duration, with clinically useful outcomes should provide more robust conclusions about both efficacy and harm.”</p>

Reference	Abstract
<p>Pool et al, A randomised double-blinded crossover study comparing pain during anaesthetising the eyelids in upper blepharoplasty: First versus second eyelid and lidocaine versus prilocaine (2015)⁸⁶</p>	<p>“AIM: The aim of this study was to investigate whether infiltration of the upper eyelid skin is less painful with prilocaine than with lidocaine.</p> <p>METHODS: In 40 consecutive patients scheduled for bilateral upper blepharoplasty, one upper eyelid was anaesthetised with lidocaine with epinephrine and the other with prilocaine with felypressin. After injection of each upper eyelid, the patient scored the pain experienced on infiltration using a visual analogue scale (0-10). In addition, the surgeon scored the need for reinjection during the operation; differences in perioperative bleeding; and degree of oedema, erythema and haematoma before discharge on a four-point rating scale (no, minimal, moderate or severe).</p> <p>RESULTS: Pain scores were significantly lower in upper eyelids injected with lidocaine than in those injected with prilocaine (p = 0.036). In addition, scores for oedema, erythema and haematoma were significantly lower in upper eyelids anaesthetised with lidocaine than in those anaesthetised with prilocaine (respectively, p = 0.001, p = 0.004 and p = 0.000).</p> <p>CONCLUSIONS: Compared with prilocaine with felypressin, lidocaine with epinephrine is significantly less painful in anaesthetising the upper eyelids; gives significantly less postoperative oedema, erythema and haematoma; and provides better haemostasis during upper blepharoplasty.</p> <p>LEVEL OF EVIDENCE: This was a level II, randomised double-blinded crossover study.”</p>
<p>Mihara et al, The efficacy of lidocaine to prevent laryngospasm in children: a systematic review and meta-analysis (2014)⁸⁷</p>	<p>“The purpose of this meta-analysis was to determine the efficacy of lidocaine in preventing laryngospasm during general anaesthesia in children. An electronic search of six databases was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were adhered to. We included randomised controlled trials reporting the effects of intravenous and/or topical lidocaine on the incidence of laryngospasm during general anaesthesia. Nine studies including 787 patients were analysed. The combined results demonstrated that lidocaine is effective in preventing laryngospasm (risk ratio (RR) 0.39, 95% CI 0.24-0.66; I(2) = 0). Subgroup analysis revealed that both intravenous lidocaine (RR 0.34, 95% CI 0.14-0.82) and topical lidocaine (RR 0.42, 95% CI 0.22-0.80) lidocaine are effective in preventing laryngospasm. The results were not affected by studies with a high risk of bias. We conclude that, both topical and intravenous lidocaine are effective for preventing laryngospasm in children.”</p>
<p>Pergialiotis et al, Analgesic options for placement of an intrauterine contraceptive: a meta-analysis (2014)⁸⁸</p>	<p>“OBJECTIVE: Several randomised controlled trials have been published in the last few years which evaluated the efficacy of various analgesics in reducing visual analogue (VAS) pain scores during intrauterine device (IUD) placement. Their results seem to be conflicting and inconclusive.</p> <p>METHODS: We searched Medline (1966-2013), Scopus (2004-2013), Clinicaltrials.org (1997-2013), Popline (1973-2013), Cochrane CENTRAL (1999-2013) and Google Scholar (2004-2013) engines for published randomised controlled trials, as well as the reference lists from all electronically retrieved studies.</p> <p>RESULTS: Thirteen studies, involving 1353 women, were finally included in the present meta-analysis. Among the products used, and with respect to their mode of delivery, only paracervical lidocaine was effective in producing lower VAS pain scores related to tenaculum placement (mean difference [MD]: - 20.54; 95% confidence interval [CI]: - 39.92, - 1.15) and IUD insertion (MD: - 28.99; 95% CI: - 53.14, - 4.84). Misoprostol produced higher VAS pain scores for the immediate post-insertion period (MD: 2.83; 95% CI: - 0.79, 6.45) and it caused various side effects.</p> <p>CONCLUSION: Paracervical administration of lidocaine prior to IUD insertion reduces VAS pain scores. In view of the small number of studies assessing its efficacy further studies should confirm our findings.”</p>

Reference	Abstract
<p>Mayor-Subirana et al, Anesthetic efficacy of Oraqix® versus Hurracaine® and placebo for pain control during non-surgical periodontal treatment (2014)⁸⁹</p>	<p>OBJECTIVES: To evaluate the efficacy of Oraqix® during scaling and root planing (SRP) in comparison with 20% benzocaine and placebo.</p> <p>STUDY DESIGN: 15 patients requiring 4 sessions of SRP were enrolled. For each patient, Oraqix®, Hurracaine®, vaseline or no anesthetic product were randomly assigned each to a quadrant. Treatment pain was evaluated on a 100 mm Visual Analog Scale (VAS) and on a Verbal Rating Scale (VRS). The amount of product administered, the need to re-anesthetise, patient and operator satisfaction and the onset of side-effects were also recorded.</p> <p>RESULTS: Oraqix® was significantly better than nothing, with a reduction of VAS score to 13.3 units, but without significant differences with Vaseline or Hurracaine®. Oraqix® was better in VRS reduction than not using any anesthetic (p=0.001) or using vaseline (p=0.024), but similar to Hurracaine® (p=0.232).</p> <p>CONCLUSIONS: Oraqix® effectively controls pain in SRP procedures, with few side-effects and a good acceptance on the part of patients and clinicians.”</p>
<p>Özkiriş et al, Comparison of topical anesthetic effects of lidocaine, prilocaine, ropivacaine, and bupivacaine in transnasal fiberoptic nasopharyngology (2014)⁹⁰</p>	<p>BACKGROUND: This study was designed to investigate the topical anesthetic efficacy of four different solutions including lidocaine spray, bupivacaine, ropivacaine, and prilocaine used in patients undergoing transnasal fiberoptic nasopharyngology examination (TFL).</p> <p>METHODS: The study included 200 patients who underwent anterior rhinoscopy and TFL examination as a part of routine otolaryngological evaluation in our outpatient clinics. Of these, 111 were female and 89 were male patients. The mean age of the patients was 32 ± 8 years (aged between 19 and 55 years). The patients were randomly divided into five groups. Five groups received one of the local anesthetics studied in our trial (10% lidocaine, 0.5% ropivacaine, 0.25% bupivacaine, 2% prilocaine, and saline solution) in each right side of the nose for 10 minutes before TFL. Each separate examination was performed on the right side of the nasal cavity. After the examination, the patients were asked to note the intensity of the pain that they have experienced during the TFL, by using a 100-mm visual analog scale (VAS).</p> <p>RESULTS: The mean VAS scores were 2.08 (SD, 0.62) in the lidocaine group, 2.21 (SD, 0.66) in the prilocaine group, 3.92 (SD, 0.58) in the ropivacaine group, 4.15 (SD, 0.64) in the bupivacaine group, and 6.35 (SD, 0.65) in the saline solution group. The lidocaine and prilocaine groups had significantly better VAS scores versus ropivacaine, bupivacaine, and saline solution groups (p < 0.05).</p> <p>CONCLUSION: To provide ideal examination comfort and optimum patient tolerability during TFL evaluation of upper respiratory airway topical lidocaine and prilocaine applications were found to be more efficacious and effective medication for anesthesia of the intranasal mucosa compared with bupivacaine and ropivacaine solutions.”</p>

Appendix 2: Drug Information

Table 1. Comparison of the Topical Analgesic and Anesthetic Agents^{5,6}

Topical Agent	Dosage Form	Indications	Dosing Recommendations	Generic Availability
Benzocaine (Anbesol® [OTC], Cepacol® [OTC], others)	Aerosol, Gel, Liquid, Lozenge, Ointment, Solution, Mouth Strip, Mouth Swab	Temporary relief of pain associated with pruritic dermatosis, pruritus, minor burns, acute congestive, bee stings, insect bites, mouth/gum irritations, sunburn, and hemorrhoids; used as anesthetic lubricant for passage of catheters and endoscopic tubes.	Apply topically 2-4 times daily; Lozenge can be taken up to every 2 hours	Product dependent
Benzocaine/ Butamben/ Tetracaine (Cetacaine®)	Aerosol, Gel, Liquid	Topical anesthetic to control pain in surgical or endoscopic procedures; anesthetic for accessible mucous membranes except for the eyes.	Aerosol: Apply for ≤1 second Gel: Apply ~1/2 inch x 3/16 inch Liquid: Apply 6-7 drops	No generic available
Benzyl Alcohol (Ulesfia; Zilactin [OTC])	Gel, Lotion	Gel: Temporary relief of pain from cold sores/fever blisters. Lotion: Treatment of head lice infestation.	Gel: Apply to affected area up to 4 times/day Lotion: Apply, leave on for 10 minutes, rinse; repeat in 7 days	No generic available
Capsaicin (various)	Cream, Gel, Liquid, Lotion, Patch	Patch: Management of post-herpetic neuralgia (PHN). OTC labeling: Temporary relief of minor pain.	Patch: Apply to affected area up to 3-4 times/day for up to 8 hours for 7 days Topical products (cream, gel, liquid, lotion): Apply to affected area 3-4 times/day	Generic only available for Cream
Dibucaine (Nupercainal [OTC])	Ointment (topical and rectal)	Fast, temporary relief of pain and itching due to hemorrhoids or minor burns.	Apply to affected areas; <30 g for adults or <7.5 g for children in 24-hour	Generic

Diclofenac (Flector [®] , Pennsaid [®] , Voltaren [®] , others)	Solution (ophthalmic), Transdermal (gel, patch, solution)	<p>Ophthalmic: Treatment of postoperative inflammation following cataract extraction or corneal refractive surgery.</p> <p>Transdermal: Relief of osteoarthritis pain, acute, localized joint/muscle injuries, actinic keratosis, and pain due to minor strains, sprains, and contusions.</p>	<p>Ophthalmic: 1-2 drops prior to surgery, following surgery, and continue 4 times/day, up to 2 weeks</p> <p>Transdermal gel/solution: Apply to affected area 4 times/day</p> <p>Transdermal patch: Apply 1 patch twice daily</p>	<p>Ophthalmic: Generic</p> <p>Transdermal: Product dependent</p>
Dyclonine (Dyclocaïne [®] , Sucrets [®] [OTC])	Lozenge	Temporary relief of pain associated with oral mucosa.	One lozenge every 2 hours as needed (maximum: 10 lozenges/day)	No generic available
Ethyl Chloride	Aerosol	Local anesthetic in minor operative procedures, minor sport injury, bruises, myofascial and visceral pain syndromes.	Spray for a few seconds until the tissue becomes white (3-10 seconds)	Generic
Hexylresorcinol (Sucrets [®] [OTC])	Lozenge	Minor antiseptic and local anesthetic for sore throat	One lozenge every 2 hours as needed (maximum: 10 lozenges/day)	No generic available
Lidocaine (Akten, AneCream [OTC], Lidoderm, Xylocaine, others)	Cream, Gel (topical, ophthalmic), Kit, Lotion, Ointment, Patch, Solution	<p>Rectal: Temporary relief of pain and itching due to anorectal disorders</p> <p>Topical: Local anesthetic for oral mucous membrane, minor surgeries, minor burns, cuts, and abrasions of the skin</p> <p>Oral topical solution: Topical for irritated oral mucous membranes</p> <p>Ophthalmologic: To provide local anesthesia to ocular surface during procedures</p> <p>Patch: Relief of allodynia, chronic pain in post-herpetic neuralgia, and temporary relief of localized pain</p>	<p>Cream, Gel, Lotion, Ointment, Solution: Apply 2-4 times daily</p> <p>Patch: Place for up to 12 hours in any 24-hour period</p>	Product dependent
Lidocaine/Prilocaine (EMLA [®] , Oraqix [®])	Cream, Gel (periodontal)	Cream: Topical anesthetic for use on normal intact skin to provide local analgesia for minor procedures	Apply to skin for 10 minutes to two hours	<p>Cream: Generic</p> <p>Gel: No generic available</p>

		Periodontal gel: Topical anesthetic for use in periodontal pockets during dental procedures		
Lidocaine/Tetracaine (Synera®)	Transdermal (patch)	Topical anesthetic for use on normal intact skin for minor procedures	Prior to procedure, apply to intact skin for 20-30 minutes	No generic available
Methyl Salicylate/Menthol (BenGay® [OTC]; Icy Hot® [OTC], others)	Aerosol, Balm, Cream, Patch, Stick	Temporary relief of minor aches and pains of muscle and joints associated with arthritis, bruises, simple backache, sprains, and strains	Patch: Apply to affected area for up to 8 hours not more than 3-4 times daily Topical products: Apply to affected area up to 3-4 times/day	No generic available
Pramoxine (Itch-X [OTC], Proctofoam [OTC], others)	Foam (rectal), Gel, Lotion	Temporary relief of pain and itching associated with hemorrhoids, burns, minor cuts, scrapes, or minor skin irritations	Apply to affected area up to 3-5 times daily	Product dependent
Proparacaine (Fluaine)	Solution (ophthalmic)	For use in ophthalmic procedures when a topical disclosing agent is needed along with an anesthetic	Instill 1 drop in each eye just before procedure and every 5-10 minutes for 5-7 doses, if needed	Generic
Tetracaine (Altacaine®, Pontocaine®, others)	Solution (mouth, ophthalmic)	Applied to nose and throat for diagnostic procedures Local anesthesia for various ophthalmic procedures of short duration	Mouth/throat solution: 0.25-0.5% solution by direct application or nebulization; total dose <20 mg Ophthalmic: 1-2 drops into affected eye prior to procedure and every 5-10 minutes, if needed, up to 5 doses.	Mouth solution: No generic available Ophthalmic solution: Generic
Trolamine (Arthricream [OTC], Myoflex [OTC], others)	Cream, Lotion	Relief of pain of muscular aches, rheumatism, neuralgia, sprains, arthritis on intact skin	Apply to affected area as needed up to 3-4 times/day	Product dependent

Table 2. Summary of Pharmacokinetics of the Topical Analgesic and Anesthetic Agents^{5,6}

Type	Agents	Mechanism	Route	Systemic Absorption	Onset of Action	Duration	Metabolism	Excretion	
Esters:	Benzocaine	Blocks the initiation and conduction of nerve impulses by decreasing permeability to sodium ions in the neuronal membrane	Topical, rectal,	Poor through intact skin; Well absorbed from mucous membranes	<5 minutes	15-45 min?	Hepatic and plasma esterases	Urine (metabolites)	
	Proparacaine		ophthalmic	NR	rapid	10-20 min	Plasma esterases	urine	
	Tetracaine		Ophthalmic, topical	NR	5-10 minutes (rhinolaryngology)	30min (rhinolaryngology)	Hepatic, plasma esterases	urine	
Amides	Articaine		Injection only						
	Dibucaine		Topical/rectal	Poor through intact skin; well absorbed through mucous membranes	15 min	2-4 hours	hepatic	Urine	
	Lidocaine		Topical	~3-5% transdermal, depends on exposure	3-5 minutes in mucous membrane and damaged skin	45 min	90% hepatic; Active metabolites	Urine (<10% as unchanged drug)	
	Prilocaine		Topical (with Lidocaine)	Depends on duration of application and site: 6-33.5% prilocaine	1 hour More rapid in mucosa	1-2 hours after removal 15-20 min in mucosa	Hepatic, and hydrolyzed by amidases	Urine	

				over 24 hours				
Ether	Pramoxine		Topical, rectal	Minimally absorbed	3-5 minutes	NR	hepatic	NR
Ketone	Dyclonine (Dyclocaine) (Sucrets) (OTC)		Oral lozenge	NR	<10 min	<60 min	NR	NR
NSAID	Diclofenac	Inhibits cyclooxygenase, resulting in the reduced formation of prostaglandins, thromboxanes and prostacyclin.	Topical	Gel: 6-10% Solution: 2-3%	NR	NR	Hepatic	<1% renal
Salicylate	Trolamine	Inhibits cyclooxygenase, resulting in the reduced formation of prostaglandins, thromboxanes, and prostacyclin	Topical	Minimal	NR	NR	NR	NR
Capsaicinoids	Capsaicin	Activates TRPV1 cation channels on nociceptive nerve fibers. Repeated exposure results in desensitization of the sensory axons and inhibition of pain transmission	Topical cream/patch	Minimal	Slow	long	hepatic	NR
Cryoanalgesic	Ethyl Chloride	Freezes and numbs the skin	Topical spray	NR	Rapid	Seconds to 1 minute	NR	NR

Other	Hexylresorcinol (Sucrets)	Blocks voltage-gated neuronal sodium channels to inhibit initiation and conduction of nerve impulses	Oral lozenge	NR	Rapid	NR	NR	NR
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