

# Summary Report

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## Epinephrine hydrochloride

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Food and Drug Administration

Clinical use of bulk drug substances nominated for inclusion on the 503B Bulks List

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## Frequently Used Abbreviations

API	Active Pharmaceutical Ingredient
ASCA	Ambulatory Surgery Center Association
AAO	American Academy of Ophthalmology
EMA	European Medicines Agency
EMLA	Eutectic mixture of local anesthetics
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
IFIS	Intraoperative floppy iris syndrome
IM	Intramuscular
IRB	Institutional Review Board
IV	Intravenous
LET	Lidocaine, epinephrine (adrenaline), and tetracaine
OTC	Over-the-counter
PCEA	Patient-controlled epidural analgesia
PF	Preservative-free
ROA	Route of administration
SC	Subcutaneous
SME	Subject matter expert
TAC	Tetracaine, epinephrine (adrenaline), and cocaine
UK	United Kingdom
US	United States

## INTRODUCTION

This report was created to assist the Food and Drug Administration (FDA) in their evaluation of the use of epinephrine hydrochloride (epinephrine HCl; UNII code: WBB0470038), which was nominated for use as a bulk drug substance in compounding by outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic Act.

The aim of this report was to describe how epinephrine HCl is used in clinical research and practice to diagnose, prevent, or treat disease. Due to the broad, exploratory nature of this aim, scoping review methodology was used. Following the scoping review framework, a systematic literature review was conducted and healthcare practitioners were consulted to identify how epinephrine HCl has been used historically and currently.<sup>1-3</sup> Assessment of study quality and risk of bias were not performed because the aim of this report was not to make specific recommendations on the use of this substance in clinical practice.<sup>1,4,5</sup> Rather, the aim was to summarize the available evidence on the use of epinephrine HCl and thereby assist the FDA to determine whether there is a need for the inclusion of this substance on the 503B Bulks List.

## REVIEW OF NOMINATION

Epinephrine HCl was nominated for inclusion on the 503B Bulks List by Pine Pharmaceuticals.

While the exact medical condition for which the compounded product was requested is generally unknown, Pine Pharmaceuticals provided the following FDA-approved indications and common uses for epinephrine HCl:

- Hypersensitivity (anaphylaxis)
- Hypotension
- Shock (cardiogenic, septic)
- Preoperative mydriasis for intraocular surgery
- Open-angle glaucoma
- Vasoconstriction with localized anesthesia
- Acute severe asthma attack
- Asystole/pulseless arrest
- Ventricular fibrillation
- Bradycardia unresponsive to atropine or pacing.

Epinephrine HCl was nominated as a single-agent preparation in the following formulations:

- Ophthalmic solutions 0.25-2%
- Ophthalmic preservative-free (PF) solution 1.44%
- Topical cream 0.1%
- Dental solution 8%
- Inhalation PF solution 2.25%
- Nasal spray 2.25%
- Oral PF spray 0.22 mg/0.1 mL
- Injection PF solution 0.5-1 mg/mL

Epinephrine HCl was nominated for use in combination products with additional Active Pharmaceutical Ingredients (APIs) in the following formulations:

- Epinephrine 0.001% / Lidocaine HCl 1% ophthalmic solution
- Epinephrine 0.025% / Lidocaine HCl 0.75% ophthalmic solution
- Epinephrine 0.05% / Cocaine HCl 11.8% / Tetracaine HCl 2% ophthalmic solution
- Epinephrine HCl 0.1% / Lidocaine HCl 4% topical gel
- Lidocaine HCl 4% / Epinephrine HCl (adrenaline) 0.05% / Tetracaine HCl 0.5% (LET) topical gel and spray
- Tetracaine 1 g/100 mL / Epinephrine HCl (adrenaline) 25 mL of a 1:1000 / Cocaine 4 g/100 mL solution (TAC) topical solution
- Epinephrine 1:100,000 / Procaine HCl 2% injection solution
- Epinephrine 1:50,000 / Lidocaine HCl 2% PF dental injection solution
- Epinephrine 0.0005% / Bupivacaine HCl 0.5% injection solution
- Epinephrine 0.0005% / Alcohol 4% / Bupivacaine HCl 0.5% PF injection solution
- Epinephrine HCl 6.9 mL of 1:100,000 / Bupivacaine 8.75 mL of 0.5% / 2.5 mL Fentanyl citrate 2.5 mL of 50 mcg/ml (per 100 mL) epidural injection

The nominator provided references from published peer-reviewed literature to describe the pharmacology, and support the clinical use, of epinephrine HCl.<sup>6-44</sup>

Reasons provided for nomination to the 503B Bulks List included:

- Different concentrations may be needed in elderly or young populations or those with sensitivities to inactive ingredients.
- There are no FDA-approved ready-to-use products that are formulated for intracameral injection. Use of intracameral mydriatics during phacoemulsification has been shown to be more effective for managing patients with intraoperative floppy iris syndrome (IFIS) and is less likely to induce toxicity or cardiovascular side effects compared to that of topical mydriatics. Intracameral mydriatics have been shown to have a faster onset of action, which decreases surgical procedure time. Intracameral epinephrine with lidocaine or in combination with other products has also been found to reduce the risk of developing IFIS during phacoemulsification and is highly effective in managing IFIS patients.
- Preservatives, like sodium bisulfite, in ophthalmic medications can increase incidence of undesirable side effects. This can be avoided by either making a bisulfite-free epinephrine product or mixing a bisulfite containing epinephrine product with a balanced salt solution or epi-Shugarcaine. Preservative and bisulfite-free formulations for intracameral epinephrine injections have been shown to reduce risk of endothelial toxicity and provide a greater safety margin compared to that of diluted sulfite-containing epinephrine formulations. Additionally, patients with sulfite allergies and sensitive patients could experience allergic reactions from the sulfite-containing epinephrine products.
- The most common pediatric dose of FDA-approved epinephrine autoinjector is 0.15 mg, which is greater than the recommended dose for children less than 15 kg. The lowest possible pediatric dose is 0.1 mg with the Auvi-Q® injector, but this is only approved for children greater than 7.5 kg. There is a need for individualized epinephrine dosing. Currently epinephrine vials/ampules and syringes are used to properly treat the pediatric population in an emergency anaphylactic situation. However, this practice is not recommended due to the increased risk of wrong dose or wrong routes resulting in potentially life-threatening consequences.

- Epinephrine is stable at a pH of 3.5-5.5. The FDA-approved injectable products containing epinephrine with lidocaine are formulated to an acidic pH to enhance stability of epinephrine. However, dermatologic injections at this acidic pH can cause injection site pain and may delay the onset of anesthesia agents. Many studies have shown that adding sodium bicarbonate to epinephrine and lidocaine formulations or other local anesthetics can provide a buffer effect and reduce the unwanted side effects and complications associated with the acidic pH of epinephrine injections.
- FDA-approved formulations of lidocaine with epinephrine are commonly prepared for dermatologic injections by dermatologists in conditions that would classify the resulting injectable product as a high-risk level compounded sterile preparation. Compounding on site provides less sterility assurance. There is a clinical need for dermatologic injectable products to be prepared in a safe environment with sterility assurance.
- FDA-approved epinephrine products are prepared at concentrations indicated for intramuscular (IM) injection. To achieve an appropriate concentration for intravenous (IV) use, dilution into IV solution by a healthcare provider is required. This process is prone to human error and IV epinephrine use is for critical, life-threatening, and time-sensitive indications. By utilizing a compounded product, it is possible to minimize dosing errors and adverse reactions by eliminating the critical steps involved in preparing the IV solution.
- Some providers have transitioned to using epinephrine vials or ampules in “anaphylaxis kits” to provide patients with epinephrine injections. This started despite the known risk for error due to rising costs of autoinjectors, lack of appropriate available dosing for autoinjectors, and administration errors due to unfamiliarity with various autoinjector mechanics. A study identifies the need for a safely and accurately compounded unit dose formulation of IM epinephrine that can be administered rapidly and consistently with minimal chance for user error in inpatient settings to treat or prevent anaphylaxis.<sup>15</sup> Patients requiring IV epinephrine in the emergency setting would be a candidate for an epinephrine product compounded ahead of time for emergency situations to minimize the risk of adverse effects associated with improper IV preparation by healthcare providers.
- FDA-approved epinephrine products are formulated in ampules and vials, typically used by physicians to compound combination products and customized dosing for anesthesia. Any patient being treated with localized anesthesia could be at risk of developing an infection or other harmful effects from contamination due to on site compounding. Utilizing a product with sterility assurance, compounding in an FDA-approved environment reduces the risk of contamination for any patient requiring localized anesthesia or preoperative mydriasis.
- It is impractical to use FDA-approved products containing epinephrine hydrochloride as a starting material due to supply shortages. Epinephrine products are currently on the FDA drug shortage list, making it acceptable to compound products from bulk substances in order to meet supply demands.

## **METHODOLOGY**

### *Background information*

The national medicine registers of 13 countries and regions were searched to establish the availability of epinephrine HCl or epinephrine (salt form not specified) products in the United States (US) and around the world. The World Health Organization, the European Medicines Agency (EMA), and globalEDGE were used to identify regulatory agencies in non-US countries. The medicine registers of non-US regulatory agencies were selected for inclusion if they met the following criteria: freely accessible; able to

search and retrieve results in English language; and desired information, specifically, product trade name, active ingredient, strength, form, route of administration (ROA), and approval status, provided in a useable format. Based on these criteria, the medicine registers of 13 countries/regions were searched: US, Canada, European Union (EU), United Kingdom (UK), Ireland, Belgium, Latvia, Australia, New Zealand, Saudi Arabia, Abu Dhabi, Hong Kong, and Namibia. Both the EMA and the national registers of select EU countries (Ireland, UK, Belgium, and Latvia) were searched because some medicines were authorized for use in the EU and not available in a member country and vice versa.

Each medicine register was searched for epinephrine HCl or epinephrine (salt form not specified); name variations of epinephrine HCl or epinephrine (salt form not specified) were entered if the initial search retrieved no results. The following information from the search results of each register was recorded in a spreadsheet: product trade name; active ingredient; strength; form; ROA; status and/or schedule; approval date. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations.

In addition to the aforementioned medicine registers, the DrugBank database (version 5.1.5) and the Natural Medicines database were searched for availability of over-the-counter (OTC) products containing epinephrine HCl or epinephrine (salt form not specified). The availability of OTC products (yes/no) in the US and the ROA of these products were recorded in a spreadsheet. Individual product information was not recorded.

### *Systematic literature review*

#### Search strategy

A medical librarian constructed comprehensive search strategies for Ovid MEDLINE and Embase. The search strategies used a combination of controlled vocabulary terms and keywords to describe two concepts: epinephrine and inhalation, topical, ophthalmic (including intracameral), or epidural administration. A third concept, therapeutic use, was added to the Embase search (refer to Appendix 1 for full search strategies). Due to the availability of FDA-approved products for IV, IM and subcutaneous (SC) injection, these routes were not included in the literature review. Keywords for brand or proprietary products were not included in the search strategy because studies that utilized such products were excluded. Results were limited to original research articles or conference abstracts in English language. Searches were conducted on January 17, 2020. The reference lists of relevant systematic reviews and meta-analyses, retrieved in a separate search of Ovid MEDLINE on November 11, 2019, were reviewed to identify additional studies. In addition, the ECRI Guidelines Trust<sup>®</sup> repository was searched on November 11, 2019 for clinical practice guidelines that recommended the use of epinephrine and provided sufficient information on dosing and administration.

Results were exported to EndNote for Windows version X9.2 (Clarivate Analytics), and duplicates were removed. The de-duplicated results were uploaded to Covidence (Veritas Health Innovation) for screening.

#### Study selection

Studies in which epinephrine HCl or epinephrine (salt form not specified) were used in the nominated dosage form, ROA, and/or combination product to diagnose, prevent, or treat the nominated disease or condition, or other conditions not specified in the nomination, were included. Studies that used epinephrine (salt form not specified) were included because authors often did not specify salt form, and survey results indicated that the majority of respondents (42%) were unsure which salt form of

epinephrine they utilized. Studies were excluded if they were: written in a language other than English; reviews or meta-analyses; surveys or questionnaires (cross-sectional design); designed to evaluate cost-effectiveness, mechanism of action, pre-clinical use, safety, or toxicity; or any study design other than a randomized controlled trial conducted in a non-US country. Studies were also excluded if epinephrine HCl or epinephrine (salt form not specified) were used as: a brand or proprietary product; an FDA-approved product in the nominated dosage form, ROA, or combination; or a dosage form, ROA, or combination that was not nominated. Studies in which epinephrine HCl or epinephrine (salt form not specified) were used to diagnose, prevent, or treat autism were excluded due to a separate project examining the use of compounded substances in individuals with autism. Studies that did not meet the inclusion criteria but provided valuable information about the pharmacological or current or historical use of the substance were noted and put in a separate group in the EndNote library. Two reviewers independently screened titles and abstracts and reviewed full-text articles. A third reviewer reconciled all disagreements.

### Data extraction

The following information was recorded in a standard data extraction form: author names; article title; journal; year of publication; country; study type; historical use of epinephrine; setting; total number of patients; number of patients who received epinephrine; patient population; indication for use of epinephrine; dosage form and strength; dose; ROA; frequency and duration of therapy; use of epinephrine in a combination product; use and formulation of epinephrine in a compounded product; use of epinephrine compared to FDA-approved drugs or other treatments; outcome measures; authors' conclusions. One reviewer extracted data from the included studies; a second reviewer checked the data extraction.

### *Interviews*

Semi-structured interviews with subject matter experts (SMEs) were conducted to understand how and in what circumstances epinephrine was used in a clinical setting. The systematic literature review and indications from the nomination were reviewed to identify the following medical specialties that would potentially use epinephrine: anesthesiology, dermatology, ophthalmology, pain management, pediatrics, and surgery. Potential SMEs within the relevant medical specialties were identified through recommendations and referrals from professional associations, colleagues' professional networks, and authors of relevant literature. In addition, the American Society of Health-System Pharmacists (ASHP) and select outsourcing facilities were contacted for interviews and referrals to additional SMEs. SMEs provided oral informed consent to be interviewed and audio recorded. Interviews lasting up to 60 minutes were conducted via telephone, audio recorded, and professionally transcribed. The transcriptions and notes were entered into NVivo 12 (QSR International) for qualitative data analysis. Several members of the research team independently coded the transcriptions of two representative interviews for themes. The team members discussed the codes that emerged from their independent analysis, as well as those codes that were determined a priori. The code book was developed out of the integration of these coding schemes.

### *Survey*

A survey was distributed to the members of professional medical associations to determine the use of epinephrine in clinical practice. The online survey was created using Qualtrics® software (refer to Appendix 3 for complete surveys). A Google™ search was conducted to identify the professional associations in the US for the relevant medical specialties. An association's website was searched to identify the email of the executive director, regulatory director, media director, association president,

board members, or other key leaders within the organization to discuss survey participation. If no contact information was available, the “contact us” tab on the association website was used. An email describing the project and requesting distribution of the survey to the association’s members was sent to the identified person(s). Associations that declined, did not respond, or did not provide significant data in project Year 1 were not contacted to distribute the project Year 2 surveys.

The survey was posted on the project website and the survey link was distributed to the associations that agreed to participate (refer to Appendix 4 for associations that participated and those that did not).

Participation was anonymous and voluntary. The estimated time for completion was 15 minutes with a target of 50 responses per survey.

The University of Maryland, Baltimore Institutional Review Board (IRB) and the FDA IRB reviewed the interview and survey methods and found both to be exempt. The Office of Management and Budget approved this project.

## CURRENT AND HISTORIC USE

### *Results of background information*

- Epinephrine is available as an FDA-approved product in the nominated dosage forms and ROA. The combination of epinephrine and lidocaine as a 2% topical solution and epinephrine and prilocaine as an 1-2% injection was discontinued, not for safety or efficacy reasons.
- Epinephrine is available OTC as a dental solution and aerosol metered inhalation solution in the US.
- There is a current United States Pharmacopeia (USP) monograph for epinephrine.
- Epinephrine is available in the nominated dosage forms and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK.

Table 1. Currently approved products – US<sup>a</sup>

Active Ingredient	Concentration	Dosage Form	Route of Administration	Status	Approval Date <sup>b</sup>
Epinephrine	0.1-0.3 mg/delivery 1-2 mg/mL EQ 1 mg base/mL	Injectable, solution	Intramuscular, intravenous, subcutaneous	Prescription	12/22/1987
Epinephrine	EQ 1 mg base/mL	Solution	Intraocular, intramuscular, intravenous, subcutaneous	Prescription	7/29/2014
Epinephrine / Bupivacaine HCl	0.25-0.5% / 0.005 mg/mL	Injectable	Injection	Prescription	6/16/1988
Epinephrine / Lidocaine HCl	0.5-2% / 0.005-0.02 mg/mL	Injectable	Injection	Prescription	Approved prior to 1/1/1982

Abbreviation: “EQ”, equivalent concentration.

<sup>a</sup>Source: US FDA *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

<sup>b</sup>If multiple approval dates and/or multiple strengths, then earliest date provided.

Table 2. Currently approved products – select non-US countries and regions<sup>a</sup>

Active Ingredient <sup>b</sup>	Concentration	Dosage Form	Route of Administration	Approved for Use		
				Country	Status	Approval Date <sup>c</sup>
Epinephrine	0.1-2 mg/mL	Solution	Injection, intramuscular, intravenous, subcutaneous	Abu Dhabi	Active	–
				Australia	Pharmacist-only medicine	3/25/2014
				Belgium	Prescription	6/14/1998
				Canada	Ethical	8/23/2018
				Ireland	Prescription	4/1/1979
				Latvia	Prescription	10/19/2005
				Namibia	–	8/18/2004
				New Zealand	Restricted	2/7/1997
				Saudi Arabia	Prescription	–
				UK	Prescription	3/28/1996
Epinephrine / Bupivacaine	0.0005% / 0.25-0.5%	Solution	Injection	Abu Dhabi	Active	–
				UK	Prescription	3/15/1991
Epinephrine / Lidocaine HCl	5-20 mcg/mL / 1-2%	Solution	Infiltration, injection, intravenous	Abu Dhabi	Active	–
				Australia	Prescription	7/13/1994
				Hong Kong	Prescription	11/11/1985
				Ireland	Prescription	2/16/1988

				Namibia	–	7/2/1982
				New Zealand	Prescription	8/14/1984
				Saudi Arabia	Prescription	–

Abbreviation: “–”, not mentioned.

<sup>a</sup>Medicine registers of national regulatory agencies were searched if they met the following criteria: freely accessible; able to search and retrieve results in English language; and desired information (product trade name, active ingredient, strength, form, ROA, and approval status) provided in a useable format. Information was recorded only for products with strengths, forms, and/or ROA similar to those requested in the nominations. See Methodology for full explanation.

<sup>b</sup>Epinephrine used as the standard for name variations, including epinephrine HCl, epinephrinum, adrenaline and adrenalin.

<sup>c</sup>If multiple approval dates and/or multiple strengths, then earliest date provided.

## *Results of literature review*

### Study selection

Database searches yielded 8201 references; 2 additional references were identified from searching ECRI Guidelines Trust® and the references of relevant systematic reviews. After duplicates were removed, 6347 titles and abstracts were screened. After screening, the full text of 475 articles was reviewed. One hundred twenty-three studies were included; after multiple reports of the same study were merged, there were 121 included studies. Three hundred fifty-two studies were excluded for the following reasons: wrong study design (160 studies); wrong dosage form or ROA (58); FDA-approved dosage form or ROA (56); epinephrine used as brand or proprietary product (20); wrong substance (20); epinephrine not used clinically (10); language other than English (9); epinephrine only mentioned briefly (9); duplicate study (6); unable to obtain (4).

Refer to Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

### Characteristics of included studies

The 121 included studies were published between 1950 and 2019. There were 94 experimental studies, 14 observational studies, 14 descriptive studies, and 0 clinical practice guidelines. The 121 studies were conducted in the following countries: Australia, Canada, China, Germany, Hong Kong, Iran, Ireland, Italy, Japan, Norway, Singapore, Spain, Sweden, Switzerland, Taiwan, UK, and US.

A total of 17,263 patients participated in the 121 included studies. The number of patients in each study ranged from 1 to 4493.

Outcome measures differed among the included studies and included: blood loss, degree of motor block, duration and quality of analgesia/anesthesia, heart rate, pain scores, pupillary size/diameter, patient compliance during suturing, pupil reactivity, postoperative visual acuity, nasal cavity temperature changes, differences in intraocular pressure, reduction/cessation of alveolar hemorrhage, average premature ventricular contractions, time to epithelialization, side effects/complications, urethral pressure, supplemental analgesic interventions.

Refer to Table 5 for summary of study country, design, patient population, intervention and comparator, and outcome measures.

### Use of epinephrine

Four thousand ninety-five patients received epinephrine with other APIs epidurally in various dosing regimens for analgesia/anesthesia. Duration of treatment ranged from once to until delivery.

Three thousand thirty-one patients received epinephrine with other APIs for local analgesia/anesthesia, administered as a topical gel or solution in doses ranging from 0.1 mL to 10 mL once. Some studies dosed based on weight (0.09-0.1 mL/kg) while another administered 0.5-1 mL/cm of wound.

Five hundred twenty-four patients received epinephrine to reduce intraocular pressure, administered as an ophthalmic solution or drop in doses ranging from 1 to 4 drops/day. Duration of treatment ranged from once to 10 years.

Sixty-two patients received epinephrine to measure pupil responsiveness, administered as an ophthalmic drop once. The dose was not specified.

Six hundred ninety-one patients received epinephrine to induce mydriasis, administered via the intracameral, intraocular, irrigation, and ophthalmic routes in doses ranging from 0.3 mL to 40 mL once.

One hundred seventy-six patients received epinephrine for hemostasis, administered topically as a solution or spray once. One study specified a dose of 1.9 mL while the other studies did not provide dose information.

One thousand one hundred ninety-seven patients received epinephrine to induce vasoconstriction, administered via the intranasal, topical, or subconjunctival route as a solution in doses ranging from 0.3 mL to 30 mL. Duration of treatment was once.

One patient received epinephrine as a treatment for alveolar hemorrhage, administered topically once. The dose used and duration of treatment were not specified.

An unspecified number of patients received epinephrine as a vasodilator to aid in massage, administered as a 0.1% topical cream for 2 weeks. The dose was not specified.

Refer to Tables 6 and 7 for summaries of dosage by indication.

Epinephrine was used as compounded products (topical gel/solution and ophthalmic drops/solution) and was used in various combination products (refer to Tables 8-10).

In 58 studies, the authors' concluding statement recommended the use of epinephrine alone and/or in combination for anesthesia/analgesia,<sup>45-57</sup> local anesthesia/analgesia,<sup>58-83</sup> hemostasis,<sup>84,85</sup> mydriasis,<sup>28,86-92</sup> reducing intraocular pressure,<sup>93-98</sup> stabilizing the iris,<sup>99</sup> and vasoconstriction.<sup>100</sup> One study found epinephrine to be an effective vasoconstrictor but noted that it should not be recommended for routine use because of its cardiovascular side effects.<sup>101</sup> In 18 studies, the authors' concluded that the use of epinephrine and/or in combination was not recommended or further studies were necessary for anesthesia/analgesia,<sup>102,103</sup> local anesthesia/analgesia,<sup>104-106</sup> hemostasis,<sup>107</sup> mydriasis,<sup>44,108-111</sup> reducing intraocular pressure,<sup>112-117</sup> and vasoconstriction.<sup>118,119</sup> In 6 studies, the authors' recommended other combinations that included lidocaine and epinephrine,<sup>120</sup> cocaine and epinephrine,<sup>121</sup> tetracaine and phenylephrine,<sup>122</sup> prilocaine and phenylephrine,<sup>123</sup> bupivacaine and norepinephrine,<sup>124</sup> and a eutectic mixture of local anesthetics (EMLA)<sup>125</sup> instead of TAC for local anesthesia/analgesia. For 2 studies, the authors concluded that dipivefrin was an alternative to epinephrine therapy for reducing intraocular pressure.<sup>126,127</sup> In 15 studies, the authors did not provide a definitive conclusion for the recommendation of epinephrine.<sup>128-142</sup> In 21 studies, the authors' concluding statement was not specific to epinephrine.<sup>143-163</sup> Refer to Table 5 for summary of authors' conclusions.

## Pharmacology and historical use

There were 34 studies identified that provided valuable information about the pharmacology and historical use of epinephrine.

As a sympathomimetic drug, epinephrine interacts with the alpha, beta-1, and beta-2 adrenergic receptors.<sup>91</sup> The stimulation of the receptors depends on the epinephrine plasma concentration.<sup>91</sup> At lower concentrations, the beta adrenergic receptors are mainly stimulated, causing increased heart rate via beta-1 and peripheral vasodilation via beta-2 receptors.<sup>91</sup> At higher concentrations, alpha adrenergic activity begins to appear with increased blood pressure and vascular tone.<sup>91</sup>

Epinephrine has been shown to help with pain relief when added to epidural medications.<sup>134</sup> In the combination of bupivacaine, fentanyl, and epinephrine for labor analgesia, bupivacaine has a slow onset for pain relief and “its brief duration necessitates repeated injections or continuous infusion for labor analgesia.”<sup>133</sup> Epinephrine helps enhance the analgesia provided by bupivacaine while fentanyl also helps speed up the onset and prolongs the duration of analgesia.<sup>133</sup> The mechanism in which epinephrine improves pain relief is not completely understood but “one possibility is that epinephrine acts primarily via alpha-1 adrenergic activity, resulting in vasoconstriction of the epidural blood vessels.”<sup>52</sup> Vasoconstriction allows more of the active substances, such as the local anesthetics and opioids, to remain in the epidural space.<sup>134</sup> The other possibility is “epinephrine produces pain relief via a spinal cord mechanism – alpha-2 adrenergic receptors have been shown to produce analgesia.”<sup>52</sup> In a study by Li et al, they concluded that adding epinephrine to epidural bupivacaine reduced the bupivacaine concentration needed for labor pain relief.<sup>51</sup> The authors believe this is due to epinephrine’s effect on alpha-2 adrenergic receptors since “the alpha-1 adrenergic mediated vasoconstriction would not affect the initiation of labor analgesia.”<sup>52</sup>

Epinephrine was nominated topically for use in combination with other APIs. When Pryor et al reported on the use of TAC in 1980, they challenged the use of “traditional methods of anesthesia with lidocaine infiltration.”<sup>74</sup> Although lidocaine infiltration was a “safe, established method of achieving local anesthesia for laceration repair, its use in children [was] often painful and frightening.”<sup>67</sup> Since then, use of topical anesthetics for non-mucous-membrane injuries has become more prevalent.<sup>58,142</sup> Topical anesthetics have the advantage of being less invasive than lidocaine infiltration, improving patient cooperation.<sup>67,76</sup> A disadvantage of topical anesthetics is they have a slow rate of onset, some may require up to an hour.<sup>78</sup> TAC is a combination shown to have 80 to 95% efficacy when used alone as a topical anesthetic for facial lacerations; however for use in extremity lacerations, its efficacy ranges from 43-55%.<sup>125</sup> The rationale for this combination is that tetracaine and cocaine would provide local anesthesia while epinephrine and cocaine cause vasoconstriction, which “minimizes bleeding from the wound, decreases the amount of local anesthetic absorbed through the skin, and limits toxicity.”<sup>76</sup> A 1985 study by Schaffer found TAC to be superior to a tetracaine with adrenaline solution while a 1986 study by White et al found TAC superior to tetracaine alone.<sup>73,75,83,121</sup> Cocaine is a controlled substance, which requires special storage procedures and documentation.<sup>77,119</sup> In addition, improper use of TAC has led to hypertension, seizures, and death.<sup>77,81,120</sup> Because of these concerns with TAC, an alternative topical combination with LET topical gel was tested by Schilling et al in a 1995 study.<sup>74,76</sup> Schilling et al found LET to be an effective alternative to TAC for anesthesia during suturing of uncomplicated lacerations of the face and scalp in children.<sup>74,76</sup> In a 2004 study by White et al, they mentioned that use of epinephrine containing topical anesthetic agents is “theoretically contraindicated in areas of the body with end artery blood supply, such as the finger.” However, there have been surgeons who have safely used lidocaine and epinephrine during digital blocks and a review of the literature did not identify any

cases with finger necrosis caused by these digital blocks.<sup>82</sup> A 2016 guideline by the American Academy of Dermatology (AAD) for the use of local anesthesia (defined for the guideline as topical, infiltrative, nerve blocks, and infiltrative tumescent) in office-based dermatologic surgery also found no reported cases of necrosis.<sup>164</sup> The guideline stated that “the addition of epinephrine to local infiltration anesthesia is safe and recommended for use on the ear, nose, hand, feet, and digits.”<sup>164</sup> LET is less costly, easier to prepare, and “[compares] favorably with TAC without the risks and administrative hassles associated with cocaine.”<sup>74,77</sup> However, there have been toxicity reports involving lidocaine and tetracaine related to “mucous membrane application with large concentrations applied or ingested.”<sup>63</sup> In the 2016 AAD guideline, they conducted a systematic review and found “no significant difference in efficacy among topical [TAC] and 6 different cocaine-free formulations, but the addition of cocaine was associated with a higher cost and potential for adverse effects.”<sup>164</sup> The guideline suggested that “non-cocaine anesthetics are preferred over those containing cocaine.”<sup>164</sup> A 2019 study by Konigs et al stated that most pediatric emergency departments use the topical combination LET gel or EMLA with infiltration of local anesthetic, such as lidocaine or mepivacaine, for pain control during skin repair.<sup>68</sup>

Another topical formulation nominated was epinephrine as a cream, which has been used for treatment of rheumatic conditions.<sup>140</sup> The mechanism in which epinephrine cream works is unclear but is hypothesized to “[increase] blood supply to the painful muscles due to the vasodilation produced by [epinephrine] in skeletal muscle,...which might well be augmented by the mechanical effect of the massage, and possibly also by the vasoconstriction which [epinephrine] produces in the skin vessels.”<sup>140</sup> It was first used by Moss in 1949, “on the grounds that it might be absorbed sufficiently to cause vasodilation in muscle and thus aid massage in patients suffering from fibrositis.”<sup>140</sup> Moss found all patients except those with early osteoarthritis improved; however, because there was no comparison group with patients receiving a massage, “it is not possible to assess the effect of the adrenaline component from Moss’s results.”<sup>140</sup> A 1950 study by Howell in patients with fibrositis secondary to rheumatoid arthritis or osteoarthritis found that epinephrine cream resulted in a longer duration pain relief compared to a “blank” cream.<sup>140,165</sup> Howell noted a disadvantage of the epinephrine cream was that it had a short duration action in some patients, and that the base in which the epinephrine was administered made a difference in its effects.<sup>165</sup> In 1951, Bywaters studied 39 patients with “conditions associated with deep pain of symmetrical distribution” and found the difference in relief was not significant between the epinephrine cream and plain cream.<sup>140</sup> In 1953, a study by Lawrence and Sladden investigated the use of epinephrine cream compared to a control cream and compared epinephrine cream with massage to no massage, dry massage, and simple cream with massage in patients with rheumatic diseases.<sup>140</sup> They found that epinephrine cream provided greater relief than simple cream and that dry massage provided greater relief than no massage or massage with the control cream.<sup>140</sup> There was no significant difference in relief between dry massage and massage with epinephrine cream.<sup>140</sup> They noted that “repeated application of [epinephrine] cream appears to delay recovery in rheumatic diseases.”<sup>140</sup>

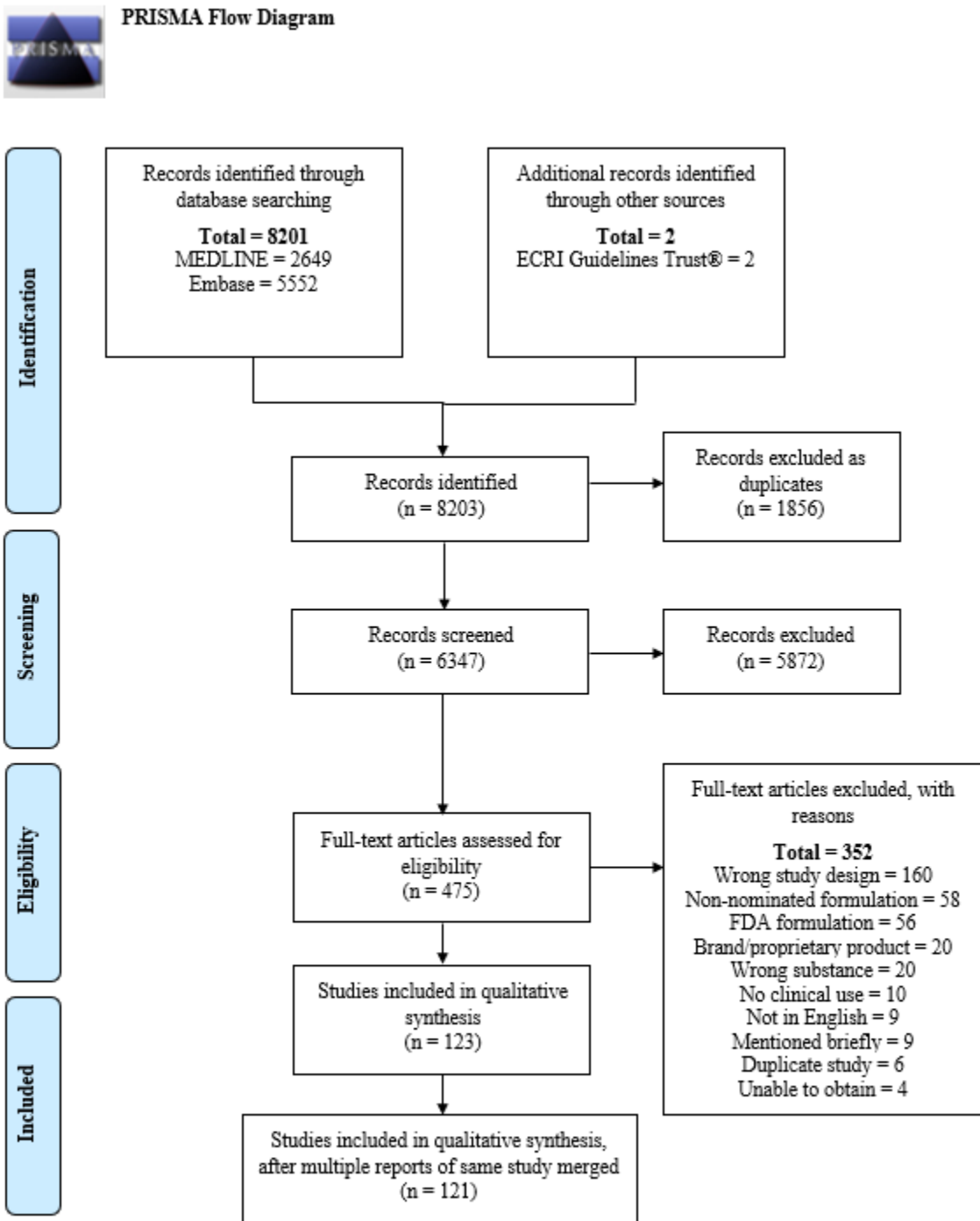
Epinephrine is also used in ophthalmic surgeries. To perform a safe operation, the pupil often needs to be dilated preoperatively and “preferably remain dilated throughout the procedure.”<sup>144</sup> For pupil dilation, a combination of adrenergic and cycloplegic agents, such as cyclopentolate and phenylephrine, are instilled several times before cataract surgery.<sup>28</sup> Limitations of this method include long nursing time and possible epithelial toxicity.<sup>28</sup> Intracameral dilation avoids both of those limitations.<sup>28</sup> According to Myers and Shugar, the first intracameral dilation reported was with non-preserved lidocaine HCl 1% alone in a study by Cionni et al.<sup>28</sup> Around the same time, Lundberg and Behndig formulated a solution containing phenylephrine 1.5%, cyclopentolate 0.1%, and lidocaine

HCl 1% (LB solution).<sup>28</sup> In the US, the LB solution would have to be made in a compounding pharmacy due to the inclusion of phenylephrine, making it expensive and inconvenient.<sup>28</sup> In contrast, Shugar made a formulation with lidocaine HCl 4%, epinephrine 1:1000, and fortified balanced salt solution (Epi-S).<sup>28</sup> Epinephrine is “universally available and can be compounded to physiologic pH and osmolality by dilution in [balanced salt solution].”<sup>28</sup> However, another study noted that epinephrine is “unstable in a solution at physiological pH [thus] time-consuming repeated blending procedures are needed.”<sup>110</sup> Epinephrine with lidocaine compared to lidocaine alone provides a longer duration of action and improved efficacy, helps with hemostasis, and “markedly reduces or eliminates risk for IFIS in eyes with risk factors such as exposure to tamsulosin.”<sup>28</sup> A disadvantage of Epi-S is that the mixture only stays stable for about 4 hours at room temperature.<sup>28</sup> By refrigerating the mixture right after it is compounded, stability can be increased.<sup>28</sup>

Other techniques, such as preoperative diclofenac, naproxen, viscous phenylephrine HCl, or intraoperative intracameral epinephrine (as an irrigation solution or single bolus dose), have been suggested for maintaining mydriasis during ophthalmic surgery.<sup>144</sup> Epinephrine maintains mydriasis by acting directly on the dilator pupillae of the iris.<sup>88,90</sup> Many surgeons use epinephrine as an intraocular infusion or bolus injection during surgery.<sup>88,90,110</sup> An advantage of administering epinephrine as an infusion is that “it continues to enter the eye while the stimulus to miosis persists.”<sup>88</sup> A more dilute concentration can be used as epinephrine is administered over a longer time period by infusion.<sup>88</sup> There were a few reported cases of severe corneal decompensation that resulted from the sodium bisulphite preservative in the intraocular epinephrine 1:1000 preparation.<sup>88,90</sup> The osmolarity and pH of the solution were also suggested as possible contributing factors.<sup>88,90</sup> According to a 2007 study by Lundberg and Behndig, “preservative-free epinephrine in low concentrations is commonly used in the irrigating solution to maintain mydriasis.”<sup>28</sup> This avoids problems encountered with preserved epinephrine such as low pH and toxic preservatives.<sup>28</sup>

Beta-blockers frequently reduce the intraocular pressure at initiation in glaucoma patients.<sup>96</sup> However, in some patients, the intraocular pressure will gradually raise again later.<sup>96</sup> When this occurs, non-selective beta-blockers or a beta-1 selective blocker with an adrenergic agonist, such as epinephrine or dipivefrin HCl, can be used.<sup>96</sup> One study reported that epinephrine has been used as an ocular hypotensive agent for glaucoma since at least 1899.<sup>113</sup> The mechanism by which epinephrine reduces intraocular pressure is possibly by decreasing aqueous humor production via beta receptors, and the “long-term ocular hypotensive effects may be explained by increasing outflow facility in the angle structures, probably at alpha-receptors.”<sup>98,113,115</sup>

Figure 1. PRISMA flow diagram showing literature screening and selection.



Adapted from:  
 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol.* 2009;62(10):1006-1012. Available from: <http://www.prisma-statement.org/>.

Table 3. Types of studies

Types of Studies <sup>a</sup>	Number of Studies
Descriptive <sup>52,71,72,82,84,86,92,100,105,129,132,145,151,155</sup>	14
Experimental <sup>128,44-51,53-59,62-70,74-81,83,85,87-91,93,96-98,101-104,106-110,112-127,130,131,133,134,136,137,139-144,149,150,152-154,156-163</sup>	94
Observational <sup>60,61,73,94,95,99,111,128,135,138,141,146-148</sup>	14

<sup>a</sup>Study 141 was counted as both experimental and observational.

Table 4. Number of studies by country

Country	Number of Studies
Australia <sup>69,103</sup>	2
Canada <sup>48,66,89,96,112,114,152</sup>	7
China <sup>44</sup>	1
Germany <sup>68</sup>	1
Hong Kong <sup>57</sup>	1
Iran <sup>91</sup>	1
Ireland <sup>71</sup>	1
Italy <sup>149,160,161</sup>	3
Japan <sup>46,54,55</sup>	3
Norway <sup>52,53,134,157</sup>	4
Singapore <sup>106</sup>	1
Spain <sup>128,143</sup>	2
Sweden <sup>110,136,144,153</sup>	4
Switzerland <sup>141,148</sup>	2
Taiwan <sup>90</sup>	1
UK <sup>56,87,88,109,119,140,159</sup>	7
US <sup>28,45,47,49-51,58-65,67,70,72-86,92-95,97-99,101,102,104,105,107,108,111,113,115-118,120-127,129-133,135,137-139,142,145-147,150,151,154-156,158,162,163,166</sup>	80
Total US: 80 Total Non-US Countries: 41	

Table 5. Summary of included studies

*Refer to Appendix 2*

Table 6. Dosage by indication – US

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Local analgesia/anesthesia <sup>58-65,67,70,72-83,104,105,120-125,130,132,142,154</sup>	–	–	Cream	Topical	–
	1-5 mL	0.001-0.1%	Gel, solution	Topical	Once
	0.1-10 mL 0.5-1 mL/cm of wound 0.09-0.1 mL/kg	0.025-0.05%	Solution	Topical	Once
Analgesia/anesthesia <sup>45,47,49-51,102,129,131,133,135,150,151,156,158,162,163</sup>	2.5-20 mL	1.67-10 mcg/mL	Solution	Epidural	Once-Twice Until delivery
	12 mL loading dose 6-16 mL/h	0.5-5 mcg/mL			2 days Until delivery
Patient-controlled analgesia <sup>47,150,158,162</sup>	10 mL bolus/2 hours as needed	0.5-2.5 mcg/mL	Solution	Epidural	2 days
	2-4 mL boluses with 10 min lockout				
Reduce intraocular pressure <sup>93-95,97,98,113,115-117,126,127,137,138,155</sup>	1-4 drops/day	0.025-2%	Drops, solution	Ophthalmic	Once – 10 years Long-term
Mydriasis <sup>28,86,92,108,111,139,147</sup> and stabilize the iris <sup>99</sup>	0.3 mL	0.00004-0.1%	Solution	Intracameral, irrigation, ophthalmic	Once

Hemostasis <sup>84,85,107,146</sup>	1.9 mL	5 mcg/mL – 1 mg/mL	Solution	Topical	Once
	–	0.1 mg/mL	Spray		
Vasoconstriction <sup>100,101,118</sup>	0.3 mL	1 mg/mL	Solution	Intranasal	Once
	Max 30 mL	1 mg/mL	Solution	Topical	Once
	–	–	Solution	Subconjunctival	Once
Alveolar hemorrhage <sup>145</sup>	–	–	–	Topical	Once

Abbreviation: “–”, not mentioned.

Table 7. Dosage by indication – non-US countries

Indication	Dose	Concentration	Dosage Form	Route of Administration	Duration of Treatment
Analgesia/anesthesia <sup>46,48,52-57,134,136,141,148,149,153,157,159-161</sup>	–	2 mcg/mL	Solution	Epidural	–
	30-100 mcg 0.1-24 mL 0.2 mL/kg bolus	1.25-5 mcg/mL			Once Until delivery
	2-13 mL/hr	2-5 mcg/mL			48-72 hours Until the onset of second stage of labor Until delivery
	0.2 mL/kg/hr	2 mcg/mL			16-70 hours
	Loading dose 30-37.5 mcg (15 mL) Infusion 10-12 mL/hr	For infusion: 0.00025%			Until delivery
Patient-controlled analgesia <sup>48,103,134,136,143,153</sup>	2-6 mL/hr bolus	2 mcg/mL	Solution	Epidural	-
	2 ml/hr with supplementary bolus of 0.5 mL/6 minutes	2.5 mcg/mL			2 days
	2-6 mL bolus Lockout 10-30 minutes	2-4 mcg/mL			Until the onset of second stage of labor Until delivery
Local analgesia/anesthesia <sup>66,68,69,71,106</sup>	3-5 mL	0.05-1%	Gel	Topical	Once
	0.1 mg/kg (max 5 mL)	0.05%	Solution	Topical	Once

Mydriasis <sup>44,87-91,109,110,144,152</sup>	–	0.6-10 mcg/mL	Solution	Intracameral, intraocular irrigation, ophthalmic	–
	0.3 mL	0.1%	Solution	Irrigation	–
	0.1-0.4 mL	0.001-0.01%	Solution	Intracameral	Once
	40 mL	0.001%	Solution	Intracameral	–
	Median 0.25-0.28 mL	0.01%	Solution	Intraocular injection	–
Reduce intraocular pressure <sup>96,112,114</sup>	1-2 drops/day	2%	Drops	Ophthalmic	Once-twice
Pupil responsiveness in diabetics <sup>128</sup>	–	1%	Drops	Ophthalmic	Once
Vasoconstriction <sup>119</sup>	2.2 mL	1 mg/mL	Solution	Intranasal	Once
Vasodilation to aid in massage <sup>140</sup>	–	0.1%	Cream	Topical	Two weeks

Abbreviation: “–”, not mentioned.

Table 8. Number of studies by combination

	Combination Formula	Number of Studies
Nominated	Epinephrine 0.1% / Lidocaine HCl 5% – ophthalmic solution <sup>28</sup>	1
	Epinephrine / Lidocaine HCl 2% – subconjunctival solution <sup>118</sup>	1
	Epinephrine / Cocaine HCl / Tetracaine HCl – ophthalmic solution	0
	Epinephrine 0.025-0.05% / Cocaine HCl 4-11.8% / Tetracaine HCl 0.25-1% – topical gel or solution <sup>58-63,65,67,69,70,73,75,76,79-81,83,105,120-125,142,154</sup>	26
	Epinephrine 0.001-1% / Lidocaine HCl 1-4% / Tetracaine HCl 0.5-4% – topical gel, solution, or spray <sup>63-65,68,71,74,76-78,82,104,106,130,132,167</sup>	15
	Epinephrine 0.5-10 mcg/mL / Bupivacaine HCl 0.1-6.25 mg/mL / Fentanyl citrate 1-20 mcg/mL – epidural <sup>45-</sup> 57,102,103,129,131,133-136,141,143,148-151,153,156-163	36

Table 9. Compounded products – US

Indication	Publication Year	Compounding Method <sup>a</sup>	Dosage Form	Final Strength										
Local analgesia/anesthesia <sup>63,64,80,82,83,105</sup>	1986-2004	LET or TAC was prepared by a pharmacist from dried ingredients mixed with water and added to hydroxyethyl cellulose gel <sup>63,64</sup>	Gel	0.05%										
		Prepared by pharmacy as mixture of lidocaine 4%, tetracaine 0.5%, and epinephrine 1:2000 with methylcellulose and preservatives <sup>82</sup>	Solution	0.05%										
		TAC was prepared by the pharmacy <sup>83</sup>												
		13 cocaine 135 mg tablets dissolved in 3.75ml of 0.9% sodium chloride for injection, added 3.75ml of tetracaine HCl 2% and 7.5 ml of adrenaline 1% <sup>105</sup>												
		<table border="0"> <tr> <td><u>Ingredients:</u><sup>80</sup></td> <td><u>Amount:</u></td> </tr> <tr> <td>Tetracaine 2%</td> <td>30 mL</td> </tr> <tr> <td>Adrenalin 1:1000</td> <td>60 mL</td> </tr> <tr> <td>Cocaine crystals</td> <td>14.16g</td> </tr> <tr> <td colspan="2">Sterile water (to bring to 120 mL)</td> </tr> </table>	<u>Ingredients:</u> <sup>80</sup>	<u>Amount:</u>	Tetracaine 2%	30 mL	Adrenalin 1:1000	60 mL	Cocaine crystals	14.16g	Sterile water (to bring to 120 mL)		Solution	0.05%
		<u>Ingredients:</u> <sup>80</sup>	<u>Amount:</u>											
Tetracaine 2%	30 mL													
Adrenalin 1:1000	60 mL													
Cocaine crystals	14.16g													
Sterile water (to bring to 120 mL)														
<table border="0"> <tr> <td><u>Ingredients:</u><sup>80</sup></td> <td><u>Amount:</u></td> </tr> <tr> <td>Pontocaine Niphanoids</td> <td>50</td> </tr> <tr> <td>Adrenalin 1:100</td> <td>2.5 mL</td> </tr> <tr> <td>Cocaine HCl 10%</td> <td>70 mL</td> </tr> <tr> <td colspan="2">Sterile water 27.5 for Niphanoids</td> </tr> </table>	<u>Ingredients:</u> <sup>80</sup>	<u>Amount:</u>	Pontocaine Niphanoids	50	Adrenalin 1:100	2.5 mL	Cocaine HCl 10%	70 mL	Sterile water 27.5 for Niphanoids		Solution	0.025%		
<u>Ingredients:</u> <sup>80</sup>	<u>Amount:</u>													
Pontocaine Niphanoids	50													
Adrenalin 1:100	2.5 mL													
Cocaine HCl 10%	70 mL													
Sterile water 27.5 for Niphanoids														
<table border="0"> <tr> <td><u>Ingredients:</u><sup>80</sup></td> <td><u>Amount:</u></td> </tr> <tr> <td>Tetracaine 2%</td> <td>50 mL</td> </tr> <tr> <td>Adrenalin 1:100</td> <td>2.5 mL</td> </tr> <tr> <td>Cocaine HCl 10%</td> <td>40 mL</td> </tr> <tr> <td colspan="2">Sterile water</td> </tr> <tr> <td></td> <td>7.5 mL</td> </tr> </table>	<u>Ingredients:</u> <sup>80</sup>	<u>Amount:</u>	Tetracaine 2%	50 mL	Adrenalin 1:100	2.5 mL	Cocaine HCl 10%	40 mL	Sterile water			7.5 mL		
<u>Ingredients:</u> <sup>80</sup>	<u>Amount:</u>													
Tetracaine 2%	50 mL													
Adrenalin 1:100	2.5 mL													
Cocaine HCl 10%	40 mL													
Sterile water														
	7.5 mL													
Mydriasis <sup>28</sup>	2009	Prepared as according to the published protocol of Shugar	Solution	0.025%										

Reduce intraocular pressure <sup>97</sup>	1970	"L-epinephrine as the borate complex dissolved in phenyl-mercuric acetate 0.002% with sufficient sodium bisulfite and oxine sulphate to buffer the final pH to 7.4"	Drops	0.06-2%
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<sup>a</sup>Epinephrine is also spelled as adrenaline or adrenalin; for accuracy, the substance name that the study authors used is presented in this table. Most studies did not specify the salt form, so HCl is not included unless the study specified use of this salt form.

Table 10. Compounded products – non-US countries

Indication	Compounding Method	Dosage Form	Final Strength
Local analgesia/anesthesia <sup>66</sup>	"Our pharmacy prepares 3mL syringes of lidocaine-epinephrine-tetracaine from raw materials in-house at a cost of \$1.58 [Canadian dollars] per dose (including the cost of the actual syringe)."	Gel	–

Abbreviation: "–", not mentioned.

## *Results of interviews*

Two hundred eighty-five SMEs were contacted for interviews; 96 agreed to be interviewed, and 189 declined or failed to respond to the interview request. Seventeen SMEs discussed epinephrine. Amongst these 17 SMEs, there were 8 medical doctors, 2 dentists, 4 pharmacists, 2 nurse practitioners, and 1 physician assistant. The SMEs specialized and/or were board-certified in anesthesiology, critical care, dermatology, neonatal/perinatal medicine, oncology/hematology, oral and maxillofacial surgery, orthopedics, pain medicine, palliative care, pediatrics, and pharmacotherapy, working in academia, academic medical centers, consulting, hospital/health systems, and retired. The SMEs had been in practice for 6 to 40 years.

In the past, epinephrine has been combined with local anesthetics to prolong blocks. This is not done anymore because blood flow is limited to the nerves, which increases the risk of neurological injury post-operation. Nowadays, Precedex® (dexmedetomidine) and Decadron® (dexamethasone) are added to blocks instead. Several SMEs stated that epinephrine is used mainly in resuscitation; one SME specified that IV epinephrine is used for blood pressure support or refractory bradycardia and sometimes as a local infiltration to cause vasoconstriction. Epinephrine can also be used with lidocaine epidurally for cesarean sections. One SME mentioned using epinephrine if someone is having an allergic reaction, with another SME specifying that IM or sublingual epinephrine could be used for anaphylaxis. Another SME mentioned using epinephrine as a test dose before certain injections because it helps them determine whether the needle is positioned properly. If the heart rate increases with the test dose, then that means the needle position needs to be adjusted. One SME also mentioned a compounded injection combination of morphine, bupivacaine, and epinephrine made in the hospital pharmacy for pain control in knee patients. This combination is injected around the incision site because there is a lot of soft tissue trauma with total knee procedures. A SME expressed a need to get epinephrine prefilled if possible (varies due to shifts with shortages and supplies) and stated that mistakes such as mislabeling of epinephrine concentrations can be harmful.

Several SMEs commented on epinephrine as a topical/local anesthetic product. One SME, who is a maxillofacial surgeon, used a commercially available combination local anesthetic product (epinephrine and lidocaine) daily and did not see a need for this to be compounded. This SME has had patients with allergies to the preservative in the product, but it is very rare. For those cases, the SME sends the patient to the primary care doctor to find out what the available options are and/or switches to other medications, such as Carbocaine® (mepivacaine), that do not have epinephrine. One SME specializing in palliative care would like a topical formulation to limit local bleeding for “tacky” wounds but stated this would not be a commonly used product. Another SME stated that at the beginning of a surgery they would inject epinephrine around the incision site to prevent bleeding. Epinephrine is not used at the end of surgery due to the risk of increasing the heart rate or blood pressure. A SME specializing in dermatology mentioned using lidocaine with a low dose of epinephrine when performing skin biopsies. Lidocaine has a low pH, so it is buffered with sodium bicarbonate to lessen the stinging and burning. The combination LET is also used in a lot of cosmeceutical procedures as a topical anesthetic. Epinephrine is for vasoconstriction so that there will be less bleeding. This SME stated that there is a potential for LET to be stocked in the office. Another SME also mentioned they have used compounded LET cream and mentioned that their trauma pain service unit has been interested in compounding drugs for pain management. As for the TAC combination, a SME mentioned that cocaine is a scheduled drug and that they were not sure if “you can dispense that relatively easily out of bulk compounding.” The only place they have seen cocaine used was for people getting rhinoplasty. Some other general SME comments include a SME who could see epinephrine used as a dental solution mixed with other substances.

Another SME expressed that the nominated combinations made sense to them and stated they see the potential benefits because “people like [epinephrine since] it reduces any bleeding.” This SME also mentioned being careful before using epinephrine in the patients with glaucoma.

A SME expressed that using outsourcing facilities to compound epinephrine helps with efficiency and stated it is nice that drugs from outsourcing facilities have “extended stability dating.” While a hospital representative commented that they compound or outsource approximately half of their high-volume products, including epinephrine. Epinephrine “drips” and syringes for use in the operating room are compounded in-house.

### *Results of survey*

Sixteen people responded to the survey distributed via professional medical associations and available on the project website (refer to Appendices 3.1-3.6 for survey instruments). A separate survey was distributed by the American Academy of Ophthalmology (AAO) (refer to Appendix 3.7 for survey instrument); 30 people responded to this survey. Refer to Table 11 for respondent characteristics.

Forty-five respondents (98%) reported using epinephrine either alone or in combination with other substances.

Respondents utilized the following salt forms of epinephrine: hydrochloride (11, 24.4% of 45 respondents who used epinephrine), bitartrate (0, 0%), unsure (19, 42.2%), other (1, 2.2%) with respondent entering “lidocaine with epinephrine (purchased as such) then buffered with 8.4% sodium bicarbonate”, or did not respond to this question (14, 31.1%).

Among respondents, 16 (35.6% of 45 respondents who used epinephrine) used epinephrine as a single-agent product, 22 (48.9%) used epinephrine in combination with lidocaine, 8 (17.8%) used epinephrine in combination with lidocaine and tetracaine, 0 (0%) used epinephrine in combination with cocaine and tetracaine, and 0 (0%) used epinephrine in combination with bupivacaine and fentanyl.

Respondents used single-agent epinephrine as an epidural, intracaudal, or perineural injectable solution (2, 4.4% of 45 respondents who used epinephrine), topical cream (1, 2.2%), intracameral/intraocular injection (6, 13.3%), ophthalmic solution (6, 13.3%), and ‘none of the above’ (1, 2.2%). Respondents used epinephrine as a single-agent product for anaphylaxis/hypersensitivity reactions (1, 2.2% of 45 respondents who used epinephrine), surgical bleeding (1, 2.2%), open-angle glaucoma (1, 2.2%), and to induce mydriasis for intraocular surgery (6, 13.3%).

Respondents used epinephrine in combination with lidocaine as an ophthalmic solution (10, 22.2% of 45 respondents who used epinephrine) and via an unspecified route (12, 26.7%). Respondents used epinephrine in combination with lidocaine for local anesthesia (9, 20%), to induce mydriasis for intraocular surgery (9, 20%), and for open-angle glaucoma (1, 2.2%). Respondents used epinephrine in combination with lidocaine and tetracaine as a topical gel (6, 13.3% of 45 respondents who used epinephrine) and via an unspecified route (2, 4.4%). Respondents used epinephrine in combination with lidocaine and tetracaine to provide local anesthesia (6, 13.3%). Refer to Table 12 for conditions for which single-agent or combination epinephrine was used.

The 45 respondents used compounded epinephrine either alone or in combination due to lack of commercial products in an appropriate dosage form, strength, or combination (20, 44.4% of respondents, where respondents were allowed to select multiple reasons), patient allergies (6, 13.3%), other patient conditions preventing use of commercial products (3, 6.7%), or no commercially available products with

epinephrine alone or in combination (11, 24.4%). One (2.2%) respondent used compounded epinephrine in combination with lidocaine due to cost. One (2.2%) respondent used compounded epinephrine in combination with lidocaine and tetracaine due to “cost, efficacy, access.” Refer to Table 13 for reasons for using compounded single-agent or combination epinephrine. Explanations for using compounded epinephrine either alone or in combination with other substances due to lack of appropriate commercial products included “when pf/bilslfate [*sic*] free product unavailable will dilute commercial 1/1000 vial ¼ to protect cornea from bisulf issues”, “must be preservative free and special dosage” and “Epi-Shugarcaine is standard of care.”

Nine respondents (20%) stocked non-patient-specific compounded epinephrine either alone or in combination with other substances at their practice. Respondents that did stock non-patient-specific epinephrine compounded the product at their practice (2, 22.2% of respondents that stocked non-patient-specific compounded epinephrine, where respondents were allowed to select more than one option), had the product compounded by an in-house pharmacy (2, 22.2%), purchased, or had the patient purchase the product from a compounding pharmacy (6, 66.7%) or outsourcing facility (1, 11.1%). Refer to Table 14 for how respondents obtained compounded epinephrine.

A separate survey was distributed by the Ambulatory Surgery Center Association (ASCA); 230 people responded to this survey (refer to Appendix 3.8 for survey instrument).

Amongst respondents to the ASCA survey, 97 (42% of 230 total respondents) were very familiar with the term ‘503B outsourcing facility’, 86 (37%) were somewhat familiar with this term, and 47 (20%) were not familiar with this term (refer to Table 15).

One hundred ten survey respondents (54% of 203 people who responded to this question) utilized a 503B outsourcing facility to acquire compounded drugs; 93 survey respondents (46%) did not utilize a 503B outsourcing facility. Eleven respondents (3.8% of 290 responses, where respondents were allowed to select multiple drug products) obtained single-agent epinephrine from a 503B outsourcing facility, 16 (5.5%) obtained epinephrine for ophthalmic administration, 31 (10.7%) obtained epinephrine in combination with lidocaine for ophthalmic administration, 13 (4.5%) obtained epinephrine in combination with lidocaine and tetracaine, 3 (1%) obtained epinephrine in combination with bupivacaine and fentanyl (refer to Table 16).

The most common types of procedures performed at the facilities where the ASCA survey respondents worked were: ophthalmology (115, 17% of responses, where respondents were allowed to select multiple procedure types); orthopedics (89, 13%); pain (80, 12%); podiatry (74, 11%); and plastics (72, 10%) (refer to Table 17).

Table 11. Characteristics of survey respondents

<b>Terminal Clinical Degree</b>	<b>Responses, n (N=36)<sup>a</sup></b>
Doctor of Medicine (MD)	35
Doctor of Osteopathic Medicine (DO)	1
Doctor of Medicine in Dentistry (DMD/DDS)	0
Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)	0
Naturopathic Doctor (ND)	0
Nurse Practitioner (NP)	0
Physician Assistant (PA)	0
<b>Practice Setting</b>	<b>Responses, n (N=52)<sup>a</sup></b>
Physician office or private practice	27
Outpatient clinic	5
Hospital or health system	4
Academic medical center	8
Emergency room	1
Operating room	6
Compounding pharmacy	1

<sup>a</sup>Some respondents reported more than one terminal clinical degree and/or practice setting.

Table 12. Conditions for which single-agent or combination epinephrine prescribed or administered

<b>Condition</b>	<b>Responses, n (N=34)<sup>a,b</sup></b>
Anaphylaxis/hypersensitivity reaction	1
Local anesthesia	15
Mydriasis for intraocular surgery	15
Open-angle glaucoma	2
Surgical bleeding	1

<sup>a</sup>Out of 46 respondents, 45 reported prescribing or using single-agent or combination epinephrine.

<sup>b</sup>Survey respondents allowed to select multiple conditions.

Table 13. Reasons for using compounded single-agent or combination epinephrine

<b>Reason</b>	<b>Responses, n (N=42)<sup>a,b</sup></b>
Commercial product not available in desired dosage form, strength, or combination	20
Patient allergies prevent use of commercial products	6
Patient conditions prevent use of commercial products	3
No commercial products	11
Other <sup>c</sup>	2

<sup>a</sup>Out of 46 respondents, 45 reported prescribing or using single-agent or combination epinephrine.

<sup>b</sup>Survey respondents allowed to select multiple reasons.

<sup>c</sup>Cost and “cost, efficacy, access”.

Table 14. Use of non-patient-specific compounded single-agent or combination epinephrine

<b>Do you stock non-patient-specific compounded single-agent or combination epinephrine at your practice?</b>	<b>Responses, n (N=26)<sup>a</sup></b>
Yes	9
No	14
Not sure	3
No response	19
<b>How do you obtain your stock of non-patient-specific compounded single-agent or combination epinephrine?</b>	<b>Responses, n (N=11)<sup>a</sup></b>
Compound yourself at practice	2
Product compounded by in-house pharmacy	2
Purchase from compounding pharmacy	6
Purchase from outsourcing facility	1

<sup>a</sup>Out of 46 respondents, 45 reported prescribing or using single-agent or combination epinephrine.

Table 15. Ambulatory Surgery Center Association respondents' familiarity with compounding terms

<b>Compounded drugs (medications prepared to meet a patient-specific need)</b>	<b>Responses, n (N=230)</b>
Very familiar	153
Somewhat familiar	70
Not familiar	7
<b>503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed to meet a patient-specific need)</b>	<b>Responses, n (N=230)</b>
Very familiar	118
Somewhat familiar	91
Not familiar	21
<b>503B Outsourcing facility (a facility that compounds larger quantities without a patient-specific prescription)</b>	<b>Responses, n (N=230)</b>
Very familiar	97
Somewhat familiar	86
Not familiar	47

Table 16. Products obtained from a 503B outsourcing facility

<b>Product</b>	<b>Responses, n (N=290)<sup>a</sup></b>
Amitriptyline / Ketoprofen / Oxymetazoline	1
Budesonide	2
Calcium gluconate	2
Droperidol	2
Epinephrine	11
Epinephrine for ophthalmic administration	16
Epinephrine / Lidocaine for ophthalmic administration	31
Epinephrine / Bupivacaine / Fentanyl	3
Fentanyl	10

Flurbiprofen	3
Flurbiprofen for ophthalmic administration	6
Hydromorphone	5
Ipamorelin	1
Ketoprofen / Nifedipine	3
Lidocaine / Epinephrine / Tetracaine	13
Meperidine	3
Morphine	5
Naloxone	5
Neomycin	5
Phentolamine	1
Promethazine	5
Remifentanyl	4
Sufentanyl	2
Tramadol	2
None of the above	75
Do not obtain any compounded drugs from 503B outsourcing facility	74

<sup>a</sup>Survey respondents allowed to select multiple products.

Table 17. Type of specialty procedures performed at ambulatory surgery facility

<b>Procedure Type</b>	<b>Responses, n (N=686)<sup>a</sup></b>
Dental	23
Dermatology	9
Endoscopy	65
Neurosurgery	22
Obstetrics/gynecology	39
Ophthalmology	115
Otolaryngology	58
Orthopedics	89
Pain	80
Plastics	72
Podiatry	74
Other <sup>b</sup>	40

<sup>a</sup>Survey respondents were allowed to select multiple procedure types.

<sup>b</sup>No respondents provided description for 'Other' procedure type.

## CONCLUSION

Epinephrine HCl was nominated for inclusion on the 503B Bulks List for a variety of medical conditions via various single and multi-agent preparations. Epinephrine is available as an FDA-approved product as an intraocular, IM, IV, and SC solution. It is also available as a combination with bupivacaine HCl for injection. The combination with epinephrine and lidocaine as a topical solution 2% and epinephrine and prilocaine as an 1-2% injection was discontinued not for safety or efficacy reasons. Epinephrine is available in the nominated dosage form and ROA in Abu Dhabi, Australia, Belgium, Canada, Hong Kong, Ireland, Latvia, Namibia, New Zealand, Saudi Arabia, and UK.

From the literature review, epinephrine is commonly used in various indications related to analgesia/anesthesia, hemostasis, mydriasis, and reducing intraocular pressure. Other indications mentioned from the literature review include alveolar hemorrhage and vasodilation to aid in massage. Epinephrine with bupivacaine and fentanyl epidurally, TAC and LET as topical products were the most common combinations found in the literature review. As a single agent product, epinephrine was used as an ophthalmic/intracameral/intraocular solution, topical cream/solution/spray, and intranasal solution.

From the interviews, all SMEs had experience using epinephrine. Several SMEs stated that epinephrine is used mainly in resuscitation, with one SME who specified that IV epinephrine was used for blood pressure support or refractory bradycardia and sometimes as a local infiltration to cause vasoconstriction. Another SME mentioned using epinephrine as a test dose before certain injections. Several SMEs commented on epinephrine as a topical/local anesthetic product. One SME used a combination local anesthetic product (epinephrine and lidocaine) daily and did not see a need for this to be compounded. This SME had rarely had patients with allergies to the preservative in the product. A SME specializing in palliative care would like a topical formulation to limit local bleeding for “tacky” wounds, but this would not be a commonly used product. Another SME stated that they always see epinephrine in sprays when they perform surgery. A SME specializing in dermatology mentioned using lidocaine with low dose epinephrine for skin biopsies. One SME expressed that the nominated combinations made sense to them and stated that they see the potential benefits because “people like [epinephrine since] it reduces any bleeding.”

There were several interview comments related to compounded products and use of outsourcing facilities. One SME stated that there is a potential use for LET to be stocked in the office, while another SME mentioned they have compounded LET cream. For TAC, a SME expressed that cocaine is a scheduled drug and that they were not sure if “you can dispense that relatively easily out of bulk compounding.” A SME expressed that using outsourcing facilities to compound epinephrine helps with efficiency and drugs from outsourcing facilities have “extended stability dating.” While a hospital representative commented that they compound or outsource approximately half of their high-volume products (which includes epinephrine). For epinephrine drips and operating room epinephrine syringes, they compound those in-house. A SME also expressed trying to get epinephrine prefilled if possible due to shifts with shortages and supplies.

From the responses to the surveys distributed to the AAO and other professional medical associations, 45 out of 46 respondents (98%) used epinephrine either alone or in combination with other substances. The most common indication respondents used compounded epinephrine for were anaphylaxis/hypersensitivity reactions, local anesthesia, to induce mydriasis for intraocular surgery, open-angle glaucoma, and surgical bleeding. The 45 respondents used compounded epinephrine either alone or in combination due to a lack of commercial products in an appropriate dosage form, strength or combination, other patient conditions preventing use of commercial products, or no commercially available products with epinephrine alone or in combination. One respondent used compounded epinephrine in combination with lidocaine due to cost, and another due to “cost, efficacy, access”. Nine

respondents stocked non-patient-specific compounded epinephrine either alone or in combination with other substances at their practice.

Two hundred thirty people responded to the survey distributed via the ASCA. Eleven respondents obtained single-agent epinephrine from a 503B outsourcing facility, 16 obtained epinephrine for ophthalmic administration, 31 obtained epinephrine in combination with lidocaine for ophthalmic administration, 13 obtained epinephrine in combination with lidocaine and tetracaine, and 3 obtained epinephrine in combination with bupivacaine and fentanyl.

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## APPENDICES

### *Appendix 1. Search strategies for bibliographic databases*

#### MEDLINE search strategy

- Platform: Ovid
- Years searched: Ovid MEDLINE and epub ahead of print, in-process and other non-indexed citations and daily 1946 to January 16, 2020
- Date last searched: January 17, 2020
- Limits: Humans (search hedge); English language; Publication type (search hedge)
- Number of results: 2649

1	exp epinephrine/	55661
2	adrenalin\$.tw.	22297
3	adrenal hydrochloride.tw.	0
4	epinephrine.tw.	0
5	epinefran\$.tw.	0
6	epinefrin\$.tw.	16
7	epinephran\$.tw.	1
8	epinephrin\$.tw.	33357
9	levoadrenalin\$.tw.	0
10	levoepinephrin\$.tw.	3
11	racepinephrin\$.tw.	4
12	or/1-11	78384
13	administration, inhalation/	30122
14	administration, topical/	37906
15	administration, cutaneous/	21647
16	administration, intranasal/	14311
17	administration, ophthalmic/	1108
18	injections, intraocular/	995
19	infusions, spinal/	149
20	injections, epidural/	2833

21	epidural space/	4456
22	inhal\$.tw.	106240
23	topical\$.tw.	101954
24	intranasal\$.tw.	25988
25	nasal\$.tw.	112253
26	((intraocular\$ or ocular\$ or ophthalm\$) adj2 (administrat\$ or inject\$ or solution?)).tw.	4711
27	intracameral\$.tw.	1841
28	intra cameral\$.tw.	20
29	epidural\$.tw.	41205
30	extradural\$.tw.	6652
31	extra dural\$.tw.	138
32	peridural\$.tw.	2055
33	peri dural\$.tw.	6
34	nasal sprays/	483
35	emulsions/	17485
36	gels/	28464
37	liniments/	122
38	ointments/	12718
39	skin cream/	958
40	pharmaceutical solutions/	3292
41	ophthalmic solutions/	13650
42	emulsion?.tw.	31635
43	spray?.tw.	26825
44	liniment?.tw.	141
45	ointment?.tw.	11600
46	salve?.tw.	336

47	unguent\$.tw.	110
48	lotion?.tw.	2238
49	cream?.tw.	18347
50	(eye adj2 drop?).tw.	6070
51	eyedrop?.tw.	2123
52	or/13-51	534823
53	and/12,52	4168
54	exp animals/ not humans/	4665122
55	53 not 54	3463
56	(review or systematic review or meta analysis).pt.	2666817
57	55 not 56	3111
58	limit 57 to english language	2649

## Embase search strategy

- Platform: Elsevier
- Years searched: 1947 to present
- Date last searched: January 17, 2020
- Limits: Humans (search hedge); English language; Publication type: article, article in press, conference abstract, conference paper, data papers, erratum, letter, note
- Number of results: 5552
- Notes: Tested Emtree term 'conjunctival drug administration' and epinephrine; three results, none of which were relevant.

1	epinephrine'/de	129765
2	adrenalin*':ti,ab,tn	38157
3	adrenal hydrochloride':ti,ab,tn	0
4	epimephrine':ti,ab,tn	2
5	epinefran*':ti,ab,tn	0
6	epinefrin*':ti,ab,tn	29
7	epinephran*':ti,ab,tn	0
8	epinephrin*':ti,ab,tn	47948
9	levoadrenalin*':ti,ab,tn	0
10	levoepinephrin*':ti,ab,tn	4
11	racepinephrin*':ti,ab,tn	7
12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	144928
13	inhalation drug administration'/de	49841
14	topical drug administration'/exp	110252
15	cutaneous drug administration'/de	597
16	intraocular drug administration'/de	4161
17	intracameral drug administration'/de	258
18	epidural drug administration'/de	8822
19	inhal*':ti,ab	158877
20	topical*':ti,ab	144765
21	intranasal*':ti,ab	34762

22	((intraocular* OR ocular* OR ophthalm*) NEAR/2 (administrat* OR inject* OR solution*)):ti,ab	6477
23	intracameral*:ti,ab	2236
24	intra cameral*:ti,ab	26
25	epidural*:ti,ab	58260
26	extradural*:ti,ab	8807
27	extra dural*:ti,ab	236
28	peridural*:ti,ab	2981
29	peri dural*:ti,ab	12
30	eye drops'/de	14082
31	gel'/exp	71878
32	liniment'/de	247
33	lotion'/de	2784
34	nose drops'/de	749
35	nose spray'/de	3019
36	ointment'/exp	18261
37	salve'/de	165
38	solution and solubility'/de	25629
39	emulsion\$:ti,ab	43356
40	cream\$:ti,ab	28741
41	liniment\$:ti,ab	230
42	lotion\$:ti,ab	3912
43	spray\$:ti,ab	35927
44	ointment\$:ti,ab	21144
45	salve\$:ti,ab	468
46	unguent*:ti,ab	239
47	(eye NEAR/2 drop\$):ti,ab	9325

48	eyedrop\$:ti,ab	2792
49	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48	711864
50	drug therapy'/de	699728
51	drug dose':lnk	620401
52	drug administration':lnk	1704600
53	drug therapy':lnk	3813480
54	drug combination':lnk	820364
55	therap*':ti,ab	4026948
56	pain'/de	333833
57	epidural anesthesia'/exp	33826
58	epidural analgesia'/de	2155
59	vasoconstriction'/de	39149
60	venoconstriction'/de	1674
61	mydriasis'/de	9057
62	pain*':ti,ab	1022277
63	anesthe*':ti,ab	376021
64	anaesthet*':ti,ab	89997
65	analges*':ti,ab	176305
66	vasoconstrict*':ti,ab	58193
67	venoconstrict*':ti,ab	812
68	((vein OR vessel) NEAR/3 constrict*):ti,ab	780
69	(pupil* NEAR/2 dilat*):ti,ab	5628
70	mydria*':ti,ab	6339
71	#50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70	8781867
72	#12 AND #49 AND #71	9194

73	[animals]/lim NOT [humans]/lim	5981204
74	#72 NOT #73	8448
75	#72 NOT #73 AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [data papers]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim)	6318
76	#72 NOT #73 AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [data papers]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim) AND [english]/lim	5552

Appendix 2. Summary of included studies

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Aguilar <i>et al.</i> , 1996, Spain <sup>143</sup>	Double-blind, placebo-controlled, crossover	<p>45 Patients who underwent posterolateral thoracotomy for lung resection</p> <p>Group 1 (87%, mean 60.5 y)</p> <p>Group 2 (80%, mean 58.8 y)</p> <p>Group 3 (73%, mean 57 y)</p>	<ul style="list-style-type: none"> <li>• Group 1: Bupivacaine and adrenaline before skin incision and saline after skin incision</li> <li>• Group 2: Saline before skin incision and bupivacaine and adrenaline after skin incision</li> <li>• Group 3: Saline before and after skin incision</li> </ul> <p>Study randomly allocated patients to 1 of these 3 groups, did not specified how many patients per group.</p> <p>*Post-op all 45 patients were started on an extradural infusion of bupivacaine, adrenaline, and fentanyl using a patient-controlled extradural analgesia pump system.</p>	Pain scores at rest, during abduction of the ipsilateral arm and after cough, arterial blood gas, total successful patient-controlled extradural analgesia demands	<p>“Thoracic extradural block with bupivacaine did not produce an early preemptive effect after thoracotomy. Found no significant difference in pain scores b/w pre-incisional and post-incisional administration of thoracic extradural with 0.5% bupivacaine.”</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Alfonso <i>et al.</i> , 1988, US <sup>86</sup>	–	65 Patients who underwent extracapsular cataract extraction with posterior chamber intraocular lens (IOL) implantation (46%, mean 62 y)	<ul style="list-style-type: none"> <li>• Timolol, phenylephrine, and epinephrine (65)</li> </ul>	Pupillary size	“This promising new dilating regimen [timolol, phenylephrine, epinephrine] is a simple, effective, and reversible method of obtaining operative dilation during extracapsular cataract extraction and IOL implantation.”
Alio <i>et al.</i> , 1989, Spain <sup>128</sup>	–	124 Total subjects 62 insulin-dependent diabetics (50%, age range 15-65 y) 62 normal subjects (sex and age-matched with the diabetics group)	<ul style="list-style-type: none"> <li>• Cocaine, phenylephrine, epinephrine, homatropine, and pilocarpine (62)</li> </ul>	Pupil reactivity	"Our results clearly support the hypothesis that sympathetic denervation does exist in the diabetic pupil and that this is related to the duration of diabetic disease. The abnormal reactions to cocaine 4%, epinephrine 1%, and phenylephrine 1% with conservation of pupil responses to light and convergence indicate that this sympathetic abnormality arises ten years after the onset of [diabetes] and is frequent after 15 years."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Allen <i>et al.</i> , 1965, US <sup>101</sup>	–	185 Patients (gender and age not mentioned)	<ul style="list-style-type: none"> <li>• Normal saline solution (25)</li> <li>• Cocaine 5% (33)</li> <li>• Cocaine 10% (25)</li> <li>• Phenyl-alanine 2-lysine 8-vasopressin (29)</li> <li>• Naphazoline HCl (28)</li> <li>• Epinephrine (25)</li> </ul>	Temperature change in the nasal cavity (deviations from the medium temperature of 37° C)	"Epinephrine 1/1000 solution was demonstrated as the most efficient vasoconstrictor; however, it cannot be recommended for routine use because of the cardiovascular side effects...Epinephrine 1/1000 and 10 per cent cocaine were found to be the most efficacious drugs in producing vasoconstriction of nasal mucous membrane."
Allen and Epstein, 1986, US <sup>93</sup>	Pilot study, continuation of double-masked randomized trial	19 Patients with primary open angle glaucoma or glaucoma suspects (42%, range 29-77 y)	<ul style="list-style-type: none"> <li>• Epinephrine HCl (16)</li> <li>• Dipivefrin (3)</li> </ul> <p>All patients given epinephrine except for a few patients with prior intolerance or allergy to epinephrine who were given dipivefrin</p>	Analysis of tonometric and tonographic measurements, specifically difference in IOP and outflow facility before and after initiation of epinephrine	"Consistent with previous reports, patients receiving timolol exhibited no significant changes in IOP or outflow facility after the addition of epinephrine to their treatment regimen. These results suggest that epinephrine's agonist effect on the outflow channels is mediated through beta2-adrenergic receptors and that combined therapy with betaxolol and epinephrine may be clinically useful."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Ambalu <i>et al.</i> , 2016, US <sup>129</sup>	Case report	1 In-patient presenting for a repeat cesarean section (C-section) and elective bilateral tube ligation (0%, 31 y)	<ul style="list-style-type: none"> <li>• Combined spinal epidural analgesia: bupivacaine, fentanyl, epinephrine, cerebral spinal fluid (CSF)</li> </ul>	Pain-free procedure	"This case demonstrates the successful use of combined spinal epidural analgesia for a C-section and bilateral tubal ligation in a patient with a history of chronic back pain, two lumbosacral laminectomies, and a spinal cord stimulator."
Anderson <i>et al.</i> , 1990, US <sup>58</sup>	Randomized, placebo-controlled, double-blind study	<p>151 Patients who presented to the pediatric emergency department with a laceration length of 5 cm or less in a well-vascularized, non-mucous membrane area</p> <p>TAC (gender not mentioned, mean 7.49 y)</p> <p>Lidocaine (gender not mentioned, mean 6.77 y)</p> <p>Placebo (gender not mentioned, mean 8.11 y)</p>	<ul style="list-style-type: none"> <li>• TAC (56)</li> <li>• Lidocaine (53)</li> <li>• Placebo (42)</li> </ul>	Patient compliance during suturing	"TAC is well accepted by patients and facilitates [for] wound repair. TAC does not differ significantly from lidocaine with regard to anesthetic efficacy or wound complications and is superior to lidocaine with regard to patient compliance. Because of this exceptional effect on patient compliance, TAC may be the preferred anesthetic for use in the repair of pediatric lacerations 5 or fewer cm in length located in well-vascularized, nonmucous membrane areas."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Antcliff and Trew, 1997, UK <sup>87</sup>	Randomized	64 Patients who underwent routine phacoemulsification Control – no diclofenac (40%, range 58-94 y) Diclofenac (22%, range 54-92 y)	<ul style="list-style-type: none"> <li>Control (32)</li> <li>Diclofenac (32)</li> </ul> Irrigating solutions of balanced salt solution containing adrenaline 1:10 <sup>6</sup> used during the procedure	Pupil diameter	"This study shows that in the presence of irrigating solutions containing adrenaline, topical diclofenac has a statistically significant but clinically small additive effect in maintaining peri-operative mydriasis."
Backstrom and Behndig, 2006, Sweden <sup>144</sup>	Randomized, double-blind	80 Patients with age-related cataracts who underwent unilateral phacoemulsification and IOL implantation Epinephrine group with intracameral mydriatics (ICM) (46.7%, mean 74 y ± 11) Epinephrine group with placebo (43.3%, mean 75 y ± 11) Non-epinephrine group with ICM (5%, mean 76 y ± 8) Non-epinephrine group with placebo (50%, mean 80 y ± 8)	<ul style="list-style-type: none"> <li>Epinephrine group with ICM (30)</li> <li>Epinephrine group with placebo (30)</li> <li>Non-epinephrine group with ICM (10)</li> <li>Non-epinephrine group with placebo (10)</li> </ul> *intracameral mydriatics: cyclopentolate, phenylephrine, xylocaine **placebo: balanced salt solution	Pupil size, postoperative visual acuity, IOP, inflammatory reaction and corneal swelling	"We have shown that in cases with an intraoperative pupil contraction, ICM is effective in redilating the pupil. Insufficient adrenergic stimulation of the pupil dilator appears to be a major factor causing intraoperative pupil contraction during phacoemulsification cataract surgery."
Barret <i>et al.</i> , 1999, US <sup>107</sup>	Prospective cohort	42 Pediatric patients who underwent total burn wound excision and autografting within 24 hours of admission Epinephrine group (57%, mean 7.4 y ± 3.9) Saline group (62%, mean 7 y ± 4.5)	<ul style="list-style-type: none"> <li>Epinephrine group (21)</li> <li>Saline group (21)</li> </ul>	Blood loss, pre and post-operative hematocrit and hemoglobin	"In conclusion, no differences in blood loss were found between the groups. The routine use of local epinephrine during total wound excision in combination with topical thrombin in pediatric patients operated within 24 h after the admission may not be necessary."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Beck and Keenan., 2018, US <sup>145</sup>	Case study	1 Patient with systemic lupus erythematosus with diffuse alveolar hemorrhage (0%, 52 y)	<ul style="list-style-type: none"> <li>• Thrombin and epinephrine</li> </ul>	Reduction/cessation of alveolar hemorrhage and associated clinical signs such as hemoptysis and impaired oxygenation	"First-line treatment [for pulmonary hemorrhage] involves high doses of corticosteroids followed by a second immunosuppressive agent... Uncontrolled active bleeding is a relative contraindication due to need for systemic anticoagulation. When instituted in the setting of active hemorrhage, careful attention to and adjustments in anticoagulation may be necessary."
Becker <i>et al.</i> , 1977, US <sup>94</sup>	–	32 Patients with primary open angle glaucoma or secondary glaucoma (69%, mean 59.3 y ± 11.1)	<ul style="list-style-type: none"> <li>• Primary glaucoma (16)</li> <li>• Secondary glaucoma (16)</li> </ul> <p>*15 patients in each group received epinephrine 2%, while 1 patient in each group received epinephrine 1% twice daily</p>	Average reduction in applanation pressure for all readings available, average premature ventricular contractions	"Topical application of epinephrine lowers intraocular pressure effectively and produces [premature ventricular contractions] in significantly more patients with [primary glaucoma] than in a matched group with secondary glaucoma."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Becker and Shin, 1976, US <sup>95</sup>	–	80 Patients with spontaneous bilateral hypertension who were also homozygous responders to topical corticosteroids (gender and age not provided)	<ul style="list-style-type: none"> <li>• Epinephrine HCl 1% or 2% (80)</li> </ul>	Decrease of over 5 mmHg in the treated eye, glaucomatous visual field defects	"The data presented demonstrates clearly that in selected homozygous ocular hypertensive patients, the prevalence of epinephrine responsiveness (over 5 mm Hg decrease in IOP) is significantly greater in those individuals who developed field loss (85%) than in those who did not (28%)."
Beilin <i>et al.</i> , 2002, US <sup>102</sup>	Prospective, randomized, double-blinded study	<p>89 Nulliparous patients experiencing contractions at least once every 5 minutes and had greater than 5 cm cervical dilation at the time they requested labor analgesia</p> <p>Placebo group (0%, range 18-41 y)</p> <p>Fentanyl with:</p> <ul style="list-style-type: none"> <li>• Group bupivacaine 0.125% (0%, range 24-44 y)</li> <li>• Group bupivacaine 0.0625% (0%, range 19-40 y)</li> <li>• Group bupivacaine 0.04% and epinephrine 1:600,000 (0%, range 18-44 y)</li> </ul>	<ul style="list-style-type: none"> <li>• Placebo group (23)</li> <li>• Group bupivacaine 0.125% (22)</li> <li>• Group bupivacaine 0.0625% (22)</li> <li>• Group bupivacaine 0.04% and epinephrine (22)</li> </ul>	Self-reported pain scale, duration of epidural anesthetic, assess degree of motor block (modified Bromage scale)	"In conclusion, initiating an epidural infusion 15 minutes after subarachnoid medication is administered and 5 minutes after an epidural test dose will maintain the analgesia with minimal side effects. Using an infusion of bupivacaine 0.125% with fentanyl 2 g/mL maintains the analgesia for longer than either bupivacaine 0.0625% with fentanyl 2 g/mL or bupivacaine 0.04% with fentanyl 2 g/mL and epinephrine 1:600,000, but it produces more motor block."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Blackburn <i>et al.</i> , 1995, US <sup>120</sup>	Prospective, double-blind design	35 Patients with facial and scalp lacerations greater than 6 cm Tetracaine, epinephrine, cocaine (TAC) group (gender not provided, mean 15.8 y ± 8) Lidocaine and epinephrine group (gender not provided, mean 18.5 y ± 10.4)	<ul style="list-style-type: none"> <li>• TAC (18)</li> <li>• Lidocaine and epinephrine (17)</li> </ul>	Necessity to inject local anesthetic due to ineffective topical anesthesia, amount of pain felt via Facial Effective Scale, diameter of skin blanching after anesthetic application	"This pilot study demonstrated that [lidocaine and epinephrine] is clinically equivalent to TAC in producing topical anesthesia and showed a correlation between larger anesthetic halos and improved wound anesthesia. In addition, use of [lidocaine and epinephrine] instead of TAC will lead to considerable cost savings."
Blome-Eberwein <i>et al.</i> , 2016, US <sup>146</sup>	Retrospective chart review	104 Patients who received new DL-lactide dressing material to second degree burns (gender and age not provided)	<ul style="list-style-type: none"> <li>• DL-lactide (104)</li> </ul> DL-lactide was applied after hemostasis with topical epinephrine	Time to epithelialization, infection rate, pain	"The application of the new DL-lactide dressing to 2nd degree wounds offers a new simple option of treatment with potential for better outcomes and less pain."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Blondeau and Cote, 1984, Canada <sup>112</sup>	Randomized, double-blind	<p>30 Patients with ocular hypertension or primary open-angle glaucoma and all used timolol 0.5% twice daily in both eyes at least 1 month before experiment</p> <p>Placebo (gender not provided, mean 68.9 y ± 8.6)</p> <p>Epinephrine HCl (gender not provided, mean 65.6 y ± 8)</p> <p>Dipivefrin HCl (gender not provided, mean 61.8 y ± 15.3)</p>	<ul style="list-style-type: none"> <li>• Placebo (10)</li> <li>• Epinephrine HCl (10)</li> <li>• Dipivefrin HCl (10)</li> </ul>	IOP, pupil size, tonography, heart rate	<p>"Our study suggests that arrhythmias or increases in blood pressure can be expected in individuals with hypertension or other cardiovascular diseases who use both epinephrine and timolol. We would not recommend such combined use in view of the limited additive effect on the IOP and the cardiovascular effects in predisposed patients... From our results and those of others, the benefit in terms of the IOP of instilling dipivefrin in a timolol-treated eye appears to be clinically insignificant."</p>
Bonadio, 1996, US <sup>59</sup>	Prospective	<p>22 Patients with minor laceration of the oral cavity that were 2 cm or less and required single-layer closure (gender not provided, children &gt;5 y)</p>	<ul style="list-style-type: none"> <li>• TAC (22)</li> </ul>	Pain scores during wound repair	<p>"Despite the small number of patients studied, this preliminary report suggests that this method of TAC application for anesthesia of minor oral lacerations is safe and highly effective when only a single, two-drop dose is properly applied under continuous, direct physician supervision."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Bonadio and Wagner, 1988, US <sup>60</sup>	Prospective evaluation	103 Patients with minor laceration of the skin who received TAC for wound repair (61.5%, range 11 month-17 y)	<ul style="list-style-type: none"> <li>• TAC (103)</li> </ul>	Complications related to TAC or wound healing; sutures placed eliciting pain	"We conclude that TAC is a safe, effective method of achieving anesthesia for the repair of minor dermal lacerations in children. It is especially efficacious in anesthetizing wounds located on the face and lip. Its painless method of application enhances patient compliance with the wound repair procedure, which optimizes accurate approximation of lacerated tissue."
Bonadio and Wagner, 1990, US <sup>121</sup>	Prospective study in which managing physician was blind to which preparation was administered; assistant randomly selected one of the two solutions for application; physician informed of solution composition after procedure	55 Patients with minor dermal lacerations of the face (gender and age not provided)	<ul style="list-style-type: none"> <li>• TAC (24)</li> <li>• Adrenaline and cocaine (31)</li> </ul>	Complications related to topical anesthetic or wound healing; sutures placed eliciting pain	"The tetracaine component of TAC is superfluous for obtaining topical anesthesia of minor dermal lacerations of the face in children. The TAC formulation can be simplified by omitting tetracaine without compromising anesthetic efficacy."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Bonadio and Wagner, 1988, US <sup>61</sup>	Prospective evaluation	75 Patients with minor laceration of the skin who received TAC for wound repair (Male to female ratio 1.6:1, range 11 month-17 y)	<ul style="list-style-type: none"> <li>• TAC (75)</li> </ul>	Sutures placed eliciting pain, complications related to topical anesthetic or wound healing	"We conclude that TAC that contains 5.9% cocaine, 0.25% tetracaine and 1:4000 epinephrine provides excellent anesthesia for dermal lacerations of the face, lip and scalp that require minor surgical repair. Use of this diluted preparation will help diminish the risk of potential systemic toxicity from absorbed component medications of TAC without compromising anesthetic efficacy."
Breen <i>et al.</i> , 1993, US <sup>45</sup>	Prospective, randomized, double-blind	<p>130 Patients having a single term fetus in vertex presentation, requesting epidural analgesia, ASA class I or II in labor</p> <p>Fentanyl only (0%, mean 30.3 y ± 5.2)</p> <p>Bupivacaine, epinephrine, and fentanyl (0%, mean 30.8 y ± 4.9)</p>	<ul style="list-style-type: none"> <li>• Fentanyl only (53)</li> <li>• Bupivacaine, epinephrine, and fentanyl (77)</li> </ul>	Pain score (VAS), pruritus score, motor block evaluation (modified Bromage score), duration of analgesia, patient's ability to ambulate, mode of delivery, fetal heart rate	"In summary, many patients receiving epidural analgesia for relief of the pain of labor obtain satisfactory analgesia with fentanyl alone or a low-dose mixture of bupivacaine, fentanyl, and epinephrine."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Breivik and Niemi, 2001, Japan <sup>46</sup>	Patients randomly divided into 2 groups	77 ASA Class I or II patients scheduled for elective abdominal surgery under anesthesia with or without general anesthesia Adrenaline (40%, mean 62 y ± 12) No adrenaline (40%, mean 55 y ± 17)	<ul style="list-style-type: none"> <li>Adrenaline, bupivacaine, fentanyl (40)</li> <li>Bupivacaine and fentanyl (37)</li> </ul>	Post-operative pain (VAS), number of rescue analgesics, side effects, muscle weakness, hypotension	"In conclusion, the results of the present study demonstrate that the addition of adrenaline to a combination of fentanyl and bupivacaine improves the quality of epidural analgesia after abdominal surgery. Under the conditions of the study, we did not detect any disadvantage from the addition of adrenaline."
Bucci <i>et al.</i> , 2017, US <sup>147</sup>	Retrospective chart review	1919 Patients who under routine cataract surgery* Control group (47.1%, mean 68.34 y ± 10.4) Treatment group (42.3%, mean 68.23 y ± 9.9)	<ul style="list-style-type: none"> <li>Control group* (1004)</li> <li>Treatment group: Phenylephrine and ketorolac (915)</li> </ul> <p>*Epinephrine was selectively administered to patients (64) in the control group with intraoperative floppy ire syndrome or poorly dilating pupils</p>	Number of times a Malyugin Ring (pupil expansion device) was used, how often a femtosecond laser was used	"The frequency of use of the Malyugin Ring was significantly reduced (P<0.001) from 7.87% to 2.95% with the phenylephrine and ketorolac 1%/0.3% treatment. These results strongly suggest that the antimiotic/anti-inflammatory effects of this phenyl/keto injection reduced facility costs, surgical time, and other complexities related to the use of the Malyugin Ring during phacoemulsification."
Burkhard <i>et al.</i> , 2012, Switzerland <sup>148</sup>	Open, observational study	28 Patients with no lower urinary tract symptoms who underwent open renal surgery and received thoracic epidural anesthesia (0%, age not provided)	<ul style="list-style-type: none"> <li>Bupivacaine (8)</li> <li>Bupivacaine and fentanyl (7)</li> <li>Bupivacaine, fentanyl, epinephrine (13)</li> </ul>	Urethral pressure measurements	"[Thoracic epidural analgesia] appears to decrease urethral closing pressure in women. The addition of fentanyl may reduce this effect."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Camras <i>et al.</i> , 1985, US <sup>113</sup>	Prospective, randomized, double-masked study	13 Patients with established diagnosis of early, chronic open-angle glaucoma or ocular hypertension (54%, mean 52 y ± standard error of mean of 4)	<ul style="list-style-type: none"> <li>• Indomethacin group (6)</li> <li>• Placebo group (7)</li> </ul> <p>All patients received epinephrine HCl with indomethacin or placebo</p>	IOP, tonography	"The blockade of the epinephrine-induced reduction of intraocular pressure by indomethacin shown in this study suggests that prostaglandins or other cyclo-oxygenase products are mediating the hypotensive effect. This, in turn, would suggest that topical epinephrine treatment for glaucoma patients taking systemic prostaglandin synthesis inhibitors...would be less effective in reducing intraocular pressure."
Celleno and Capogna, 1988, Italy <sup>149</sup>	Double-blind study	<p>95 Patients in labor with a single fetus in vertex position and uncomplicated pregnancy</p> <p>Group A (0%, mean 26.4 y ± 2.4)</p> <p>Group B (0%, mean 25.1 y ± 2.7)</p> <p>Group C (0%, mean 24 y ± 3.5)</p>	<ul style="list-style-type: none"> <li>• Group A: Bupivacaine and epinephrine (35)</li> <li>• Group B: Bupivacaine, epinephrine, and fentanyl 50 mcg (30)</li> <li>• Group C: Bupivacaine, epinephrine, and fentanyl 100 mcg (30)</li> </ul>	Pain score (VAS), quality of anesthesia (excellent, good, incomplete, failure, not possible to evaluate, motor block evaluation (Bromage criteria), duration of analgesia, peak effect, neonatal outcome	"Only the addition of 100 microgram of fentanyl significantly improved the quality of analgesia (43.3 per cent of excellent scores vs 6.6 per cent in Group B and 5.7 per cent in Group A). Addition of fentanyl did not affect the duration of labour, the method of delivery and the neonatal neurobehaviour scores."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Chale <i>et al.</i> , 2006, US <sup>130</sup>	Single-center, prospective randomized controlled trial	55 Patients with simple, short traumatic lacerations on one of the fingers (71%, mean 38.1 y ± 16.8)	<p>All patients received topical LET then randomized to either group:</p> <ul style="list-style-type: none"> <li>• Digital block (28)</li> <li>• Local infiltration (27)</li> </ul>	Pain of needle insertion, anesthetic injection and suturing (VAS)	"This study demonstrated that the pain of needle insertion, anesthetic infiltration, and suturing are similar after digital or local anesthesia preceded by topical application of LET."
Cohen <i>et al.</i> , 1992, US <sup>150</sup>	–	78 Patients at full-term pregnancy who were scheduled for elective C-section under epidural anesthesia (0%, age not provided)	<p>All patients received chloroprocaine with epinephrine followed by bupivacaine with epinephrine before being randomly allocated to one of these groups:</p> <ul style="list-style-type: none"> <li>• Group 1: Buprenorphine, bupivacaine, epinephrine (26)</li> <li>• Group 2: Fentanyl, bupivacaine, epinephrine (26)</li> <li>• Group 3: Fentanyl and bupivacaine (26)</li> </ul>	Pain intensity (VAS), overall satisfaction with infusion, plasma levels of fentanyl and buprenorphine	"Epidural patient-controlled analgesia in all three groups provided excellent analgesia, permitted ambulation, and was without serious side effects. Epidural buprenorphine offered no advantages over epidural fentanyl."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Cohen <i>et al.</i> , 1998, US <sup>47</sup>	–	<p>100 Full-term patients scheduled to undergo elective C-section</p> <p>Group fentanyl (0%, mean 28.8 y ± 5.2)</p> <p>Group fentanyl and bupivacaine (0%, mean 29.6 y ± 4.5)</p> <p>Group fentanyl and epinephrine (0%, mean 30.4 y ± 4.3)</p> <p>Group fentanyl, bupivacaine, and epinephrine (0%, mean 30.2 y ± 3.8)</p>	<p>Before surgery, patients received lidocaine 2.5% with epinephrine 5 mcg/mL followed by lidocaine 2% and epinephrine 5 mcg/mL via a lumbar catheter and then randomly allocated to one of the groups:</p> <ul style="list-style-type: none"> <li>• Group fentanyl (25)</li> <li>• Group fentanyl and bupivacaine (25)</li> <li>• Group fentanyl and epinephrine (25)</li> <li>• Group fentanyl, bupivacaine, and epinephrine (25)</li> </ul>	<p>Quality of analgesia (VAS), side effects, complication, motor block (modified Bromage score), overall satisfaction with treatment, breast-fed neonates assessed using the Neurologic and Adaptive Capacity Score</p>	<p>"The addition of epinephrine and bupivacaine to a 3 mcg/mL epidural fentanyl solution for post C-section pain relief provided superior analgesia compared with fentanyl alone or fentanyl with epinephrine. Whether increasing the concentration of fentanyl alone might improve the efficacy of fentanyl remains unclear."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Cohen <i>et al.</i> , 2002, US <sup>131</sup>	Randomized, double-blinded design	100 Patients scheduled to undergo elective cesarean delivery under epidural anesthesia (0%, age not provided)	<p>Before surgery, patients received lidocaine 2%, fentanyl mcg/mL, and epinephrine 5 mcg/mL via a lumbar catheter and then randomly allocated to one of the groups:</p> <ul style="list-style-type: none"> <li>• Group I: Epidural bupivacaine, epinephrine, and fentanyl (25)</li> <li>• Group II: Epidural bupivacaine and epinephrine, IV fentanyl (25)</li> <li>• Group III: Epidural saline, IV fentanyl (25)</li> <li>• Group IV: Epidural saline and fentanyl (25)</li> </ul>	Quality of analgesia (VAS), side effects, complications, motor block (modified Bromage score), overall satisfaction with treatment assessed at discontinuation	“In conclusion, our data support the growing body of evidence that epidural fentanyl analgesia occurs primarily by a spinal mechanism and our data further show that the enhancement of fentanyl’s efficacy by very small dose epidural bupivacaine and epinephrine requires an interaction of these drugs at the spinal level.”
Corbett and Richards, 1994, England <sup>88</sup>	Prospective, double-blind controlled trial	70 Patients who underwent routine extracapsular cataract extraction (47%, mean 75 y)	<p>Intraocular irrigation with:</p> <ul style="list-style-type: none"> <li>• Adrenaline (27)</li> <li>• No adrenaline (43)</li> </ul>	Mean pupil diameter	"Intraocular irrigation with adrenaline 1:1 000 000 is a safe and effective means of maintaining mydriasis during cataract surgery."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Cutbush <i>et al.</i> , 1998, US <sup>151</sup>	Retrospective study	213 Patients who had single pregnancies with uncomplicated deliveries at a military hospital Combined spinal epidural (CSE) (0%, 24.6 y) Group epidural (0%, 26 y) Group intrathecal (0%, 24.8 y) Group no regional anesthesia (0%, 24.9 y)	<ul style="list-style-type: none"> <li>• Group CSE (76)</li> <li>• Group epidural (41)</li> <li>• Group intrathecal (49)</li> <li>• Group no regional anesthesia (47)</li> </ul>	Length of each stage of labor	"These results imply that the use of intrathecal opioids in the obstetrical patient does not prolong labor and seems to shorten the first stage of labor in both primipara and multipara patients."
Dong <i>et al.</i> , 2014, US <sup>84</sup>	Case report	1 Patient with idiopathic pulmonary fibrosis, single lung transplant and prior pulmonary embolism who underwent bronchoscopy (0%, 63 y)	<ul style="list-style-type: none"> <li>• Topical epinephrine</li> </ul>	Cessation of bleeding	Bleeding stopped after administration of topical epinephrine.
Donnenfeld and Shojaei, 2019, US <sup>108</sup>	Prospective, single-masked comparative study	60 Patients who underwent femtosecond laser-assisted cataract surgery or conventional phacoemulsification under topical anesthesia Phenylephrine and ketorolac (46%, mean 72.1 y ± 8.8) Epinephrine (42%, mean 73.5 y ± 7.2)	<ul style="list-style-type: none"> <li>• Phenylephrine and ketorolac (41)</li> <li>• Epinephrine (19)</li> </ul>	Pain experienced during surgery (VAS), use of IV fentanyl during surgery,	"We found that the intraoperative delivery of phenylephrine and ketorolac 1.0%/0.3% resulted in a nearly 80% reduction in the need for intraoperative opioid analgesics during cataract surgery while decreasing mean VAS pain scores by approximately 50%, significantly reducing the risk of moderate-to-severe pain."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Drance <i>et al.</i> , 1991, Canada <sup>96</sup>	Randomized	50 Patients with glaucoma suspects with IOP > 22 mmHg (gender and age not provided)	<ul style="list-style-type: none"> <li>• Epinephrine (9)</li> <li>• Timolol and epinephrine (7)</li> <li>• Timolol (13)</li> <li>• Pindolol (8)</li> <li>• Placebo (13)</li> </ul>	IOP	"All agents reduced the pressure significantly but with varying time courses. The mixture of timolol and epinephrine reduced the pressure significantly more than did timolol or epinephrine alone, especially at 12 h after the last administration of the drops."
Drance <i>et al.</i> , 1978, Canada <sup>114</sup>	–	50 Patients total, with 32 patients who have elevated IOP and 18 patients with untreated chronic open-angle glaucoma (gender and age not provided)	<ul style="list-style-type: none"> <li>• Epinephrine HCl (50)</li> </ul>	IOP	There is a lack of difference in the prevalence of responders between the two patient groups. "The present study suggests that the findings may not apply to the general group of people with elevated pressures, and it is far too early to rely on the response to epinephrine as a prognostic indicator or as a practical guide to the need for therapy in ocular hypertensive patients until further scientific information is available."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Dube <i>et al.</i> , 1990, Canada <sup>152</sup>	Randomized, double-masked trial	<p>46 Patients who underwent extracapsular lens extraction with posterior chamber intraocular lens implantation</p> <p>Control group: Artificial tears (27%, range 39-80 y)</p> <p>Indomethacin (47%, range 46-86 y)</p> <p>Prednisolone (37%, range 22-80 y)</p>	<ul style="list-style-type: none"> <li>• Control group (15)</li> <li>• Indomethacin (15)</li> <li>• Prednisolone (16)</li> </ul> <p>All patients received intra-op solution with epinephrine</p>	Pupillary diameter	<p>"During surgery the indomethacin group lost significantly less mydriasis than the control group. The mydriasis losses of the prednisolone acetate group were between those of the indomethacin and control groups, but these differences did not reach significance. We conclude that prednisolone acetate is less effective than indomethacin for maintaining mydriasis during cataract surgery."</p>
Elliott and Carter, 1989, England <sup>109</sup>	Prospective, randomized study	42 Patients admitted for extracapsular cataract extraction and lens implantation under local anesthetic (gender and age not provided)	<ul style="list-style-type: none"> <li>• Epinephrine (10)</li> <li>• Acetylcholine (11)</li> <li>• Epinephrine and acetylcholine (9)</li> <li>• Control (9)</li> </ul>	Vertical and horizontal pupil size, "lens show" (amount by which the pupil was wider than the implant, overall measurements)	<p>"Epinephrine reduced peroperative pupil constriction, but its effect was insignificant thereafter. The pupil constriction following acetylcholine was maximal at 2 hours and was still significant at 4 hours, but pupils redilated by 6 hours. Neither drug had any effect after this time. The edge of most lens implants was visible at 6 hours, after which most pupils steadily constricted."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Ellis <i>et al.</i> , 2013, US <sup>104</sup>	Randomized, controlled study	15 Patients with cutaneous abscess (gender and age not provided)	<ul style="list-style-type: none"> <li>• LET (8)</li> <li>• Lidocaine (7)</li> </ul>	Pain during procedure and patient satisfaction	"At the time of our interim analysis there is no statistically significant difference in overall patient satisfaction or difference in perceived pain when comparing local infiltration of lidocaine anesthetic to topical administration of anesthetic. However, at this time our study is underpowered to conclude that LET gel is noninferior to [local anesthetic]. At this time we believe no sweeping conclusions can be made about the optimal management of pain control for abscess."
Ernst <i>et al.</i> , 1990, US <sup>62</sup>	Randomized, double-blind study	139 Patients who had lacerations of <5 cm in length TAC (62%, age not provided) Cocaine (64%, age not provided)	<ul style="list-style-type: none"> <li>• TAC (69)</li> <li>• Cocaine (70)</li> </ul>	Effectiveness	"This study shows that TAC works better than cocaine alone as an anesthetic for the repair of small lacerations...We believe that when properly used, TAC provides adequate anesthesia for the repair of small lacerations without serious increase in the risk of complications."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Ernst <i>et al.</i> , 1995, US <sup>63</sup>	Randomized, double-blinded clinical trial	95 Patients with lacerations on the face or scalp of <7 cm with no mucosal involvement LAT (79%, range 5-16 y) TAC (72%, range 5-17 y)	<ul style="list-style-type: none"> <li>• LAT (48)</li> <li>• TAC (47)</li> </ul>	Effectiveness, number of sutures causing pain	"LAT gel worked as well as TAC gel for topical anesthesia in facial and scalp lacerations. Considering the advantages of a noncontrolled substance and less expense, LAT gel appears to be better suited than TAC gel for topical anesthesia in laceration repair in children."
Ernst <i>et al.</i> , 1997, US <sup>64</sup>	Randomized prospective comparison trial	66 Patients with simple linear lacerations 1.5-10 cm long LAT (15%, mean 29 y) Lidocaine and epinephrine (39%, mean 30 y)	<ul style="list-style-type: none"> <li>• LAT (33)</li> <li>• Lidocaine and epinephrine (33)</li> </ul>	Pain of injection or application, pain of suturing (VAS)	"In conclusion, LAT gel compared favorably with injectable buffered lidocaine for local anesthesia effectiveness and was significantly less painful to apply. It may be the preferred local anesthetic for this reason."
Ernst <i>et al.</i> , 1995, US <sup>65</sup>	Prospective randomized double-blind study	100 Patients with face or scalp lacerations <7 cm with no mucosal involvement LAT (82%, mean 33 y ± 11) TAC (72%, mean 34 y ± 13)	<ul style="list-style-type: none"> <li>• LAT (50)</li> <li>• TAC (50)</li> </ul>	Physician and patient rated effectiveness of anesthesia during wound closure (VAS), patient reported number of sutures causing pain	"In conclusion, LAT worked at least as effectively as TAC for topical anesthesia in facial and scalp lacerations. Considering the advantages of a noncontrolled substance and less expense, LAT seems to be better suited than TAC for topical anesthesia in laceration repair."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Fitzmaurice <i>et al.</i> , 1990, US <sup>105</sup>	–	46 Patients with laceration < 3 cm in length that did not involve the digits, nose, ears, penis, toes, or mucous membranes (gender not provided, range 1-14 y)	<ul style="list-style-type: none"> <li>• TAC (46)</li> </ul>	Signs of toxicity (hypertension, hypotension, tachycardia, tachypnea, bradypnea, mental status change), quantitative analysis of cocaine and two metabolites in plasma 20-40 min after administration of TAC	"This study demonstrates that the use of TAC in providing anesthesia for the repair of lacerations can lead to absorption of cocaine metabolites without clinical signs of toxicity. Further studies of absorption in larger lacerations, at different times, and of the presence of norcocaine must be undertaken."
Gala <i>et al.</i> , 2013, US <sup>132</sup>	Case report	1 Patient with eyelid laceration (100%, 14 months)	<ul style="list-style-type: none"> <li>• LET</li> </ul>	Ability to suture eyelid laceration	"Our experience highlights the need for considering pharmacologic pupil in the assessment of a patient with unilateral mydriasis in the appropriate clinical context. Mydriasis should be recognized as a potential adverse reaction of LET gel when used near the eye."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Gambling <i>et al.</i> , 1993, Canada <sup>48</sup>	Double-blind, prospective study	<p>68 Patients with uncomplicated, single pregnancies in established labor and requested epidural analgesia</p> <p>Group A (0%, mean 29.5 y ± 4.89)</p> <p>Group B (0%, mean 28.3 y ± 4.32)</p> <p>Group C (0%, mean 29.7 y ± 4.8)</p> <p>Group D: (0%, mean 28.8 y ± 5.84)</p> <p>Group E: (0%, mean 28.1 y ± 3.66)</p>	<p>All received the analgesic mixture of bupivacaine, epinephrine, and fentanyl through the pump. Each group was administered the mixture at a different rate and lockout:</p> <ul style="list-style-type: none"> <li>• Group A: 2 mL bolus/10 min lockout (14)</li> <li>• Group B: 3 mL bolus/15 min lockout (14)</li> <li>• Group C: 4 mL bolus/20 min lockout (13)</li> <li>• Group D: 6 mL bolus/30 min lockout (14)</li> <li>• Group E: 8 mL/hr continuous infusion (13)</li> </ul>	<p>Pain score (VAS), satisfaction, maximum pain/minimum satisfaction in the preceding hour, sensory levels (using ice), motor block, maternal blood pressure, fetal heart rate</p>	<p>"In summary, there were no differences seen among the four dosing programmes chosen for PCEA [patient-controlled epidural analgesia] in labour...Bolus-only PCEA using bupivacaine 0.125% with 1:400,000 epinephrine and fentanyl 2.5 microgram/ml is a safe and effective technique regardless of which initial dose and lockout interval is programmed."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Gimbel, 1989, Canada <sup>89</sup>	Randomized, placebo-controlled clinical trial	216 Patients who underwent cataract intraocular lens surgery (gender and age not provided)	<ul style="list-style-type: none"> <li>• Ocufen® alone (36)</li> <li>• Ocufen® and epinephrine (36)</li> <li>• Indocid® alone (36)</li> <li>• Indocid® and epinephrine (36)</li> <li>• Placebo: Tears naturale alone (36)</li> <li>• Tears naturale and epinephrine (36)</li> </ul>	Pupil diameter	"In this study, the use of intraoperative epinephrine was by far the most effective factor in reducing progressive miosis, regardless of whether antiprostaglandins were used. Since all the patients in this study received topical alpha-adrenergic agent preoperatively, the results suggest that either the epinephrine continues to directly affect the adrenergic receptors while the effect of the preoperative drugs dissipate, or the epinephrine effects work by another mediator."
Goldberg <i>et al.</i> , 1980, US <sup>115</sup>	Prospective, crossover clinical study	20 Patients with IOP >21 mmHG in both eyes with a difference of <4 mmHG between the two eyes (50%, range 45-74 y)	<p>2 study phases (all patients participated in both phases)</p> <p>Phase A</p> <ul style="list-style-type: none"> <li>• Timolol in both eyes and then epinephrine HCl in one eye at random</li> </ul> <p>Phase B</p> <ul style="list-style-type: none"> <li>• Epinephrine HCl in both eyes and then timolol in one eye at random</li> </ul>	IOP, pupillary diameter, pulse, and blood pressure	"Our study shows that at least in short-term trials, timolol significantly diminishes the IOP reduction produced by epinephrine. The therapeutic value of maintaining epinephrine therapy if timolol is initiated, or of initiating epinephrine if timolol is maintained, remains to be clarified by long-term coadministration trials."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Grice <i>et al.</i> , 1990, US <sup>133</sup>	–	100 Patients in labor Bupivacaine and fentanyl (0%, mean 23 y ± 0.9) Bupivacaine, fentanyl, epinephrine (0%, mean 24 y ± 1.1) Note there were 2 parts to this study but just part 1 is reported here since part 2 looked at the effect of 2-chloroprocaine.	<ul style="list-style-type: none"> <li>• Bupivacaine and fentanyl (50)</li> <li>• Bupivacaine, fentanyl, epinephrine (50)</li> </ul>	Patient-assessed adequacy of pain relief, sensory analgesia to pin testing	"Epinephrine prolonged the median duration of pain relief (180 vs. 138 min, P<0.05) without affecting duration of first or second stages of labor, or neonatal Apgar scores."
Gulle <i>et al.</i> , 2011, Sweden <sup>153</sup>	Prospective, randomized trial	150 Patients treated for posterior instrumented lumbar spine fusion Bupivacaine, epinephrine, fentanyl (43%, mean 51.6 y ± 10.2) Ropivacaine and oral oxycodone (41%, mean 50.2 y ± 10.6)	<ul style="list-style-type: none"> <li>• Bupivacaine, epinephrine, fentanyl (76)</li> <li>• Ropivacaine and oral oxycodone (74)</li> </ul>	Pruritus (measured on scale of 0-3), motor block (Bromage), pain (VAS)	"Pruritus could be reduced with a combination of epidural ropivacaine and oral oxycodone, at the price of a slightly higher pain level. Ropivacaine was not found to be superior to bupivacaine with regard to motor blocks."
Haidl <i>et al.</i> , 2018, Norway <sup>134</sup>	Randomized, parallel group, double-blinded	41 Patients in active labor and requested epidural anesthesia Control group using bupivacaine and fentanyl (0%, mean 29 y ± 4) Adrenaline, bupivacaine, and fentanyl group (0%, mean 28 y ± 5)	<ul style="list-style-type: none"> <li>• Control (20)</li> <li>• Adrenaline, bupivacaine, and fentanyl (19)</li> </ul>	Pain during contraction (scale of 0-10), motor block (modified Bromage score), maternal blood pressure and heart rate and fetal heart rate, serum fentanyl concentration	"The addition of adrenaline to an epidural solution containing fentanyl lowered maternal systemic serum fentanyl concentration during the first 2 hours, but did not lower serum fentanyl concentration in the umbilical vein and mother at delivery."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Harman <i>et al.</i> , 2013, Canada <sup>66</sup>	Randomized, placebo-controlled, blinded trial	203 Patients with laceration < 3 cm in length on face, torso, trunk, or extremities considered appropriate for tissue adhesive repair Placebo (57%, mean 4.21 y ± 3.62) LET (62%, mean 5.07 y ± 3.04)	<ul style="list-style-type: none"> <li>• Placebo (98)</li> <li>• LET (105)</li> </ul>	Pain reported during application of tissue adhesive (VAS), physician rating of difficulty of repair, wound hemostasis	"Pretreatment of minor lacerations with lidocaine–epinephrine–tetracaine before tissue repair with adhesive decreased patient discomfort and increased the proportion of pain-free repairs."
Harris <i>et al.</i> , 1970, US <sup>97</sup>	–	25 Patients with open-angle glaucoma (gender and age not provided)	<ul style="list-style-type: none"> <li>• Epinephrine (25)</li> </ul> <p>Epinephrine used on the right eye, unmedicated left eye served as the control for each patient</p>	IOP	"The data obtained in this study suggest that 1-epinephrine may be an effective ocular hypotensive drug for the therapy of open angle glaucoma in concentrations as low as 0.06%."
Hegenbarth <i>et al.</i> , 1990, US <sup>67</sup>	Prospective, randomized, unblinded study	467 Patients with dermal lacerations (66%, mean 6.3 y ± 4.2)	<ul style="list-style-type: none"> <li>• TAC (262)</li> <li>• Lidocaine (205)</li> </ul>	Response to needle, physician-rated efficacy of anesthetic, parent satisfaction with anesthesia, wound dehiscence or associated problems	"The use of TAC promotes a more pleasant experience for the child who requires suturing of a superficial laceration. TAC is safe and effective on facial and scalp lacerations when carefully used, with no significant increase in wound complications. It is less useful for anesthetizing extremity wounds."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Hennes <i>et al.</i> , 1990, US <sup>154</sup>	Double-blind randomized clinical trial	<p>55 Patients with dermal laceration with an initial anxiety level of 3 or 4</p> <p>Placebo (64%, mean 28 months <math>\pm</math> 16)</p> <p>Midazolam (60%, mean 31 months <math>\pm</math> 15)</p>	<ul style="list-style-type: none"> <li>• Placebo (25)</li> <li>• Midazolam (30)</li> </ul> <p>Patients were given TAC (37) or lidocaine (18) as the anesthetic</p>	Anxiety level	<p>“We conclude that a single oral dose of midazolam (0.2 mg/kg) is a safe and effective treatment for alleviating anxiety in children less than 6 years old during laceration repair in the [emergency department].”</p>
Hepner <i>et al.</i> , 2000, US <sup>49</sup>	Prospective, randomized, double-blind	50 Patients who requested labor analgesia (gender and age not provided)	<ul style="list-style-type: none"> <li>• CSE group: Bupivacaine and fentanyl (26)</li> <li>• Epidural group: Bupivacaine, fentanyl, and epinephrine (24)</li> </ul> <p>Note: If patients requested additional analgesia, both groups received bupivacaine, fentanyl, sodium bicarbonate, and epinephrine as well as an infusion of bupivacaine, fentanyl, and epinephrine. It is unclear how many patients received additional analgesia and thus not included in the count here.</p>	Pain (VAS), parturient satisfaction, maternal Bromage score, need for supplemental analgesia and/or treatment of pruritus, hypotension, nausea, vomiting or fetal heart rate changes	<p>“Although epidural analgesia with a low concentration of local anesthetic and opioid mixture takes longer to produce complete analgesia, it is a satisfactory alternative to [combined spinal-epidural].”</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Hess <i>et al.</i> , 2006, US <sup>135</sup>	Retrospective observational study	4493 Patients in labor who received epidural analgesia Low (0%, 30.2 y ± 5.6) Medium (0%, 29.7 y ± 5.6) High (0%, 29.8 y ± 5.6)	<ul style="list-style-type: none"> <li>• Low: Bupivacaine 0.04%, fentanyl 1.67 mcg/mL, epinephrine 1.7 mcg/mL (2507)</li> <li>• Medium: Bupivacaine 0.0635% with fentanyl 2 mcg/mL (1285)</li> <li>• High: Bupivacaine 0.125% with fentanyl 2 mcg/mL (701)</li> </ul>	Total interventions requiring an anesthesia care provider, analgesic interventions (any supplemental medications given via epidural catheter or increases in rate of infusion), side effect interventions	"In conclusion, the groups in our study had a similar total number of interventions despite receiving different concentrations of bupivacaine for labor epidural analgesia. The types of intervention differed, however, with women receiving the lower concentration of bupivacaine requiring more interventions for breakthrough pain, while those who received the higher concentration having more side effects."
Kass and Becker, 1978, US <sup>116</sup>	—	76 Patients total, 43 with ocular hypertension and 33 who were ocular normotensive patients (gender and age not provided)	<ul style="list-style-type: none"> <li>• Epinephrine HCl in one eye (76)</li> </ul>	Change in IOP	"The present study demonstrates a significant correlation between the results of epinephrine testing... The authors wish to emphasize that proof of the prognostic value of epinephrine responsiveness will require prospective studies on less select populations."
Kass <i>et al.</i> , 1979, US <sup>126</sup>	Randomized, double-masked study	42 Patients total, 20 with primary open-angle glaucoma and 22 with ocular hypertension (55%, range 27-79 y)	<ul style="list-style-type: none"> <li>• Dipivefrin drops and epinephrine HCl (42)</li> </ul>	Change in IOP, pupil diameter, side effects	"Dipivefrin appears to be an effective and safe alternative to epinephrine therapy for the reduction of elevated IOP."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Katz and Markowitz, 2013, US <sup>99</sup>	–	40 Patients with uncomplicated cataract extraction (gender and age not provided)	<ul style="list-style-type: none"> <li>• Intracameral epinephrine (8)</li> <li>• No epinephrine (32)</li> </ul>	Cumulative dissipated energy, total phacoemulsification time, and one day and one-week post-op visual acuity	"Intracameral epinephrine can be used in difficult cases involving iris instability to produce similar visual outcomes and [total phacoemulsification time] as routine cases. Although a higher [cumulative dissipated energy] was required in the epinephrine group, one day and one week [visual acuity] were not significantly changed. "
Keates, 1979, US <sup>155</sup>	–	<p>45 Patients with chronic open-angle glaucoma</p> <p>Group 1 (36%, range 51-80 y)</p> <p>Group 2 (58%, range 21-70 y)</p> <p>Group 3 (45%, range 41-80 y)</p> <p>Group 4 (55%, range 21-90 y)</p> <p>Note that the age of the patients studied were given in interval ranges in a table, for each group presented here the lower number in the interval was considered for the lower range number and for the higher range number, the higher number in the interval was considered.</p>	<ul style="list-style-type: none"> <li>• Group 1: Pilocarpine 2% (11)</li> <li>• Group 2: Epinephrine 2% (12)</li> <li>• Group 3: Carbachol 1.5% (11)</li> <li>• Group 4: Acetazolamide 250 mg (12)</li> </ul>	IOP, visual acuity, pupil size, vital signs	"Timolol maleate appears to be effective and well tolerated when administered with other antiglaucoma medications in patients with open-angle glaucoma."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Kjohede <i>et al.</i> , 2019, Sweden <sup>136,168</sup>	Open-label, randomized, controlled, single-center study	80 Patients with proven or assumed gynecological abdominal malignancy Epidural analgesia (0%, median 59 y, interquartile range 51.5-66) Intrathecal morphine (0%, median 58.5 y, interquartile range 54-62.5)	<ul style="list-style-type: none"> <li>Epidural analgesia* (40)</li> <li>Intrathecal morphine (40)</li> </ul> *Includes bupivacaine, adrenalin, and fentanyl	Pain rating at rest and mobilization, length of hospital stay, quality of life assessment	"Compared with [epidural analgesia], [intrathecal morphine] is simpler to administer and manage, is associated with shorter hospital stay and reduces opioid consumption postoperatively with an equally good [quality of life]. [Intrathecal morphine] is effective as postoperative analgesia in gynaecological cancer surgery."
Konigs <i>et al.</i> , 2019, Germany <sup>68</sup>	Prospective, propensity score-matched multicenter study	59 Patients with dermal lacerations that need suturing LET (65%, mean 8.78 y ± 3.13) EMLA (73%, mean 9.57 y ± 4.22)	<ul style="list-style-type: none"> <li>LET (37)</li> <li>EMLA (22)</li> </ul>	Self-reported pain before and during surgical repair, pain assessment at time of anesthetic application and skin closure, wound infection, overall satisfaction	"In conclusion, it appears that LET is superior to conventional anesthesia including Mepivacaine injection in the pediatric ED. Pretreatment with LET is significantly less painful but equally effective. Hence, we recommend LET as a topical anesthetic in the pediatric ED."
Korey <i>et al.</i> , 1982, US <sup>137</sup>	Clinical trial	32 Patients with ocular hypertension (59%, range 46-79 y)	<ul style="list-style-type: none"> <li>Group 1: Epinephrine HCl in 1 eye, epinephrine HCl and timolol in 1 eye (18)</li> <li>Group 2: Timolol in 1 eye, epinephrine HCl and timolol in 1 eye (14)</li> </ul>	Change in IOP	"Results suggest that the majority of patients being treated with either drug are unlikely to have a substantial long-term reduction in IOP when the other drug is added to their therapeutic regimen."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Korkmaz <i>et al.</i> , 2015, US <sup>100,166</sup>	Retrospective review	1140 Patients who underwent endoscopic endonasal procedure (52.5%, mean 45.8 y ± 16.6)	<ul style="list-style-type: none"> <li>• Topical concentrated (1:1000) epinephrine (1140)</li> </ul>	Surgical time, estimate blood loss, hemodynamic parameters, complications	“The use of topical [concentrated epinephrine] is safe when performing endoscopic endonasal procedures. [Concentrated epinephrine] was not associated with any intraoperative complications. The profound intra-operative vasoconstriction does not confer a higher rate of postoperative rebound epistaxis.”
Kronfeld, 1971, US <sup>138</sup>	—	35 Patients with ocular hypertension or primary open-angle glaucoma (gender and age not provided)	<ul style="list-style-type: none"> <li>• L-epinephrine (35)</li> <li>• Pilocarpine and echothiophate (11)</li> </ul> <p>11 patients who received epinephrine also received pilocarpine and echothiophate</p>	IOP	"Several phases of the effect of the drug [epinephrine] could be recognized, with increases in outflow facility emerging as the dominant response of the type eye under study. During the first three weeks of treatment the magnitude of the facility response was close to that of echothiophate, with suppression of aqueous production making a recognizable contribution to the lowering of intraocular pressure in only one-third of the eyes participating in the study."

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Kuhn <i>et al.</i> , 1996, Australia <sup>69</sup>	Double-blind, randomized, prospective trial	180 Patients with simple dermal lacerations < 5 mm deep (gender and age not provided)	<ul style="list-style-type: none"> <li>• TAC (88)</li> <li>• Bupivacaine, adrenaline, cocaine (92)</li> </ul>	Adequacy of anesthesia as determined by needle prick, patient perception of discomfort	"In conclusion, our results show that topical anesthesia with either TAC or [bupivacaine, adrenaline, and cocaine] is a safe and effective means of anesthetizing selected wounds for suturing...we have changed the vehicle for the anesthetic from a solution to a gel."
Landis <i>et al.</i> , 2017, US <sup>139</sup>	Prospective, randomized single-masked study	8 Patients who underwent bilateral, sequential phacoemulsification cataract surgery (gender and age not provided)	<ul style="list-style-type: none"> <li>• Intracameral epinephrine (8)</li> <li>• Omidria® (phenylephrine and ketorolac) (8)</li> </ul> <p>All patients received both interventions, one eye received epinephrine while the other eye received Omidria®</p>	Change from baseline in pupil diameter over time to end of symptoms	"Based on the data collected to date, there is no statistically significant difference between intracameral Omidria® and intracameral epinephrine with respect to maintenance of mydriasis during phacoemulsification cataract surgery."

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Lawrence and Sladden, 1953, UK <sup>140</sup>	—	<p>Patients at a clinic for the treatment of rheumatism in miners</p> <p>2 separate investigations made for a study of palliation and the other for recover times</p> <p>1<sup>st</sup> Investigation: 65 patients: Adrenaline (100%, average 46 y) Simple cream base for control (100%, average 50 y)</p> <p>2<sup>nd</sup> Investigation: 60 patients who received adrenaline cream compared with dry massages to no massage (gender and age not provided)</p>	<p>1<sup>st</sup> Investigation:</p> <ul style="list-style-type: none"> <li>• Adrenaline cream (32)</li> <li>• Control: simple cream (32)</li> </ul> <p>2<sup>nd</sup> Investigation*:</p> <ul style="list-style-type: none"> <li>• No massage</li> <li>• Dry massage</li> <li>• Massage with simple cream</li> <li>• Massage with adrenaline cream</li> </ul> <p>*Number of patients for each group in the 2<sup>nd</sup> investigation not provided.</p>	Degree and duration of relief	<p>"Adrenaline cream applied locally in a number of rheumatic diseases gives greater relief than a simple cream. Dry massage also gives greater relief than massage with simple cream or no massage at all. No significant difference was noted between the effects of dry massage and massage with adrenaline cream. Repeated application of adrenaline cream appears to delay recovery in rheumatic diseases."</p>
Lee <i>et al.</i> , 1972, US <sup>85</sup>	—	100 Patients who underwent tonsillectomy and adenoidectomy (gender not provided, range 2-15 y)	<ul style="list-style-type: none"> <li>• Topical epinephrine (50)</li> <li>• Topical saline as control (50)</li> </ul>	Blood pressure, electrocardiogram	<p>"Topical use of 1:1000 epinephrine in small amounts (not more than 2 ml. per sponge) to adenoidal and tonsillar fossae during halothane anesthesia is safe, provided that (1) the patient is intubated and slightly hyperventilated, and (2) the surgical procedure is relatively short, preferably within 30 minutes."</p>

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Lee <i>et al.</i> , 2013, Singapore <sup>106</sup>	Prospective, randomized clinical trial	40 Patients with clean and non-bite lacerations < 6 hours old LAT (74%, mean 36.8 y ± 25.7) Lidocaine (71%, mean 46.2 y ± 23)	<ul style="list-style-type: none"> <li>LAT (23)</li> <li>Lidocaine (17)</li> </ul>	Pain score during anesthetic administration and procedure, efficacy of anesthesia assessed by needle	"In conclusion, the use of LAT gel is beneficial in Asian adults and not confined to the pediatric age group, though further studies with a larger sample size are preferred."
Leighton <i>et al.</i> , 1999, US <sup>156</sup>	Randomized, single-blinded pilot study	36 Patients carrying a singleton fetus in vertex position who underwent labor induction Lumbar sympathetic block (0%, mean 32 y ± 5) Epidural (0%, mean 32 y ± 3)	Both groups given bupivacaine, fentanyl, epinephrine via one of the methods below: <ul style="list-style-type: none"> <li>Lumbar sympathetic block (17)</li> <li>Epidural (19)</li> </ul>	Rate of cervical dilation in the first 2 hours after block, patient-reported pain score before and after block, patient sensory level to ice, motor strength, patient satisfaction with analgesia	"We found that patients receiving [lumbar sympathetic block] analgesia had more rapid cervical dilation during the first 2 h after block placement, shorter duration of the second labor stage, and a trend toward a lower dystocia cesarean delivery rate than did patients receiving epidural analgesia."
Li <i>et al.</i> , 2019, US <sup>50</sup>	Prospective, randomized, double-blind study	120 Patients in active labor with single gestation vertex presentation Bupivacaine and fentanyl (0%, mean 31.7 y ± 4.7) Bupivacaine, fentanyl, and epinephrine (0%, mean 31.5 y ± 5)	<ul style="list-style-type: none"> <li>Bupivacaine and fentanyl (46)</li> <li>Bupivacaine, fentanyl, and epinephrine (54)</li> </ul>	Average hourly rate of breakthrough labor pain (requiring supplement meds), verbal pain score, sensory level, motor block	"A low dose of epinephrine may be a useful adjuvant to epidural solutions in patients that are known to be at increased risk for breakthrough pain without increasing other side effects."

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Li <i>et al.</i> , 2019, US <sup>51</sup>	Randomized, double-blind, prospective dose-response study	<p>160 Patients with a singleton pregnancy in vertex position with the desire for epidural pain control for labor</p> <p>Bupivacaine (0%, mean 31 y ± 5.4)</p> <p>Bupivacaine and fentanyl (0%, mean 30.9 y ± 5.1)</p> <p>Bupivacaine and epinephrine (0%, mean 30.3 y ± 4.1)</p> <p>Bupivacaine, fentanyl, and epinephrine (0%, mean 31.7 y ± 5.9)</p>	<ul style="list-style-type: none"> <li>• Bupivacaine (40)</li> <li>• Bupivacaine and fentanyl (40)</li> <li>• Bupivacaine and epinephrine (40)</li> <li>• Bupivacaine, fentanyl, and epinephrine (40)</li> </ul>	Pain (VAS), determination of minimum local analgesic concentration of bupivacaine via the up-down sequential allocation technical	“The addition of either fentanyl, epinephrine or both medications in an epidural solution can reduce the effective dose of bupivacaine for the initiation of labor pain relief. The addition of these adjuvants allows for a further reduction of the concentration of bupivacaine, thereby reducing side effects.”
Liou and Yang, 1998, Taiwan <sup>90</sup>	Prospective, randomized study	<p>42 Eyes* who underwent phacoemulsification cataract surgery (gender and age not provided)</p> <p>*Authors report 42 cases in the abstract and then say 42 eyes in the study. Unsure if one eye per patient.</p>	<ul style="list-style-type: none"> <li>• Intraocular irrigation fluid with adrenaline (30 eyes)</li> <li>• Intraocular irrigation fluid without adrenaline (12 eyes)</li> </ul>	Pupil size, pulse rate, blood pressure	"In conclusion, [irrigation/aspiration] fluid containing 1:1,000,000 adrenaline can maintain mydriasis during the phacoemulsification procedure without the risk of increasing pulse rate or blood pressure. It is a safe, effective and time-saving modification in cataract surgery."

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Lovstad <i>et al.</i> , 1997, Norway <sup>52</sup>	Prospective evaluation	67 Patients who underwent surgical correction of increased femur anteversion by derotational osteotomy (gender not provided, range 4-14 y)	<ul style="list-style-type: none"> <li>Epidural bupivacaine, fentanyl, and adrenaline (67)</li> </ul>	Pain (VAS), respiratory rate, motor block (Bromage score), total quality of epidural treatment according to nurses and parents	"Epidural treatment with very low doses of fentanyl, bupivacaine and adrenaline in combination with rectal paracetamol provided excellent analgesia for children undergoing major orthopedic surgery."
Lovstad and Stoen, 2001, Norway <sup>157</sup>	Randomized study	<p>42 Patients scheduled for femoral osteotomy</p> <p>Group A (gender not provided, range 4-11 y)</p> <p>Group B (gender not provided, range 3-11 y)</p> <p>Group C (gender not provided, range 4-11 y)</p>	<ul style="list-style-type: none"> <li>Group A: Sevoflurane anesthesia and epidural infusion of bupivacaine and adrenaline (14)</li> <li>Group B: Sevoflurane anesthesia and epidural infusion of bupivacaine, adrenaline, and fentanyl (16)</li> <li>Group C: Propofol-fentanyl anesthesia and epidural infusion with bupivacaine and adrenaline (12)</li> </ul>	Pain (VAS), use of rescue analgesia, number of episodes of postoperative nausea and vomiting (PONV), motor block (Bromage score), total quality of epidural treatment (pain versus side effects)	"A satisfactory postoperative analgesia can be achieved with both epidural mixtures used in the study...Both epidural treatments result in high and similar patient satisfaction and no serious complications. The study could not show any significant difference between the effect of sevoflurane and propofol anaesthesia on PONV."

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Lundberg and Behndig., 2007, Sweden <sup>110</sup>	Prospective, randomized, double-blind study	<p>140 Patients with age-related cataracts scheduled for unilateral phacoemulsification and intraocular lens implantation</p> <p>1<sup>st</sup> Part: 90 Patients</p> <ul style="list-style-type: none"> <li>• ICM with epinephrine (gender not specified, mean 75 y ± 9)</li> <li>• ICM without epinephrine (gender not specified, mean 76 y ± 9)</li> </ul> <p>2<sup>nd</sup> Part: 50 Patients</p> <ul style="list-style-type: none"> <li>• Topical mydriatics with epinephrine (gender not specified, mean 73 y ± 11)</li> <li>• Topical mydriatics without epinephrine (gender not specified, mean 78 y ± 7)</li> </ul>	<p>1<sup>st</sup> Part</p> <ul style="list-style-type: none"> <li>• ICM with epinephrine (45)</li> <li>• ICM without epinephrine (45)</li> </ul> <p>2<sup>nd</sup> Part</p> <ul style="list-style-type: none"> <li>• Topical mydriatics with epinephrine (25)</li> <li>• Topical mydriatics without epinephrine (25)</li> </ul>	Intraoperative pupil size	<p>"Finally, we conclude that ICMs, which represent a secure and efficient alternative to [topical mydriatics] in routine phacoemulsification surgery, may potentially simplify cataract surgery procedures as ICMs obviate the need for epinephrine in irrigating solution."</p>
Lyman and McCabe, 1984, US <sup>70</sup>	Prospective, random study	<p>31 Patients with lacerations &lt;6 cm in length (gender and age* not provided)</p> <p>*children under 12 years old, no other specifics provided</p>	<ul style="list-style-type: none"> <li>• Group A: Bleeding induced in the laceration; predetermined amount of TAC applied based on laceration size with a gauze held by nursing staff member (16)</li> <li>• Group B: No bleeding induced; the proper amount of TAC was applied with gauze by person accompanying patient (15)</li> </ul> <p>All patients received TAC</p>	Number of patients requiring additional anesthetic	<p>"The findings of this study suggest the following: 1) TAC can be effectively applied by the person who universally accompanies the child to the emergency department...and 2) active bleeding need not occur in the laceration for TAC to be effective as a topical anesthetic."</p>

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Lysak <i>et al.</i> , 1990, US <sup>158</sup>	–	73 Patients with singleton fetus in vertex position Group continuous epidural infusion (CEI) (0%, mean 25 y ± 1) Group PCEA with bupivacaine (0%, mean 26 y ± 1) Group PCEA with bupivacaine and fentanyl (0%, mean 25 y ± 1) Group PCEA with bupivacaine, fentanyl, and epinephrine (0%, mean 27 y ± 2)	<ul style="list-style-type: none"> <li>• Group CEI with bupivacaine (18)</li> <li>• Group PCEA with bupivacaine (16)</li> <li>• Group PCEA with bupivacaine and fentanyl (21)</li> <li>• Group PCEA with bupivacaine, fentanyl, and epinephrine (17)</li> </ul>	Pain, motor block (Bromage scale), overall satisfaction with labor analgesia	"In summary, this study suggests that PCEA is a safe and effective method of providing labor analgesia. No complications directly related to PCEA use were encountered. Of solutions tested, low hourly infusion requirements and lack of significant adverse side effects favor use of 0.125% bupivacaine plus fentanyl, 1 microgram/ml, for PCEA during labor."
Mamidela <i>et al.</i> , 2016, Ireland <sup>71</sup>	Prospective	55 Patients who presented for facial lacerations (69%, range 1-10 y)	<ul style="list-style-type: none"> <li>• LET gel (55)</li> </ul>	Clinician and patient/parent experience scored on a logimetric scale	"This study demonstrates that [LET gel] is an important addition to the management of paediatric facial trauma, reducing the use of [general anesthetic] thus reducing admissions and costs. Patients and clinicians also have had a good experience with the use of [LET gel]."
Miratashi <i>et al.</i> , 2012, Iran <sup>91</sup>	Prospective, double-blinded, placebo controlled randomized clinical trial	88 Patients who underwent extracapsular cataract extraction Epinephrine (36%, mean 68.3 y ± 9.9) Placebo (37%, mean 67 y ± 11.7)	<ul style="list-style-type: none"> <li>• Irrigation solution with epinephrine (45)</li> <li>• Irrigation solution without epinephrine (43)</li> </ul>	Heart rate, blood pressure, arrhythmias	"Intraocular infusion of epinephrine 1:1,000,000 can be used during cataract surgery without hemodynamic side effects and so is a safe and effective method for this purpose."

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Mordasini <i>et al.</i> , 2013, Switzerland <sup>141</sup>	Pooled analysis of open observational study and double-blind randomized trial	28 Patients who underwent open renal surgery with thoracic epidural analgesia (0%, age not provided)	<ul style="list-style-type: none"> <li>• Bupivacaine (7)</li> <li>• Bupivacaine and fentanyl (8)</li> <li>• Bupivacaine, fentanyl, and epinephrine (13)</li> </ul>	Urethral pressure	"[Thoracic epidural analgesia] with bupivacaine decrease [maximum urethral closure pressure] at rest in women. The addition of fentanyl counteracts this effect. If epinephrine, which reduces the fentanyl plasma concentration by half is also added, [maximum urethral closure pressure] is again significantly decreased...The observed increase of [maximum urethral closure pressure] may further explain the negative effect of systemic opioids on voiding function."
Moss <i>et al.</i> , 1978, US <sup>117</sup>	Double-masked crossover study	<p>36 Total patients, 16 with primary open-angle glaucoma and 20 with ocular hypertension</p> <p>Open-angle glaucoma (62.5%, range 30-82 y)</p> <p>Ocular hypertension (55%, range 42-77 y)</p>	<ul style="list-style-type: none"> <li>• Epinephrine HCl (36)</li> <li>• Timolol (36)</li> </ul> <p>Patients were crossed over into the second treatment period with the other drug they did not receive yet</p>	IOP	"The mean decrease in intraocular pressure from baseline was significantly greater with timolol than with epinephrine both before crossover and overall at both the lowest and highest concentrations of drug. Significant toxicity was produced in four patients during treatment with epinephrine, but in no patients during treatment with timolol."

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Moss, 1950, US <sup>72</sup>	–	100 Patients with non-articular rheumatism, articular rheumatism, and/or rheumatoid arthritis (gender and age not provided)	<ul style="list-style-type: none"> <li>• Adrenalin cream (100)</li> </ul>	Pain relief, ability to ambulate or use arms	"The use of adrenalin cream should make a big difference in the time factor of patients suffering from chronic rheumatism and should relieve congestion at the clinics. It is a most valuable analgesic, in many case relief from pain after one application lasting many hours."
Myers and Shugar, 2009, US <sup>28</sup>	Prospective, paired-eye, single-masked randomized study	42 Patients who plan to have cataract surgery in both eyes (gender and age not provided)	<p>Before surgery, tropicamide 1% used then one eye received one of the following:</p> <ul style="list-style-type: none"> <li>• Phenylephrine, cyclopentolate, and lidocaine (42)</li> <li>• Epinephrine and lidocaine (42)</li> </ul> <p>The second eye received the alternative solution</p>	Pupil diameter	"When combined with 1 drop of tropicamide 1% preoperatively, both formulations provided safe and effective intracameral dilation for cataract surgery; however, the [epinephrine and lidocaine in fortified balanced salt solution] was the more efficacious at each step of the procedure."

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Niemi and Breivik, 1998, Norway <sup>53</sup>	Prospective, randomized, double-blind crossover study	24 Patients who underwent elective posterolateral thoracotomies, laparotomies with longitudinal or transverse incisions (54%, mean 49 y ± 14)	<ul style="list-style-type: none"> <li>• Bupivacaine and fentanyl (24)</li> <li>• Bupivacaine, fentanyl, and epinephrine (24)</li> </ul> <p>Patients randomly allocated to receive one of two epidural mixtures on the first postop day and the other mixture received on the second postop day.</p>	Pain (VAS, verbal rating scale, Prince Henry Hospital pain score), overall quality of pain relief, sensory block, motor block (Bromage score), ability to mobilize	“In this prospective, randomised and double-blind cross-over study of thoracic epidural infusion of about 10 mg bupivacaine, 20 µg fentanyl with or without 20 µg adrenaline per hour, it was clearly demonstrated that adrenaline increases sensory blockade and improves the pain-relieving effect of bupivacaine and fentanyl. Serum fentanyl concentrations doubled and sedation increased when adrenaline was removed from the epidural infusion, indicating more rapid vascular absorption and systemic effects of fentanyl.”
Nunn <i>et al.</i> , 2017, US <sup>111</sup>	Retrospective review	46 Patients who underwent cataract surgery with intraocular lens implantation (gender and age not provided)	<ul style="list-style-type: none"> <li>• Omidria® (19)</li> <li>• Epinephrine (27)</li> </ul>	Intraoperative pupil diameters	"No significant differences were identified between Omidria® and epinephrine with regards to maintenance of intraoperative mydriasis. This finding warrants further investigation in prospective randomized studies with larger sample sizes."

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Obstbaum <i>et al.</i> , 1974, US <sup>98</sup>	–	17 Patients with ocular hypertension (gender and age not provided)	<ul style="list-style-type: none"> <li>• Epinephrine HCl (17)</li> <li>• Control: no medication (17)</li> </ul> <p>One eye of each patient was treated with epinephrine HCl while the other served as a control.</p>	IOP	"The results of this study suggest that topically applied epinephrine can be used as an effective ocular hypotensive agent at concentrations lower than those generally utilized."
Okutomi <i>et al.</i> , 2003, Japan <sup>54</sup>	Double-blinded, randomized clinical trial	108 Primiparous or multiparous uncomplicated patients with singleton, vertex presentation who desired regional anesthesia (0%, mean 31 y ± 4)	<ul style="list-style-type: none"> <li>• Intrathecal bupivacaine, fentanyl, and epinephrine (54)</li> <li>• Intrathecal bupivacaine and fentanyl (54)</li> </ul> <p>All patients received epidural bupivacaine, fentanyl, and epinephrine</p>	Pain (VAS), sensory block, motor block (Bromage score), blood pressure, heart rate	"In conclusion, we have shown that the addition of epinephrine 100 microgram to intrathecal bupivacaine and fentanyl reduces epidural analgesic requirements without increasing the incidence of hypotension, nausea, or pruritus. However, the incidence of motor block may be increased without labor prolongation. Epinephrine did not affect the incidence of [fetal heart rate] abnormalities."

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Ordog and Ordog, 1994, US <sup>73</sup>	Prospective, physician-blinded, observational study	400 Patients with lacerations <5 cm (64%, range 1-12 y)	<ul style="list-style-type: none"> <li>• TAC (400)</li> </ul>	Physician noted degree of skin blanching and rated anesthetic efficacy (poor, fair, good), duration of TAC application	"TAC appears more effective as an anesthetic for the repair of small lacerations when applied for more than 20 minutes, rather than for the currently recommended 5-10 minutes. Efficacy appeared to be the same in all of the pediatric age groups examined... When properly used, TAC provides adequate anesthesia for the repair of most small lacerations; a contact time of over 20 minutes maximizes the anesthetic efficacy of TAC."
Paech, 1993, Australia <sup>103</sup>	Prospective, blinded study	<p>66 Patients with singleton cephalic fetus, no major medical or obstetric complications in established labor</p> <p>Group 1 (0%, median 28 y with interquartile range 25-32)</p> <p>Group 2 (0%, median 29 y with interquartile range 20-34)</p> <p>Group 3 (0%, median 27 y with interquartile range 20-32)</p>	<ul style="list-style-type: none"> <li>• Group 1: Bupivacaine (23)</li> <li>• Group 2: Bupivacaine and fentanyl (23)</li> <li>• Group 3: Bupivacaine, adrenaline, and fentanyl (20)</li> </ul>	Quality of anesthesia (VAS), motor block, sensory block, demand rate, staff-administered boluses, overall quality of pain relief, PCEA duration	"Although all solutions provided effective pain relief for PCEA during labour, the use of a low-dose bupivacaine-fentanyl combination offers clinical advantages and further evaluation of such solutions is warranted."

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Pryor <i>et al.</i> , 1980, US <sup>142</sup>	Prospective study	158 Patients who had suture repair for minor lacerations (gender not provided, range 10 months – 53 years)	<ul style="list-style-type: none"> <li>Lidocaine and epinephrine infiltration (76)</li> <li>Topical TAC (82)</li> </ul>	Anesthetic efficacy, time of suture repair, overall evaluation of anesthetic technique, wound complications	"Topical TAC is shown to equal in anesthetic efficacy the use of lidocaine by subcutaneous infiltration; the topical technique is preferred by many children and parents. Wound complication rates were comparable, and time of suture repair of minor lacerations was reduced in some groups of children."
Randalls <i>et al.</i> , 1991, England <sup>159</sup>	–	48 Patients who underwent C-section Group A (0%, range 18-39 y) Group B (0%, range 22-41 y) Group C (0%, range 23-36 y) Group D (0%, range 20-37 y)	<ul style="list-style-type: none"> <li>Group A: Bupivacaine (12)</li> <li>Group B: Bupivacaine and epinephrine (12)</li> <li>Group C: Bupivacaine and fentanyl (12)</li> <li>Group D: Bupivacaine, fentanyl, and epinephrine (12)</li> </ul>	Pain (VAS), time to first request for analgesia, side effects	"In conclusion, we feel that the combined needle-through-needle technique for Caesarean section is useful in that it provides the advantages of both subarachnoid block and the continuity of extradural analgesia. We recommend the use of bupivacaine with fentanyl as it offers some benefits: minimal nausea, good intraoperative and prolonged postoperative analgesia, and a low incidence of complications."
Resch <i>et al.</i> , 1998, US <sup>74</sup>	Prospective, single-blinded, randomized controlled clinical trial	197 Patients with uncomplicated laceration of the face or scalp LET gel group (71%, mean 5.8 y ± 3.5) LET solution group (64%, mean 5.6 y ± 3.1)	<ul style="list-style-type: none"> <li>LET gel (92)</li> <li>LET solution (105)</li> </ul>	Adequacy of anesthesia before suturing (using needle), effectiveness of anesthesia	"In summary, LET gel is at least as effective as LET solution for effective topical anesthesia for uncomplicated lacerations of the face and scalp in children."

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Rucci <i>et al.</i> , 1985, Italy <sup>160</sup>	Prospective, double-blind study	<p>80 Patients who underwent lower abdominal surgery (herniorrhaphy and prostatectomy)</p> <p>No fentanyl (100%, mean 56 y ± 16)</p> <p>Fentanyl 50 mcg (100%, mean 52 y ± 13)</p> <p>Fentanyl 100 mcg (100%, mean 60 y ± 12)</p> <p>Fentanyl 200 mcg (100%, mean 52 y ± 14)</p>	<p>All groups contain bupivacaine 0.5% and adrenaline 1:200,000 with different fentanyl doses:</p> <ul style="list-style-type: none"> <li>• No fentanyl (20)</li> <li>• Fentanyl 50 mcg (20)</li> <li>• Fentanyl 100 mcg (20)</li> <li>• Fentanyl 200 mcg (20)</li> </ul>	Sensory block, motor block, duration of block, patient acceptability of anesthetic technique	<p>"The advantages in adding fentanyl 200 ug to 0.5% bupivacaine 20 ml with adrenaline 1:200 000 for lumbar extradural blockade...are: shorter time of spread and greater duration of analgesic block; better sedation during operation and reduction of episodes of shivering and acute hypotension. The disadvantages are a reduction of motor blockade, greater occurrence of incomplete blockade of the 1st sacral segment, occasional appearance of itching and bladder dysfunction after surgery, and delayed intestinal transit. Smaller doses of fentanyl do not offer significant differences compared with use of anesthetic solution alone."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Rucci <i>et al.</i> , 1987, Italy <sup>161</sup>	Prospective, double-blind study	<p>161 Patients scheduled for orthopedic surgery with a thigh tourniquet</p> <p>No fentanyl (81%, mean 35 y ± 16)</p> <p>Fentanyl 200 mcg (80%, mean 35 y ± 14)</p>	<p>All groups contain bupivacaine 0.5% and adrenaline 1:200,000 with different fentanyl doses:</p> <ul style="list-style-type: none"> <li>• No fentanyl (81)</li> <li>• Fentanyl 200 mcg (80)</li> </ul>	Blood pressure, heart rate, onset of pain or restlessness due to tourniquet	<p>"Our study shows that the addition of fentanyl 200mcg to bupivacaine greatly improve the sensory block in epidural anesthesia. There has been a dramatic drop in intra-operative supplemental analgesic needs in patients treated with extradural opiates...Orthopedic surgery of the limb can confidently be undertaken after epidural blockade performed with an appropriate bupivacaine-fentanyl mixture."</p>
Sakaguchi <i>et al.</i> , 2000, Japan <sup>55</sup>	—	<p>77 Patients scheduled for elective epidural anesthesia with or without general anesthesia</p> <p>Group 1 (40%, mean 55 y ± 17)</p> <p>Group 2 (40%, mean 62 y ± 12)</p>	<ul style="list-style-type: none"> <li>• Group 1: Bupivacaine and fentanyl (37)</li> <li>• Group 2: Bupivacaine, fentanyl, and epinephrine (40)</li> </ul>	Pain relief (VAS), number of rescue analgesics, and side effects	<p>"In conclusion, the results of the present study demonstrate that the addition of adrenaline to a combination of fentanyl and bupivacaine improves the quality of epidural analgesia after abdominal surgery. Under the conditions of the study, we did not detect any disadvantage from the addition of adrenaline."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Sakr <i>et al.</i> , 2014, US <sup>162</sup>	Randomized, double-blinded	150 Primiparae and multiparae patients in labor (0%, age not provided)	<p>All groups received epidural bupivacaine 0.015% and epinephrine 2 mcg/mL with various fentanyl doses:</p> <ul style="list-style-type: none"> <li>• Fentanyl 2 mcg/mL (50)</li> <li>• Fentanyl 4 mcg/mL (50)</li> <li>• Fentanyl 6 mcg/mL (50)</li> </ul>	Pain score, side effects, and overall patient satisfaction (VAS)	<p>"Increasing the concentration of fentanyl did not impact the neonates or the outcome of labor and delivery. Increasing the concentration of fentanyl significantly decreased the bolus volume of study solution. However, total 0.25% bupivacaine required remained high."</p>
Sayed <i>et al.</i> , 2016, US <sup>118</sup>	Randomized	15 Patients (19 eyes) who received intravitreal injections of vascular endothelial growth factor inhibitors for clinically significant macular edema or exudative age-related macular degeneration (gender and age not provided)	<ul style="list-style-type: none"> <li>• Lidocaine (6 patients, 7 eyes)</li> <li>• Lidocaine and epinephrine (9 patients, 12 eyes)</li> </ul>	Post-intravitreal injection pain score and subconjunctival hemorrhage	<p>"Although the sample size is limited, the results suggest that subconjunctival 2% lidocaine with epinephrine does not improve pain scores or the severity of subconjunctival hemorrhage following intravitreal injection of vascular endothelial growth factor inhibitor."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Schaffer, 1985, US <sup>75</sup>	Randomized	<p>107 Patients with lacerations to the face and scalp</p> <p>Group TAC (65%, mean 4.7 y)</p> <p>Group tetracaine and adrenaline (65%, mean 4.5 y)</p>	<ul style="list-style-type: none"> <li>• TAC (56)</li> <li>• Tetracaine and adrenaline HCl (51)</li> </ul>	Extent of peripheral blanching around wound, effectiveness of anesthesia assessed by physician, report of infection or side effects	<p>"Our study confirmed our satisfaction with this method of anesthesia and demonstrated no significant toxic reactions or unpleasant side effects. The increased evidence of infection was not considered to be serious enough to discontinue the use of cocaine in the topical anesthetic solution. It is our contention that topical anesthesia is a worthwhile adjunct to xylocaine in selected cases."</p>
Schilling <i>et al.</i> , 1995, US <sup>76</sup>	Double-blinded, randomized controlled trial	<p>151 Patients with uncomplicated laceration to the face or scalp (66.2%, age reported in groups below)</p> <p>LET (mean 6.4 y ± 3.4)</p> <p>TAC (mean 5.9 y ± 3.3)</p>	<ul style="list-style-type: none"> <li>• LET (78)</li> <li>• TAC (73)</li> </ul>	Signs of pain with needle, adequacy of anesthesia as assessed by physician, duration of anesthesia	<p>"LET is an effective alternative to TAC for topical anesthesia during suturing of uncomplicated lacerations on the face and scalp in children. As a topical anesthetic with cocaine omitted, LET solution provides an inexpensive alternative that can be used in hospital EDs, clinics, and urgent-care centers. The removal of pure powdered cocaine should diminish hospital inventory of this controlled substance."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Scrutton <i>et al.</i> , 1998, England <sup>56</sup>	–	<p>88 Patients in active labor with singleton fetus, cephalic presentation, requesting epidural analgesia</p> <p>Group 1 (0%, mean 26.6 y ± 5)</p> <p>Group 2 (0%, mean 28.8 y ± 5.5)</p> <p>Group 3 (0%, mean 28.8 y ± 6.1)</p>	<p>Patients randomized to receive 1 of these 3 loading doses:</p> <ul style="list-style-type: none"> <li>• Group 1: Bupivacaine 9.375 mg (15 mL of 0.0625%), fentanyl 37.5 mcg, and adrenaline 37.5 mcg (28)</li> <li>• Group 2: Bupivacaine 15 mg (15 mL of 0.1%), fentanyl 30 mcg, and adrenaline 30 mcg (30)</li> <li>• Group 3: Test dose of bupivacaine 10 mg (4 mL of 0.25%) then bupivacaine 20 mg (8 mL of 0.25%) (30)</li> </ul> <p>All groups received an infusion of bupivacaine, fentanyl, and adrenaline after the loading dose.</p>	Pain score on verbal numeric scale, motor block, maternal satisfaction using verbal numeric score	<p>"The aim of our study was to assess the use of low-dose epidural loading doses as an alternative to an intrathecal loading dose. These large-volume, low-dose solutions containing 9.325 mg or 15 mg of bupivacaine in combination with fentanyl and adrenaline, made up to 15 ml total volume, produced effective epidural analgesia in labour with minimal motor block at 30 min."</p>

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Sinatra <i>et al.</i> , 1991, US <sup>163</sup>	Randomized, single-blind study	<p>45 Patients with singleton fetus in vertex position in active labor requesting epidural analgesia</p> <p>Group 1 (0%, mean 27.7 y ± 6.7)</p> <p>Group 2 (0%, mean 28.7 y ± 5)</p> <p>Group 3 (0%, mean 27.7 y ± 7)</p>	<ul style="list-style-type: none"> <li>• Group 1: Bupivacaine 0.5% (15)</li> <li>• Group 2: Bupivacaine 0.25% with lidocaine (15)</li> <li>• Group 3: Bupivacaine 0.5% with fentanyl (15)</li> </ul> <p>All solutions contained epinephrine 1:200,000.</p>	Onset time, duration, sensory block, motor block (modified Bromage score), side effects, patient satisfaction with therapy (VAS)	"In conclusion, solutions of bupivacaine alone and in combination with a second local anesthetic or opioid provided useful epidural analgesia in laboring parturients. The combination of bupivacaine and fentanyl offered the longest duration of analgesia and the lowest frequency of shivering and motor block."
Singer and Stark, 2001, US <sup>77</sup>	Randomized, double-blind clinical trial	<p>60 Patients who presented for closure of uncomplicated lacerations (% male provided based on group below, range 1-59 y)</p> <p>EMLA (77%)</p> <p>LET (76%)</p>	<ul style="list-style-type: none"> <li>• EMLA (31)</li> <li>• LET (29)</li> </ul>	Pain of lidocaine infiltration assessed by patient or guardian on visual analog scale and proportion of lacerations that were adequately anesthetized to a needlestick	"Our study suggests that pretreatment of uncomplicated lacerations at the time of patient presentation to the triage desk with LET or EMLA cream results in a similar reduction in the pain of subsequent injection of lidocaine. Since it is less expensive and not contraindicated in open wounds, we believe that LET is the preferred topical anesthetic. Early application of LET at triage also has the potential to reduce the patient's ED length of stay and should be considered in all eligible lacerations."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Singer and Stark, 2000, US <sup>78</sup>	Randomized, double-blind, controlled trial	<p>43 Patients who presented for closure of uncomplicated lacerations</p> <p>LET (73%, median 12.7 y with interquartile range of 6-34.3)</p> <p>Placebo (67%, median 13 with interquartile range of 6.5-30.5)</p>	<ul style="list-style-type: none"> <li>• LET (22)</li> <li>• Placebo – epinephrine alone (21)</li> </ul>	Pain of lidocaine infiltration assessed by patient or guardian on visual analog scale and proportion of lacerations that were adequately anesthetized to a needlestick	"Our study suggests that application of topical LET to simple lacerations in healthy patients by nurses at the time of triage is both feasible and efficacious in reducing the pain of subsequent injection of lidocaine."
Smith <i>et al.</i> , 1997, US <sup>122</sup>	Prospective, randomized, double-blind clinical trial	<p>240 Patients with laceration &lt; 5 cm in length that required suturing</p> <p>Prilocaine and phenylephrine (63%, mean 5.7 y ± 3.2)</p> <p>Tetracaine and phenylephrine (68%, mean 5 y ± 3.1)</p> <p>Tetracaine, lidocaine, and phenylephrine (62%, mean 5.6 y ± 3.1)</p> <p>TAC (67%, mean 5 y ± 3.2)</p>	<ul style="list-style-type: none"> <li>• Prilocaine and phenylephrine (60)</li> <li>• Tetracaine and phenylephrine (60)</li> <li>• Tetracaine, lidocaine, and phenylephrine (60)</li> <li>• TAC (60)</li> </ul>	Pain (VAS), anesthetic effectiveness	"This study demonstrated the effectiveness and safety of three new non-cocaine-containing topical anesthetics. Consistently, there was no statistical difference demonstrated between the effectiveness of [tetracaine and phenylephrine] and that of TAC for each outcome measure of each observer group. [Tetracaine and phenylephrine] offers an effective alternative to TAC during laceration repair in children."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Smith <i>et al.</i> , 1998, US <sup>123</sup>	Prospective, randomized, double-blind clinical trial	180 Patients with laceration < 5 cm in length that required suturing (64%, range 1-18 y)	<ul style="list-style-type: none"> <li>• Prilocaine and phenylephrine (60)</li> <li>• Bupivacaine and phenylephrine (60)</li> <li>• TAC (60)</li> </ul>	Pain (VAS), anesthetic effectiveness	"This study demonstrated the effectiveness and safety of [prilocaine and phenylephrine] and [bupivacaine and phenylephrine]. [Prilocaine and phenylephrine] statistically outperformed [bupivacaine and phenylephrine] and offers an effective alternative to TAC during laceration repair in children."
Smith <i>et al.</i> , 1997, US <sup>79</sup>	Randomized, blinded trial	<p>71 Patients with laceration on face or scalp &lt;5 cm in length that requires suturing</p> <p>Lidocaine (78%, mean 4.7 y ± 2.1)</p> <p>Mepivanor (71%, mean 4.6 y ± 3)</p> <p>TAC (63%, mean 5 y ± 2.9)</p>	<ul style="list-style-type: none"> <li>• Lidocaine (23)</li> <li>• Mepivanor (Mepivacaine and norepinephrine) (24)</li> <li>• TAC (24)</li> </ul>	Pain perceptions of suture technicians, research assistants, and videotape reviewer (VAS), pain perceptions of parents and suture technicians (Likert scale)	"Mepivanor...was found to be generally less effective than TAC and lidocaine infiltration in providing adequate anesthesia during laceration repair. This study also demonstrated for the first time that a TAC solution containing only 120mg of cocaine (3ml of 4% cocaine) is as effective as 1% lidocaine infiltration in providing local anesthesia during laceration repair. This will allow the amount of cocaine in TAC to be reduced, thereby decreasing costs and the likelihood of adverse reactions."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Smith <i>et al.</i> , 1996, US <sup>124</sup>	Randomized, blinded trial	240 Patients with laceration < 5 cm in length that requires suturing (slightly more than two-thirds, range 2-17 y)	<ul style="list-style-type: none"> <li>• Bupivanor (bupivacaine and norepinephrine) (40)</li> <li>• Etidonor (etidocaine and norepinephrine) (40)</li> <li>• Mepivanor (mepivacaine and norepinephrine) (40)</li> <li>• Prilonor (prilocaine and norepinephrine) (40)</li> <li>• TAC (40)</li> <li>• Lidocaine (40)</li> </ul>	Pain perceptions of suture technicians, research assistants, and patients (VAS), pain perceptions of parents and suture technicians (Likert scale), effectiveness of anesthesia rated by suture technician	"In conclusion, this study demonstrated the safety and effectiveness of Bupivanor as a topical anesthetic, especially on the face and scalp, where it was consistently rated as effective as TAC and 1 % lidocaine infiltration in providing anesthesia during laceration repair. Its effectiveness for suturing of face and scalp lacerations is important, because it is on the face where TAC is most likely to come into contact with mucous membranes inadvertently and result in systemic toxicity."
Smith and Barry, 1990, US <sup>80</sup>	Randomized, prospective, double-blind study	250 Patients who presented for laceration repair (68%, range 1-17 y)	<ul style="list-style-type: none"> <li>• TAC I: Tetracaine 0.5%, adrenalin 1:2000, cocaine 11.8% (83)</li> <li>• TAC II: Tetracaine 1%, adrenalin 1:4000, cocaine 7% (76)</li> <li>• TAC III: Tetracaine 1%, adrenalin 1:4000, cocaine 4% (91)</li> </ul>	Parent completed a questionnaire on pain perception, anxiety level, need for restraint or sedation, satisfaction with results; physician completed similar form with additional measures like anesthetic efficacy, characteristics of the wound and repair, and occurrence of side effects	"We found comparable efficacy of the three formulations, with similar efficacy to 1% lidocaine infiltration for facial and scalp wounds...Our findings support use of TAC for face and scalp lacerations and a change to a less concentrated TAC preparations, such as our 'TAC III,' which is presumably safer for widespread use."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Temple and Timms, 2001, UK <sup>119</sup>	Randomized, double-blind prospective study	23 Patients listed for laser turbinectomy to the inferior turbinates under general anesthesia (57%, range 17-58 y)	<ul style="list-style-type: none"> <li>• Lidocaine and epinephrine injection in conjunction with epinephrine spray (23)</li> </ul>	Blood loss from each nostril	"During nasal surgery bleeding is a common hindrance. This study demonstrates that after applying topical epinephrine, injecting the turbinates with lignocaine and epinephrine confers no additional benefit in terms of intra-operative bleeding or immediate post-operative discomfort."
Vinci and Fish, 1996, US <sup>81</sup>	Randomized, double-blind clinical trial	<p>156 Patients who received treatment for lacerations</p> <p>Group 1 (75%, mean 40 months)</p> <p>Group 2 (74%, mean 41 months)</p> <p>Group 3 (78%, mean 47 months)</p>	<ul style="list-style-type: none"> <li>• Group 1: Tetracaine 0.5%, epinephrine 1:2000, and cocaine 11.8% (49)</li> <li>• Group 2: Tetracaine 1%, epinephrine 1:2000, and cocaine 4% (49)</li> <li>• Group 3: Tetracaine and cocaine (58)</li> </ul>	Response to needle stick, physician assessment of anesthesia effectiveness	"The application of a TAC solution containing 4% cocaine is as effective as a TAC solution containing 11.8% cocaine; use of this 4% solution decreases the cost of the agent. Because topical anesthesia has many advantages in the pediatric age group, a 4% TAC solution may be a cost-effective choice. In addition, adrenaline seems to be a necessary ingredient in the anesthetic solution."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
White <i>et al.</i> , 2004, US <sup>82</sup>	Prospective, convenience sample, case series	67 Patients with finger laceration < 3 cm in length requiring suture (68%, mean 11.9 y)	<ul style="list-style-type: none"> <li>• LAT (67)</li> </ul>	LAT success/failure; patient and parental satisfaction with LAT	"LAT gel appears to be a safe and effective means of providing anesthesia for the repair of simple finger lacerations in children. It appears particularly effective on the dorsal surface of the finger. LAT gel may provide a painless and effective alternative to infiltration anesthesia."
White <i>et al.</i> , 1986, US <sup>83</sup>	Randomized, double-blind study	68 Patients with laceration < 5 cm in length (gender and age not provided)	<ul style="list-style-type: none"> <li>• TAC (36)</li> <li>• Tetracaine (32)</li> </ul>	Patient efficacy of topical anesthetic on graded scale, response to needle stick and need for lidocaine injection	"The combination of tetracaine, Adrenalin, and cocaine was effective in anesthetizing facial lacerations. Tetracaine alone on the face or TAC/tetracaine on any other areas of the body have little anesthetizing effect. Our results suggest that TAC should be used on facial lacerations in both the adult and the pediatric populations. With good cleaning and copious irrigation, cases of wound infection in TAC patients will not be any more prevalent than in conventionally anesthetized patients."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Wilson <i>et al.</i> , 2007, US <sup>92</sup>	Case report	1 Patient with bilateral cataracts associated with nystagmus (0%, 4 months)	<ul style="list-style-type: none"> <li>• Irrigation solution with epinephrine in the right eye</li> <li>• Irrigation solution without epinephrine in the left eye</li> </ul>	Intraoperative floppy iris syndrome	"This case highlights the importance of including epinephrine in the irrigating solution in pediatric cataract surgery."
Yablonski <i>et al.</i> , 1977, US <sup>127</sup>	—	12 Patients with open-angle glaucoma or ocular hypertension who had demonstrated an intolerance to topically applied epinephrine in the past (gender and age not provided)	<ul style="list-style-type: none"> <li>• Dipivefrin in one eye (12)</li> <li>• Epinephrine HCl in the other eye (12)</li> </ul>	IOP, signs of intolerance	"Topical dipivefrin 0.1% proved useful for lowering intraocular pressure in patients intolerant to topically applied epinephrine."
Yau <i>et al.</i> , 1990, Hong Kong <sup>57</sup>	Double-blind comparison	90 Patients with uncomplicated pregnancies and single fetal cephalic presentation in established labor and requested epidural analgesia (0%, mean 27.4 y ± 4.5)	<ul style="list-style-type: none"> <li>• Bupivacaine 0.125% (13)</li> <li>• Bupivacaine 0.125% and adrenaline (11)</li> <li>• Bupivacaine 0.125%, fentanyl, and adrenaline (12)</li> <li>• Bupivacaine 0.25% (13)</li> <li>• Bupivacaine 0.25% and adrenaline (13)</li> <li>• Bupivacaine 0.25%, fentanyl, and adrenaline (8)</li> </ul>	Pain (VAS), onset of analgesia (maximum percentage reduction in pain score, duration of analgesia)	"Analgesia was best with the bupivacaine 0.25% with adrenaline 2.5 µg/ml and the two fentanyl mixtures. We see no advantage in using the more concentrated mixture since the two fentanyl groups were similar. We conclude that the combination of bupivacaine 0.125% with adrenaline 1.25 µg/ml and fentanyl 50 µg gives good pain relief and is a suitable choice for obstetric epidural analgesia."

Author, Year, Country	Study Type <sup>a</sup>	Patient Population (% male, age)	Intervention/Comparator (# of patients) <sup>b</sup>	Primary Outcome Measure	Authors' Conclusions
Yu <i>et al.</i> , 2016, China <sup>44</sup>	Prospective, randomized, double-blind study	18 Patients scheduled for bilateral phacoemulsification and IOL implantation (61%, mean 63.78 y ± 3.1)	<ul style="list-style-type: none"> <li>Intracameral epinephrine HCl in one eye (18)</li> <li>Topical mydriatics with tropicamide and phenylephrine in the other (18)</li> </ul>	Pupil diameter during surgery, measured from video recordings	"In conclusion, intracameral epinephrine hydrochloride appears to be an alternative to the mydriatic modalities for phacoemulsification and IOL implantation. In comparison with topical mydriatics, intracameral epinephrine hydrochloride offers easier preoperative preparation, more rapid pupil dilation, and comparable surgical performance... Further studies of a larger number of subjects and longer follow-up periods are warranted."
Zempsky and Karasic, 1997, US <sup>125</sup>	Prospective, single-blind, randomized trial	32 Patients with extremity lacerations < 5 cm in length (gender and age not provided)	<ul style="list-style-type: none"> <li>EMLA (16)</li> <li>TAC (16)</li> </ul>	Pain (VAS) assessed by physician, patient and parent or guardian	"EMLA appears to be superior to TAC for anesthesia of simple extremity lacerations in that those wounds treated with EMLA required supplemental anesthesia less often. EMLA required approximately 1 hour to cause optimal anesthesia in open wounds. Protocols should be developed to allow efficient use of EMLA for anesthesia of extremity lacerations in the ED."

Abbreviations: “–”, not mentioned; ASA, American Society of Anesthesiologists; C-section, cesarean section; CEI, continuous epidural infusion; CSE, combined spinal epidural; CSF, cerebral spinal fluid; ED, emergency department; EMLA, eutectic mixture of local anesthetics; HCl, hydrochloride; ICM, intracameral

mydriatics; IOL, intraocular lens; IOP, intraocular pressure; IV, intravenous; LAT/LET, lidocaine/epinephrine (adrenaline)/tetracaine; PCEA, patient-controlled epidural analgesia; PONV, postoperative nausea and vomiting; TAC, tetracaine/epinephrine (adrenaline)/cocaine; VAS, visual analog scale.

<sup>a</sup>As defined by authors.

<sup>b</sup>Epinephrine is also spelled as adrenaline or adrenalin; for accuracy, the substance name that the study authors used is presented in this table. Most studies did not specify the salt form, so HCl is not included unless the study specified use of this salt form.

*Appendix 3.1. Single-agent survey instrument for medical associations*

Welcome. We want to understand your clinical use of compounded epinephrine. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:  
[compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu).

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or [hrpo@umaryland.edu](mailto:hrpo@umaryland.edu).

Thank you,

Dr. Ashlee Mattingly  
Principal Investigator  
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871  
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient- specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer epinephrine to your patients?

- Yes
- No

3. Which salt form of epinephrine do you use?

- Epinephrine bitartrate
- Epinephrine hydrochloride
- Unsure
- Other (please describe)

4. Do you prescribe or administer epinephrine by any of the following dosage forms and/or routes of administration? (check all that apply)

- Inhaled nasal spray
- Injectable solution (epidural, perineural, intracaudal)
- Topical cream
- None of the above

5. I prescribe or administer epinephrine for the following conditions or diseases: (check all that apply)

- Asthma
- Anaphylaxis, hypersensitivity reaction
- Bradycardia
- Cardiac arrhythmias and/or arrest
- Coagulation disorder
- Excessive uterine contraction
- Hypotension
- Laryngotracheobronchitis
- Local anesthetic
- Mucosal or nasal congestion
- Shock
- Surgical bleeding
- Other (please explain) \_\_\_\_\_

6. I use compounded epinephrine because: (check all that apply)

- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
- Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
- Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
- There are no commercially available products containing epinephrine.
- Other (please explain) \_\_\_\_\_

7. Do you stock non-patient-specific compounded epinephrine at your practice?

- Yes
- No
- I'm not sure

8. I obtain compounded epinephrine from the following: (check all that apply)

- Compound myself at my practice
- Have the product compounded by an in-house pharmacy
- Purchase, or have a patient purchase, from a compounding pharmacy
- Purchase, or have a patient purchase, from an outsourcing facility
- Other (please explain) \_\_\_\_\_

9. What is your practice setting? (check all that apply)

- Physician office/private practice
- Outpatient clinic
- Hospital/health system
- Academic medical center
- Emergency room
- Operating room
- Other (please describe) \_\_\_\_\_

10. What degree do you hold? (check all that apply)

- Doctor of Medicine (MD)
- Doctor of Osteopathic Medicine (DO)
- Doctor of Medicine in Dentistry (DMD/DDS)
- Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
- Naturopathic Doctor (ND)
- Nurse Practitioner (NP)
- Physician Assistant (PA)
- Other (please describe) \_\_\_\_\_

*Appendix 3.2. Epinephrine / lidocaine survey instrument for medical associations*

Welcome. We want to understand your clinical use of compounded epinephrine / lidocaine. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:  
[compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu).

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or [hrpo@umaryland.edu](mailto:hrpo@umaryland.edu).

Thank you,

Dr. Ashlee Mattingly  
Principal Investigator  
The University of Maryland School of Pharmacy

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OMB Control No. 0910-0871  
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer epinephrine / lidocaine to your patients?

- Yes
- No

3. Which salt form of epinephrine do you use?

- Epinephrine bitartrate
- Epinephrine hydrochloride
- Unsure
- Other (please describe)

4. Do you prescribe or administer epinephrine / lidocaine by any of the following dosage forms and/or routes of administration? (check all that apply)

- Ophthalmic solution
- None of the above

5. I prescribe or administer epinephrine / lidocaine for the following conditions or diseases: (check all that apply)

- Local anesthetic
- Mydriasis for intraocular surgery
- Open-angle glaucoma
- Other (please explain) \_\_\_\_\_

6. I use compounded epinephrine / lidocaine because: (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing epinephrine / lidocaine.
  - Other (please explain) \_\_\_\_\_
7. Do you stock non-patient-specific compounded epinephrine / lidocaine at your practice?
- Yes
  - No
  - I'm not sure
8. I obtain compounded epinephrine / lidocaine from the following: (check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
9. What is your practice setting? (check all that apply)
- Physician office/private practice
  - Outpatient clinic
  - Hospital/health system
  - Academic medical center
  - Emergency room
  - Operating room
  - Other (please describe) \_\_\_\_\_
10. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
  - Doctor of Osteopathic Medicine (DO)
  - Doctor of Medicine in Dentistry (DMD/DDS)
  - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
  - Naturopathic Doctor (ND)
  - Nurse Practitioner (NP)
  - Physician Assistant (PA)
  - Other (please describe)

*Appendix 3.3. Epinephrine / bupivacaine / fentanyl survey instrument for medical associations*

Welcome. We want to understand your clinical use of compounded epinephrine / bupivacaine / fentanyl. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

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[compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu).

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OMB Control No. 0910-0871  
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer epinephrine / bupivacaine / fentanyl to your patients?

- Yes
- No

3. Which salt form of epinephrine do you use?

- Epinephrine bitartrate
- Epinephrine hydrochloride
- Unsure
- Other (please describe)

4. Do you prescribe or administer epinephrine / bupivacaine / fentanyl by any of the following dosage forms and/or routes of administration? (check all that apply)

- Epidural injection
- None of the above

5. I prescribe or administer epinephrine / bupivacaine / fentanyl for the following conditions or diseases: (check all that apply)

- Analgesia
- Other (please explain) \_\_\_\_\_

6. I use compounded epinephrine / bupivacaine / fentanyl because: (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing epinephrine / bupivacaine / fentanyl.
  - Other (please explain) \_\_\_\_\_
7. Do you stock non-patient-specific compounded epinephrine / bupivacaine / fentanyl at your practice?
- Yes
  - No
  - I'm not sure
8. I obtain compounded epinephrine / bupivacaine / fentanyl from the following: (check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
9. What is your practice setting? (check all that apply)
- Physician office/private practice
  - Outpatient clinic
  - Hospital/health system
  - Academic medical center
  - Emergency room
  - Operating room
  - Other (please describe) \_\_\_\_\_
10. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
  - Doctor of Osteopathic Medicine (DO)
  - Doctor of Medicine in Dentistry (DMD/DDS)
  - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
  - Naturopathic Doctor (ND)
  - Nurse Practitioner (NP)
  - Physician Assistant (PA)
  - Other (please describe)

*Appendix 3.4. Lidocaine / epinephrine / tetracaine survey instrument for medical associations*

Welcome. We want to understand your clinical use of compounded lidocaine / epinephrine / tetracaine (LET). Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

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OMB Control No. 0910-0871  
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer lidocaine / epinephrine / tetracaine (LET) to your patients?

- Yes
- No

3. Which salt form of epinephrine do you use?

- Epinephrine bitartrate
- Epinephrine hydrochloride
- Unsure
- Other (please describe)

4. Do you prescribe or administer lidocaine / epinephrine / tetracaine (LET) by any of the following dosage forms and/or routes of administration? (check all that apply)

- Topical gel
- Topical spray
- None of the above

5. I prescribe or administer lidocaine / epinephrine / tetracaine (LET) the following conditions or diseases: (check all that apply)

- Local anesthesia
- Other (please explain) \_\_\_\_\_

6. I use compounded lidocaine / epinephrine / tetracaine (LET): (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing epinephrine.
  - Other (please explain) \_\_\_\_\_
7. Do you stock non-patient-specific compounded lidocaine / epinephrine / tetracaine (LET) your practice?
- Yes
  - No
  - I'm not sure
8. I obtain compounded epinephrine from the following: (check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
9. What is your practice setting? (check all that apply)
- Physician office/private practice
  - Outpatient clinic
  - Hospital/health system
  - Academic medical center
  - Emergency room
  - Operating room
  - Other (please describe) \_\_\_\_\_
10. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
  - Doctor of Osteopathic Medicine (DO)
  - Doctor of Medicine in Dentistry (DMD/DDS)
  - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
  - Naturopathic Doctor (ND)
  - Nurse Practitioner (NP)
  - Physician Assistant (PA)
  - Other (please describe) \_\_\_\_\_

*Appendix 3.5. Tetracaine / adrenaline / cocaine survey instrument for medical associations*

Welcome. We want to understand your clinical use of tetracaine HCl / adrenaline (epinephrine) / cocaine HCl (TAC). Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:  
[compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu).

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or  
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Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer of tetracaine HCl / adrenaline (epinephrine) / cocaine HCl (TAC) to your patients?

- Yes
- No

3. Which salt form of epinephrine do you use?

- Epinephrine bitartrate
- Epinephrine hydrochloride
- Unsure
- Other (please describe)

4. Do you prescribe or administer of tetracaine HCl / adrenaline (epinephrine) / cocaine HCl (TAC) by any of the following dosage forms and/or routes of administration? (check all that apply)

- Ophthalmic solution
- Topical solution
- None of the above

5. I prescribe or administer of tetracaine HCl / adrenaline (epinephrine) / cocaine HCl (TAC) the following conditions or diseases: (check all that apply)

- Local anesthesia
- Mydriasis
- Open-angle glaucoma
- Other (please explain) \_\_\_\_\_

6. I use compounded of tetracaine HCl / adrenaline (epinephrine) / cocaine HCl (TAC): (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing epinephrine.
  - Other (please explain) \_\_\_\_\_
7. Do you stock non-patient-specific compounded of tetracaine HCl / adrenaline (epinephrine) / cocaine HCl (TAC) your practice?
- Yes
  - No
  - I'm not sure
8. I obtain compounded epinephrine from the following: (check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
9. What is your practice setting? (check all that apply)
- Physician office/private practice
  - Outpatient clinic
  - Hospital/health system
  - Academic medical center
  - Emergency room
  - Operating room
  - Other (please describe) \_\_\_\_\_
10. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
  - Doctor of Osteopathic Medicine (DO)
  - Doctor of Medicine in Dentistry (DMD/DDS)
  - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
  - Naturopathic Doctor (ND)
  - Nurse Practitioner (NP)
  - Physician Assistant (PA)
  - Other (please describe) \_\_\_\_\_

*Appendix 3.6. Ophthalmology instrument for medical associations*

Welcome. We want to understand your clinical use of epinephrine. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

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[compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu).

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Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you prescribe or administer of epinephrine to your patients?

- Yes
- No

3. Which salt form of epinephrine do you use?

- Epinephrine bitartrate
- Epinephrine hydrochloride
- Unsure
- Other (please describe)

4. Do you prescribe or administer of epinephrine by any of the following dosage forms and/or routes of administration? (check all that apply)

- Intracameral/intraocular injection
- Ophthalmic solution
- None of the above

5. I prescribe or administer of epinephrine the following conditions or diseases: (check all that apply)

- Mydriasis for intraocular surgery
- Open-angle glaucoma
- Other (please explain) \_\_\_\_\_

6. I use compounded of epinephrine: (check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing epinephrine.
  - Other (please explain) \_\_\_\_\_
7. Do you stock non-patient-specific compounded of epinephrine your practice?
- Yes
  - No
  - I'm not sure
8. I obtain compounded epinephrine from the following: (check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
9. What is your practice setting? (check all that apply)
- Physician office/private practice
  - Outpatient clinic
  - Hospital/health system
  - Academic medical center
  - Emergency room
  - Operating room
  - Other (please describe) \_\_\_\_\_
10. What degree do you hold? (check all that apply)
- Doctor of Medicine (MD)
  - Doctor of Osteopathic Medicine (DO)
  - Doctor of Medicine in Dentistry (DMD/DDS)
  - Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
  - Naturopathic Doctor (ND)
  - Nurse Practitioner (NP)
  - Physician Assistant (PA)
  - Other (please describe) \_\_\_\_\_

*Appendix 3.7. Survey instrument for American Academy of Ophthalmology*

Welcome. We want to understand your clinical use of the following compounded drugs: epinephrine; epinephrine/lidocaine combination product; flurbiprofen; tetracycline HCl. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:

[compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu).

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or

[hrpo@umaryland.edu](mailto:hrpo@umaryland.edu).

Thank you,

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Principal Investigator

The University of Maryland School of Pharmacy

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OMB Control No. 0910-0871

Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Which of the following compounded drugs do you prescribe or administer to your patients? (please check all that apply)

- Epinephrine as a single agent product
- Epinephrine/lidocaine as a combination product
- Flurbiprofen
- Tetracycline
- None of the above

3. Which salt form of epinephrine do you use as a single agent product? (please check all that apply)

- Epinephrine bitartrate
- Epinephrine hydrochloride
- Unsure
- Other, please explain \_\_\_\_\_

4. Do you prescribe or administer epinephrine as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)

- Intracameral/intraocular injection
- Ophthalmic solution
- None of the above

5. I prescribe or administer epinephrine as a single agent product for the following conditions or diseases: (please check all that apply)

- Open-angle glaucoma
- Mydriasis for intraocular surgery
- Other (please explain) \_\_\_\_\_

6. I use compounded epinephrine as a single agent product because: (please check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing epinephrine.
  - Other (please explain) \_\_\_\_\_
7. Do you stock non-patient-specific compounded epinephrine as a single agent product at your practice?
- Yes
  - No
  - I'm not sure
8. I obtain compounded epinephrine as a single agent product from the following: (please check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
9. Which salt form of epinephrine do you use in epinephrine/lidocaine combination product? (please check all that apply)
- Epinephrine bitartrate
  - Epinephrine hydrochloride
  - Unsure
  - Other, please explain \_\_\_\_\_
10. Do you prescribe or administer epinephrine/lidocaine as a combination product by any of the following dosage forms and/or routes of administration? (please check all that apply)
- Ophthalmic solution
  - None of the above
11. I prescribe or administer epinephrine/lidocaine as a combination product for the following conditions or diseases: (please check all that apply)
- Local anesthetic
  - Mydriasis for intraocular surgery
  - Open-angle glaucoma
  - Other (please explain) \_\_\_\_\_

12. I use compounded epinephrine/lidocaine as a combination product because: (please check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing epinephrine/lidocaine.
  - Other (please explain) \_\_\_\_\_
13. Do you stock non-patient-specific compounded epinephrine/lidocaine as a combination product at your practice?
- Yes
  - No
  - I'm not sure
14. I obtain compounded epinephrine/lidocaine as a combination product from the following: (please check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
15. Do you prescribe or administer flurbiprofen as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
- Ophthalmic solution
  - None of the above
16. I prescribe or administer flurbiprofen as a single agent product for the following conditions or diseases: (please check all that apply)
- Inhibition of intraoperative miosis
  - Other (please explain) \_\_\_\_\_
17. I use compounded flurbiprofen as a single agent product because: (please check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing flurbiprofen.
  - Other (please explain) \_\_\_\_\_

18. Do you stock non-patient-specific compounded flurbiprofen as a single agent product at your practice?
- Yes
  - No
  - I'm not sure
19. I obtain compounded flurbiprofen as a single agent product from the following: (please check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_
20. Do you prescribe or administer tetracycline as a single agent product by any of the following dosage forms and/or routes of administration? (please check all that apply)
- Ophthalmic ointment
  - None of the above
21. I prescribe or administer tetracycline as a single agent product for the following conditions or diseases: (please check all that apply)
- Gonococcal ophthalmia neonatorum prophylaxis
  - Other (please explain) \_\_\_\_\_
22. I use compounded tetracycline as a single agent product because: (please check all that apply)
- Commercial products are not available in the dosage form, strength, or combination I need. (please explain) \_\_\_\_\_
  - Patient allergies prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - Patient conditions prevent me from using commercially available products. (please explain) \_\_\_\_\_
  - There are no commercially available products containing tetracycline.
  - Other (please explain) \_\_\_\_\_
23. Do you stock non-patient-specific compounded tetracycline as a single agent product at your practice?
- Yes
  - No
  - I'm not sure
24. I obtain compounded tetracycline as a single agent product from the following: (please check all that apply)
- Compound myself at my practice
  - Have the product compounded by an in-house pharmacy
  - Purchase, or have a patient purchase, from a compounding pharmacy
  - Purchase, or have a patient purchase, from an outsourcing facility
  - Other (please explain) \_\_\_\_\_

25. What is your practice setting? (please check all that apply)

- Physician office/private practice
- Outpatient clinic
- Hospital/health system
- Academic medical center
- Emergency room
- Operating room
- Other (please explain) \_\_\_\_\_

26. What degree do you hold? (please check all that apply)

- Doctor of Medicine (MD)
- Doctor of Osteopathic Medicine (DO)
- Doctor of Pharmacy (PharmD) or Bachelor of Science in Pharmacy (BS Pharm)
- Nurse Practitioner (NP)
- Physician Assistant (PA)
- Other (please explain) \_\_\_\_\_

*Appendix 3.8. Survey instrument for Ambulatory Surgery Center Association*

Welcome. We want to understand your clinical use of compounded drugs. Your feedback will help the Food and Drug Administration (FDA) develop a list of drugs that can be used in bulk compounding by 503B outsourcing facilities. Your anonymous responses will be shared with the FDA. The time required to complete this survey is approximately 10-15 minutes.

If you have additional questions or concerns about this study, please email:  
[compounding@rx.umaryland.edu](mailto:compounding@rx.umaryland.edu).

If you have questions about your rights as a research subject, please contact HRPO at 410-760-5037 or [hrpo@umaryland.edu](mailto:hrpo@umaryland.edu).

Thank you,

Dr. Ashlee Mattingly  
Principal Investigator  
The University of Maryland School of Pharmacy

An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

OMB Control No. 0910-0871  
Expiration date: June 30, 2022

1. How familiar are you with the following terms?

	Very familiar	Somewhat familiar	Not familiar
Compounded drugs (medications prepared to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503A Compounding pharmacy (a pharmacy that prepares compounded medications prescribed by practitioners to meet a patient-specific need)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
503B Outsourcing facility (a facility that compounds larger quantities without the receipt of a patient-specific prescription)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Do you utilize a 503B outsourcing facility to acquire compounded drugs?

- Yes. If yes, why? \_\_\_\_\_
- No. If no, why not? \_\_\_\_\_

3. Do you obtain any of the following products from a 503B outsourcing facility? (check all that apply)

- I do not obtain any compounded drugs from 503B outsourcing facilities
- Amitriptyline / Ketoprofen / Oxymetazoline
- Budesonide
- Calcium gluconate
- Droperidol
- Epinephrine
- Epinephrine for ophthalmic administration
- Epinephrine / Lidocaine for ophthalmic administration
- Epinephrine / Bupivacaine / Fentanyl
- Fentanyl
- Flurbiprofen
- Flurbiprofen for ophthalmic administration
- Hydromorphone
- Ipamorelin
- Ketoprofen / Nifedipine
- Lidocaine / Epinephrine / Tetracaine HCl
- Meperidine
- Morphine
- Naloxone
- Neomycin
- Phentolamine
- Promethazine
- Remifentanyl

- Sufentanil
- Tramadol
- None of the above

4. What type of specialty procedures are performed in your facility? (check all that apply)

- Dental
- Dermatology
- Endoscopy
- Neurosurgery
- Obstetrics/gynecology
- Ophthalmology
- Otolaryngology
- Orthopedics
- Pain
- Plastics
- Podiatry
- Other (please describe) \_\_\_\_\_

Appendix 4. Survey distribution to professional associations

<b>Specialty</b>	<b>Association<sup>a</sup></b>	<b>Agreed/Declined, Reason for Declining</b>
Allergy/Immunology	American Academy of Allergy, Asthma, and Immunology (AAAAI)	Declined – survey not approved
Anesthesia	American Society of Regional Anesthesia and Pain Medicine (ASRA)	Declined – failed to respond
	Society for Ambulatory Anesthesia (SAMBA)	Declined – failed to respond
	Society for Neuroscience in Anesthesiology and Critical Care	Declined – failed to respond
Critical Care	Critical Care Societies Collaborative	Declined – failed to respond
Dentistry & Oral Medicine	Academy of General Dentistry (AGD)	Declined – provided interview referrals
	American Dental Association (ADA)	Declined – failed to respond
Dermatology	American Academy of Dermatology (AAD)	Agreed
	American Osteopathic College of Dermatology (AOCD)	Declined – not interested
Endocrinology	The Endocrine Society (ENDO)	Agreed
	Pediatric Endocrine Society	Agreed
Gastroenterology	American Gastroenterological Association (AGA)	Declined – failed to respond
	Obesity Medicine Association (OMA)	Declined – did not have anyone to contribute to research
Hematology	American Society of Hematology (ASH)	Declined – does not distribute surveys
Infectious Disease	American Academy of HIV Medicine (AAHIVM)	Declined – failed to respond
Medicine	American Medical Association (AMA)	Declined – failed to respond

Naturopathy	American Association of Naturopathic Physicians (AANP)	Agreed
	The Oncology Association of Naturopathic Physicians (OncANP)	Agreed
Nephrology	American College of Clinical Pharmacists: Nephrology Practice Network	Agreed
	American Society of Nephrology	Declined – provided interview referrals
Nutrition	American Society for Parenteral and Enteral Nutrition (ASPEN)	Declined – provided interview referrals
Obstetrics and Gynecology	American Gynecological and Obstetrical Society (AGOS)	Declined – failed to respond
	Nurse Practitioners in Women’s Health	Agreed
Ophthalmology	American Academy of Ophthalmology (AAO)	Agreed
Otolaryngology	American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)	Declined – survey not approved
Pain Management	American Academy of Pain Medicine (AAPM)	Declined – survey not approved
	American Academy of Physical Medicine and Rehabilitation	Declined – failed to respond
Pediatrics and Neonatology	American Academy of Pediatrics (AAP)	Agreed
Primary Care	American College of Physicians (ACP)	Declined – failed to respond
Psychiatry	American Academy of Clinical Psychiatrists	Declined – failed to respond
	American Association for Geriatric Psychiatry	Declined – failed to respond
Rheumatology	American College of Rheumatology (ACR)	Agreed

Surgery	Ambulatory Surgery Center Association (ASCA)	Agreed
	American Academy of Orthopaedic Surgeons (AAOS)	Declined – no interest in participation from members
	American Association of Hip and Knee Surgeons (AAHKS)	Declined – only send surveys from members
	American College of Surgeons (ACS)	Agreed
	American Society for Metabolic and Bariatric Surgery (AMBS)	Declined – only send surveys from members
	The Association of Bone and Joint Surgeons	Declined – failed to respond
	Physician Assistants in Orthopaedic Surgery	Declined – failed to respond
	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	Declined – failed to respond
	Society of Gynecologic Surgeons (SGS)	Declined – policy limits number of surveys per year and do not have a method to identify if any of the SGS members are using ipamorelin
Toxicology	American Academy of Environmental Medicine (AAEM)	Declined – failed to respond
Urology	Sexual Medicine Society of North America (SMSNA)	Agreed

<sup>a</sup>Associations that declined in Year 1 were not contacted in Year 2.