Local Anesthetic Adjuvants Providing the Longest Duration of Analgesia for Single-Injection Peripheral Nerve Blocks in Orthopedic Surgery: A Literature Review

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Inadequate pain relief after surgery may delay surgical recovery, decrease patient satisfaction, increase length of stay, raise the risk of hospital readmissions, and increase overall healthcare costs. One way to decrease postoperative pain for patients undergoing orthopedic surgery is through the use of peripheral nerve blocks. Anesthesia providers can add many adjuvants to local anesthetics to improve quality and prolong duration of analgesia. The purpose of this literature review is to evaluate local anesthetic adjuvants to peripheral nerve blocks. A review of published studies using PubMed, MEDLINE, and Cochrane search engines was performed using predefined data fields. Based on this literature review, recommendations for practice are provided.

Keywords: Anesthetic adjuvant, analgesia, local anesthetics, nerve block, regional anesthesia.

More than 70 million patients in the United States undergo surgery each year. Unfortunately, up to 75% of these patients experience acute postoperative pain. Inadequate management of surgical pain can delay surgical recovery, decrease patient satisfaction, and increase length of hospitalization, readmission rates, and overall healthcare costs.1,2

In 2012, the American Society of Anesthesiologists (ASA) released an update to its Practice Guidelines for Acute Pain Management in the Perioperative Setting.3 In this report, the ASA strongly recommends use of a multimodal approach to pain management whenever possible. This includes the administration of 2 or more drugs that act by a different mechanism to provide analgesia. Additionally, the ASA strongly recommends that regional blockade with local anesthetics be considered as part of the multimodal approach for pain management.

Peripheral nerve blocks (PNBs) using local anesthetics are commonly administered to control postoperative pain in patients undergoing orthopedic surgery. They are simple and effective in providing postoperative analgesia and have fewer side effects than do conventional systemic opioid analgesics.4 Unfortunately, their duration may not be adequate to provide analgesia sufficient to ensure a seamless transition to oral analgesics.5

Anesthesia providers have addressed this limitation by adding adjunctive drugs to local anesthetics to prolong duration and enhance quality of regional blocks. However, no known single source identifies those adjuvants that are best at prolonging the duration of single-injection PNBs and extending the time to first analgesia for patients undergoing orthopedic surgery. Currently, no published recommendations or practice guidelines exist for practitioners who wish to use adjuvants for regional anesthesia. A literature review was performed to determine which adjuvants used in conjunction with local anesthetics provide the longest duration of analgesia for patients undergoing upper and lower extremity orthopedic procedures. Based on this review, recommendations for practice and future research are provided.

Methods
A literature review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature was searched for relevant studies up to June 2014 that examined the use of adjuvants with local anesthetics in PNBs for upper and lower extremity procedures. PubMed, MEDLINE, and Cochrane databases were searched using the following keywords alone and in combination: regional anesthesia, peripheral nerve block, adjuvants, local anesthetics, and analgesia. Inclusion criteria for this review included PNBs, orthopedic surgery, and upper and lower extremity surgeries. Exclusion criteria included studies involving neuraxial anesthesia, pediatric patients (age < 18 years), intravenous (IV) regional anesthesia, and continuous local anesthetic infusions.
The search was performed without language restriction. Duplicate articles were excluded. References from the articles reviewed were also searched for additional relevant articles. Results of the search are displayed in the Figure.

Results
The search resulted in 61 potential articles based on the combination of the keyword search. Abstracts of the articles were evaluated for eligibility based on the inclusion and exclusion criteria. Of these, 41 articles did not meet the criteria, with the reasons displayed in the Figure. References of the 20 remaining articles were then searched for additional relevant articles from their reference lists. This search yielded an additional 9 relevant articles for a total of 29 articles. Of these 29 articles, 3 were review articles, 4 were meta-analyses, and 22 were randomized controlled trials (RCTs). All clinical studies selected for review were then organized by type of adjuvant.

- **Epinephrine.** Epinephrine is an α- and β-agonist that causes vasoconstriction and delays diffusion of local anesthetic away from the site of injection. This action delays entry of local anesthetic into plasma, subsequently reducing the time of peak plasma concentration of local anesthetic and the risk of local anesthetic-induced systemic toxicity. In turn, this provides a longer duration and a greater intensity of effect for many local anesthetics. Although the vasoconstrictor effect of epinephrine can prolong the action of local anesthetic, it can also decrease blood supply to the neural tissue to a threshold associated with nerve damage. Therefore, epinephrine use is controversial and possibly detrimental for patients with diabetes or compromised vascular integrity that are at high risk of neurotoxicity and nerve damage.

There is limited and conflicting evidence to demonstrate that the addition of epinephrine is associated with increases in duration of analgesia for long-acting local anesthetics, particularly ropivacaine. Hickey et al found no difference in peak plasma concentrations of
ropivacaine when subjects received a PNB with epinephrine. Weber et al\textsuperscript{13} found similar results and concluded that epinephrine does not statistically extend the average duration of analgesia. They attributed this finding to the intrinsic vasoconstrictor property of ropivacaine.

Recently, the use of ultrasound has allowed anesthesia providers to visualize vascular structures and guide placement of local anesthetic during a PNB. When an in-plane technique is used, the chance of intravascular injection may be reduced. Because of the potential risks of neurotoxicity and limited evidence of prolonged analgesia with epinephrine, anesthesia providers may choose not to use epinephrine as an adjuvant with long-acting local anesthetics. However, providers may still wish to continue using epinephrine as an intravascular marker to detect any inadvertent intravascular injection during nerve block placement, especially when an out-of-plane ultrasound technique or a blind peripheral nerve stimulation technique is used. When these techniques are used, dilution of epinephrine to 2.5 μg/mL can be an effective marker for intravascular injection and is associated with few side effects. It has been suggested that this dose may also transiently increase peripheral nerve blood flow, presumably by β-adrenergic effects.\textsuperscript{10}

- **Clonidine.** Clonidine is a pure α\textsubscript{2}-agonist that produces hemodynamic and analgesic effects. Because α\textsubscript{2}-receptors are not present on the axon of the normal peripheral nerve, the mechanism of analgesia of clonidine as an adjuvant is not completely understood. Some researchers have suggested the mechanism may be related to the drug's ability to block cation current through hyperpolarization-activated cyclic nucleotide-gated channels that subsequently prevent neurons from generating action potentials.\textsuperscript{14,16} It has been reported that minor degrees of nerve conduction blockade at both local and central sites are produced with high concentrations of clonidine. Because multiple sites of action have been identified for clonidine, additional research is needed to establish the exact site or sites associated with observed enhanced duration of action with local anesthetics.\textsuperscript{14,16}

Researchers have reported mixed results in demonstrating clonidine's effect on analgesia when used as an adjuvant with local anesthetics. McCartney et al\textsuperscript{17} conducted a meta-analysis using 27 double-blind RCTs to determine analgesic benefit of clonidine in PNBs. In 15 of those studies, use of clonidine was supported, whereas in 12 studies it failed to show any benefit. These findings support use of clonidine in single-injection axillary and peribulbar nerve blocks. McCartney et al concluded that clonidine appears to improve the duration of analgesia with intermediate but not long-acting local anesthetics. Side effects such as hypotension and bradycardia were dose dependent and limited when doses were kept to 150 μg or less.

Culebras et al\textsuperscript{18} found that clonidine, 150 μg, added to 0.5% bupivacaine does not prolong analgesia in inter-scalene blocks (ISBs) but produces a significant decrease in mean arterial pressure and heart rate. They concluded that clonidine does not provide an advantage when combined with long-acting local anesthetics for PNBs and may be associated with significant adverse effects.

Popping et al\textsuperscript{19} conducted a meta-analysis of 20 RCTs to determine if differing doses of clonidine (30-300 μg) in PNBs produce varying degrees of analgesia and side effects. They were not able to determine the most efficacious analgesic dose of clonidine associated with the fewest side effects. However, they did conclude that 150 μg of clonidine increases postoperative analgesia of long-acting anesthetics by more than 2 hours. Furthermore, when clonidine is added to ropivacaine, motor blockade has a shorter duration than when added to bupivacaine. This finding may be useful because it implies that clonidine may provide long-lasting analgesia without prolonging the duration of motor blockade. The authors also reported a similar incidence of hypotension, bradycardia, and sedation to what was reported in previous studies.\textsuperscript{17,18} Clonidine is not approved by the Food and Drug Administration (FDA) for perineural use.\textsuperscript{11}

- **Dexamethasone.** Dexamethasone is a long-acting glucocorticosteroid used predominately for its anti-inflammatory and antiemetic actions. Although its mechanism of action as an adjuvant is not completely understood, it is known that as a glucocorticoid it exhibits anti-inflammatory and analgesic effects through inhibition of phospholipase A\textsubscript{2} and activation of glucocorticoid receptors. It has been demonstrated that locally administered corticosteroids inhibit signal transmission of nociceptive C-fibers, decrease ectopic neuronal discharge, and decrease the release of local inflammatory mediators.\textsuperscript{20,21}

Recent studies have demonstrated an increased duration of analgesia when dexamethasone is used with local anesthetics for PNBs. Choi et al\textsuperscript{22} conducted a meta-analysis of 9 RCTs to evaluate the duration of analgesia and motor blockade, 72-hour opioid consumption, and incidence of complications. They concluded that dexamethasone prolongs the mean analgesic duration for long-acting local anesthetics by 576 minutes and prolongs mean motor blockade by 438 minutes (Table). However, they found no statistically significant difference in opioid consumption. Although there was no reported dexamethasone-induced neuronal damage, this may be related to the small number of patients receiving dexamethasone (n = 393).

Two studies examined the effect of dexamethasone on lower extremity PNBs. Fredrickson et al\textsuperscript{23} demonstrated that patients who received 8 mg of dexamethasone in sciatic blocks reported less pain at 24 hours. However, they did not find improvements in analgesia scores for patients who received ankle blocks. Rahangdale et al\textsuperscript{24} compared the effect of IV dexamethasone and perineural
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<th>Source</th>
<th>Type of block</th>
<th>Type of local anesthetic</th>
<th>N</th>
<th>Dose of dexamethasone, mg</th>
<th>Jadad scale</th>
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| Tandoc et al, 4 2011     | Interscalene  | 0.5% Bupivacaine and epinephrine, 5 μg/mL | 90 | 4                        | 5           | Time to first pain score > 3 | 4 mg = 21.6 h
8 mg = 25.2 h
Placebo = 13.3 h (P < .05) |
| Fredrickson et al, 23 2013 | Sciatic; ankle | 0.5% Bupivacaine         | 126 | 8                       | 3           | Report of pain at 24 h | Sciatic block dexamethasone = 13% (P = .01)
Sciatic block placebo = 47%
No effect on ankle block (P = .85) |
| Desmet et al, 25 2013    | Interscalene  | 0.5% Ropivacaine         | 150 | 10                      | 5           | Time to first pain medication | ISB with dexamethasone, 10 mg IV = 1,275 min (P < .0001)
ISB with dexamethasone, 10 mg perineural = 1,405 min (P < .0001)
No dexamethasone = 757 min
No difference in time to first analgesia request |
| Movafegh et al, 28 2006  | Axillary      | 1.5% Lidocaine           | 60  | 8                       | 4           | Duration of sensory and motor blockade | Sensory block with dexamethasone = 242 ± 76 min (P < .01)
Sensory block without dexamethasone = 98 min
Motor block with dexamethasone = 310 ± 817 min (P < .01)
Motor block without dexamethasone = 130 min
Doubled duration of sensory and motor block |
| Rahangdale et al, 24 2014 | Sciatic       | 0.5% Bupivacaine with 3.3 μg/mL | 78  | 8                       | 4           | Quality of recovery; analgesia duration and time to first toe movement (TFTM) | Analgesia duration difference with perineural dexamethasone = 13 h
Analgesia duration difference with IV dexamethasone = 8 h
Analgesia duration difference perineural and IV = 6 h
TFTM difference perineural dexamethasone = 12 h
TFTM difference IV dexamethasone = 7 h (P = .008)
TFTM difference perineural and IV = 5 h
No difference in quality of recovery |
| Vieira et al, 27 2010    | Interscalene  | 0.5% Bupivacaine with clonidine, 75 μg, and epinephrine, 5 μg/mL | 88  | 8                       | 5           | Sensory analgesia | Sensory block with dexamethasone = 1,457 min (P < .0001)
Sensory block without dexamethasone = 833 min
Motor block with dexamethasone = 1,347 min (P < .0001)
Motor blockade without dexamethasone = 827 min (P < .0001)
24-h VAS score: 3.0 vs 6.0 (P < .0001)
No difference at 48 h |
| Cummings et al, 30 2011  | Interscalene  | 0.5% Ropivacaine; 0.5% bupivacaine | 218 | 8                       | 5           | Time to first analgesic request | Ropivacaine with dexamethasone = 22.2 h (P < .001)
Ropivacaine plain = 11.8 h
Bupivacaine with dexamethasone = 22.4 h (P < .001) |
| Parrington et al, 29 2010 | Supraclavicular | 1.5% Mepivacaine         | 45  | 8                       | 5           | Time to first report of pain | 8 mg dexamethasone = 332 min
No dexamethasone = 228 min (P < .008)
No difference in onset time or complication rates |

Table. Clinical Outcomes of Dexamethasone as Adjuvant
Dexmedetomidine on sciatic nerve blocks. Although perineural dexmedetomidine prolonged the duration of analgesia and motor blockade compared with the control group, there was no difference reported in pain scores or opioid consumption between the groups. Both Fredrickson et al and Rahangdale et al concluded that the addition of dexmedetomidine to long-acting local anesthetics for lower extremity PNBs provided only marginal increases in the duration of analgesia and may not be beneficial when used for lower extremity cases. It is important to note that dexmedetomidine is not approved by the FDA for perineural administration. 22

An interesting study by Desmet et al compared IV and perineural administration of dexamethasone. They found that analgesia associated with an ISB without dexamethasone lasted only 757 minutes, whereas dexamethasone administered either systematically or perineurally lasted 1,275 and 1,405 minutes, respectively, and there was no statistical difference between these 2 groups. Similar results were reported by Rahangdale and colleagues24 that compared IV and perineural dexamethasone on analgesic duration associated with lower extremity blocks. These studies raise important questions about the site or sites of action of dexamethasone and whether its regional anesthesia–enhancing properties could be achieved simply by administering dexamethasone IV, a route currently approved by the FDA.

Preservative components found in pharmaceuticals, particularly polyethylene glycol, have been linked to possible neurotoxic sequelae. 11 This has caused some to have concern about the safety profile of dexamethasone in PNBs. In one clinical study,26 researchers found increased ropivacaine-induced neurotoxicity in the rat model when dexamethasone was added to the local anesthetic. However, no study3,22,23,25,27–30 included in this literature review reported neuronal damage in humans receiving dexamethasone. Another concern associated with dexamethasone is potential transient increases in blood glucose, with the potential for subsequent wound infection. Desmet et al35 reported increases in blood glucose concentration of 3.8 mg/dL (P = .026) that were not clinically significant because no patients developed hyperglycemia. Furthermore, patients who received dexamethasone in PNBs were followed up for 6 months after surgery, and none exhibited signs of wound infection.

Dexmedetomidine. Dexmedetomidine is a lipophilic α2-agonist. It has a high affinity for α2-receptors and is 8 times more selective for α2- than α1-receptors (1620:1) than clonidine is (200:1). 11,31 This increase in selectivity and agonism of α2-receptors intensifies the sedative and analgesic effects of dexmedetomidine and is associated with hypotension and bradycardia. Although its mechanism of action in PNBs remains unclear, it is hypothesized that dexmedetomidine produces analgesia by blocking the hyperpolarization-activated cation current in the peripheral nerve. This prevents an action potential from generating and renders the nerve refractory to stimulation.14,15

There is little published about the use of dexmedetomidine in PNBs. Fritsch et al32 investigated the use of dexmedetomidine at 150 μg as well as the associated duration of analgesia that local anesthetics provided in ISBs and its safety. They concluded that dexmedetomidine (150 μg) hastened onset time of sensory and motor blockade, extended mean duration of analgesia by 240 minutes, and decreased pain scores for the first 24 hours after surgery. Although the authors found no differences in plasma levels of ropivacaine and dexmedetomidine during the intraoperative period, there was an increased incidence of hypotension (P = .004) and bradycardia (P = .01) during the perioperative period that was not associated with hemodynamic instability or increased use of vasopressors. No differences in levels of patient sedation, adverse advents, or neurologic sequelae were reported.

Marhofer et al33 investigated whether dexmedetomidine, 20 μg, administered systemically or in an ulnar nerve block prolonged the duration of analgesia. They concluded that dexmedetomidine in ulnar nerve blocks prolonged sensory and motor blockade by 205 and 248 minutes, respectively. Interestingly, sensory blockade and motor blockade were also clinically prolonged after IV administration of 20 μg of dexmedetomidine by 45 and 90 minutes, respectively. No hemodynamic side effects were noted in this study. This result raises questions about the mechanism of action of dexmedetomidine as an adjuvant.

A recent meta-analysis by Abdallah and Brull24 reviewed 4 studies of upper extremity PNB. Data from these RCTs demonstrated that perineural dexmedetomidine prolonged the time to first analgesia and prolonged the mean duration of motor blockade by 268 minutes (P = .04) and the duration of sensory block by 284 minutes (P = .05). The authors also report an increased incidence of bradycardia (P = .03) among patients who received dexmedetomidine in PNBs. Unfortunately, a wide range of doses (30 μg to 100 μg) was used. Others have suggested that a meta-regression of the data may have been helpful in determining if the duration of analgesia and any side effects are dose dependent.35

It is important to note that dexmedetomidine, like dexamethasone and clonidine, is not approved by the FDA for perineural use. However, peer-reviewed publications have demonstrated its efficacy in prolonging analgesia in PNBs.32–34 Side effects include bradycardia, hypotension, and sedation.32,33 Further research is needed to establish the most effective dose associated with the fewest side effects.

Buprenorphine. Buprenorphine is a highly lipophilic, partial μ-opioid receptor agonist with analgesic
properties. It is postulated that μ-receptors are located on peripheral nerve endings, and because of its high lipophilic properties, buprenorphine is more likely to access these receptors.36,37 When used as an adjuvant, buprenorphine stimulates these peripheral selectivity opioid receptors, produces analgesia, and dramatically increases the duration of action of local anesthetics in PNBs. Candido et al38 studied the effect of buprenorphine in upper extremity blocks. They concluded that buprenorphine extended the length of analgesia by 12 hours. Candido et al39 further examined whether the prolongation of analgesia was peripherally mediated. They concluded that the duration of analgesia was twice as long in the axillary group (15.7 hours) compared with intramuscular (IM) group (5.9 hours). Behr et al36 conducted a similar study and found that buprenorphine at 150 μg prolonged the mean duration of sensory blockade and extended the length of analgesia when given either IM or in an ISB. The duration of sensory blockade and analgesia, however, was more prolonged in patients who received buprenorphine in an ISB (856.1 and 1049.7 minutes) compared with those in the IM group (693.6 and 820.3 minutes). They also reported that none of the patients experienced opioid-related side effects. These studies36,38,39 demonstrated that buprenorphine is effective in upper extremity PNB. However, it is unclear if opioid receptors are present in lower extremity nerve endings. Candido et al40 studied whether buprenorphine was effective in lower extremity blocks, specifically the sciatic nerve block. They found that patients who received buprenorphine in sciatic nerve blocks reported lower pain scores up to 36 hours after surgery, had 6 hours longer duration of analgesia, and used fewer opioids for 24 hours compared with those who received IM administration. Although buprenorphine may enhance and prolong the analgesic effect for sciatic nerve blocks, it may not be as effective as it is in brachial plexus nerve blocks.

Although buprenorphine is associated with prolonged analgesia, some patients reported experiencing side effects similar to those of other opioids, including nausea, vomiting, pruritus, respiratory depression, and urinary retention.37 Candido et al40 reported that patients receiving buprenorphine in sciatic blocks had a higher incidence of nausea, vomiting, and pruritus than did the control group. The incidence did not reach statistical significance. Despite these side effects, patients reported they were satisfied with their anesthesia experience and pain control. Others36 have also reported that patients who have upper extremity blocks with buprenorphine experienced postoperative nausea and vomiting and respiratory depression. No neural damage has been reported.11 Like dexmedetomidine and dexamethasone, buprenorphine is not approved by the FDA for neuraxial or peripheral nerve administration.

- **Tramadol.** Tramadol is a μ-agonist opioid that inhibits reuptake of norepinephrine and serotonin. These neurotransmitters are involved in descending inhibitory pain pathways associated with pain relief.31 When used in PNBs, tramadol has been demonstrated to increase the duration of analgesia.41 Currently, the FDA does not approve tramadol for periurebral administration. Therefore, published research evaluating tramadol in PNBs is limited and has been conducted outside the United States. Alemanno et al41 concluded that patients who received tramadol (1.5 mg/kg) either IM or in an ISB experienced an increased duration of analgesia (4 and 7 hours, respectively) compared with those who received only levobupivacaine. However, 2 studies42,43 reported that no benefit was found when tramadol was used as an adjuvant in axillary blocks.

In summary, findings on the use of tramadol in PNBs are equivocal. Furthermore, tramadol is available only as an oral medication in the United States. Therefore, there are no guidelines for its use as an adjuvant in PNBs in clinical practice.

- **Neostigmine.** Neostigmine is an anticholinesterase drug that inhibits hydrolysis of acetylcholine by competing for attachment at the esteratic site on acetylcholinesterase. It is postulated that analgesic effects of neostigmine may be due to its action on muscarinic receptors identified on peripheral nerves.

The use of neostigmine in PNBs has not been associated with improvements in postoperative analgesia. Bouaziz et al44 found that neostigmine at 500 μg had no effect on sensory and motor blockade but was associated with a relatively high incidence of side effects. Other researchers have added neostigmine (500 μg) to lidocaine in axillary blocks and concluded that neostigmine does not increase duration of postoperative analgesia and offers little benefit.45

**Discussion**

The results of this review of the literature are mixed. Several studies demonstrated a prolonged duration of analgesia associated with PNBs when adjuvants were added to local anesthetics. However, the effect was not consistently demonstrated, and there appeared to be a difference when the adjuvant was added to upper vs lower extremity blocks.

Epinephrine is the only adjuvant extensively researched and frequently added to local anesthetics for PNBs.8 When epinephrine was added to ropivacaine for PNBs, there were no statistically significant differences in the length of analgesia reported.12,13 Furthermore, its use is controversial in patients with compromised vascular integrity. Thus, many practitioners only use it in small concentrations of 2.5 μg/mL as an intravascular marker.

Clinical trials36-39 have demonstrated that buprenorphine can extend the duration of analgesia up to 700
minutes for upper extremity nerve blocks. Disadvantages include undesirable side effects commonly associated with all opioids. These are likely related to systemic uptake and associated central nervous system depressant effects. These side effects have been associated with an increased length of a patient’s hospital stay, increased amount of medications to treat these side effects, and an increased overall healthcare cost.

Clonidine and dexmedetomidine prolong the duration of analgesia by 123 and 345 minutes, respectively. In addition to prolonging analgesia, clonidine is associated with sedation, hypotension, and bradycardia. This is likely due to systemic absorption of the medication and stimulation of the α₂-receptors. Although an optimal dose has not been established for dexmedetomidine, clonidine up to 150 μg has been demonstrated to prolong analgesia with the fewest side effects.

Dexamethasone is a relatively new adjuvant used with local anesthetics for perineural administration. Research has demonstrated that dexamethasone at 4 mg can extend the duration of analgesia by 10 hours for upper extremity PNBs. However, too few clinical trials have been performed to detect small increases in complication rates, particularly nerve damage associated with dexamethasone. This is important because subclinical doses in animal studies have demonstrated dexamethasone to be possibly neurotoxic. Given these concerns, researchers have recommended further clinical trials to evaluate the use of dexamethasone as an adjuvant for PNBs.

Two studies concluded that there were no clinical differences in duration of analgesia between IV dexamethasone and perineural dexamethasone. Based on these results, it is possible there is some degree of systemic absorption of dexamethasone that contributes to the extended duration of analgesia. It is important to note that mechanism of action is not clearly understood. Other adjuvants in this literature review have demonstrated that some type of systemic absorption contributes to their respective undesired side effect. Therefore, more research is needed to elucidate the mechanism by which dexamethasone administered systemically or perineurally prolongs duration of analgesia associated with PNBs.

The reviewed literature has shown an increase in duration of analgesia when adjuvants are used in upper extremity blocks. However, when epinephrine, buprenorphine, or dexamethasone is used in PNBs for lower extremity blocks, specifically sciatic blocks, the length of analgesia is shorter compared with upper extremity blocks. Although no studies were found that used an adjuvant in femoral nerve blocks, further research is needed before concluding that an adjuvant does not prolong analgesia for lower extremity blocks.

With the exception of epinephrine, the inclusion of these drugs as adjuvants in PNBs has not been approved by the FDA and its use is considered off-label. None of the research reported any occurrence of neurotoxicity or nerve damage when used in PNBs. However, isolated nerve damage in vitro has been reported when nerve tissue is exposed to clonidine, buprenorphine, midazolam, tramadol, and dexamethasone. Based on this finding, one might suspect that patients with peripheral nerve compromise or alterations in perineural microvasculature could be at higher risk of adjuvant-associated perineural complications. Therefore, anesthesia providers must weigh the risks and benefits of each adjuvant before using them with local anesthetics.

A recent report by the Institute of Medicine estimates that this nation spends upwards of $635 billion for treating pain, exceeding the economic costs of heart disease cancer, and for treating diabetes. Although opioids have long been the mainstay of postsurgical pain control, recent evidence has supported use of a multimodal approach to contain healthcare costs. One study found patients who received an interscalene block undergoing arthroscopic shoulder surgery had reduced total costs, including cost per minute of anesthesia, decreased operating room emergence time, improved anesthesia-related workflow, decreased time in the postanesthesia care unit, and decreased overall opioid consumption. It has been determined that opioid consumption and its related adverse side effects increase length of stay by 0.6 days, increase additional costs $840 per surgical patient, and increase the likelihood for readmission. Furthermore, a large-scale analysis from 380 US hospitals found that opioid-related adverse events were associated with a $4,707 increase in hospital costs and a 3.3-day increase in the average length of stay in the hospital. By finding ways to increase the quality and duration of postoperative analgesia, patient satisfaction can be enhanced and overall healthcare costs decreased.

Another interesting finding is that several studies reported an increase in duration of analgesia not consistently associated with a decrease in opioid consumption. More research is needed to explain the differences in those clinical outcomes. Of the adjuvants reviewed, dexamethasone was consistently reported to increase the duration of analgesia when used with PNBs. Whether this effect is due to its perineural or systemic action or some combination of the two needs to be determined. Future recommendations about the most effective route and dose would be informed by such research findings.

Conclusion
This literature review examined adjuvants that are used in conjunction with local anesthetics in PNBs. Epinephrine remains the most extensively used adjuvant with local anesthetics and should continue to be used as an intra-vascular marker. Dexamethasone appears to extend the length of analgesia the most with the fewest reported

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side effects despite not being FDA approved as an adjuvant for PNBs. Published results of clinical trials using dexamethasone as an adjuvant are generally positive but inconsistent, and the best route and dose have not yet been identified. Several areas for future research have been identified.

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