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Regional anesthesia in the emergency department: A review of key pharmacotherapeutic considerations

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ABSTRACT

Introduction: Opioid-associated risks and the opioid epidemic have accelerated interest in multimodal analgesia in the emergency department (ED). Regional anesthesia offers a targeted approach with reduced risk of systemic adverse effects and is increasingly used under ultrasound guidance.
Objective: This concise, evidence-based review explores pharmacological principles of local anesthetics describing key aspects of structure-activity relationship, providing context for agent selection. Additional considerations include dosing strategy, adjunctive medications, potential risks, toxicity mitigation, and operationalization of regional anesthesia in the ED.
Discussion: Regional anesthesia is used with increased frequency in the ED. Pharmacologic properties of commonly used local anesthetics and adjunctive agents determine their advantages and limitations as well as place in therapy. There are a variety of anesthetic agents, including amides (e.g., lidocaine, bupivacaine, ropivacaine, levobupivacaine) and esters (e.g., articaine, chloroprocaine) with differences in onset, duration, and toxicity profiles that influence agent selection in ED patient populations. Adjuncts such as epinephrine, dexamethasone, and alpha-2 agonists may extend nerve block duration or improve analgesia but introduce safety and operational considerations. Recognition of local anesthetic systemic toxicity (LAST) remains central to safe practice, underscoring the importance of weight-based dosing, ultrasound guidance, monitoring, and immediate access to lipid emulsion therapy. Systems-based approaches such as order sets, pharmacist involvement, and structured training support consistent and safe application of regional anesthesia in the ED setting.
Conclusions: Safe integration of regional anesthesia in the ED requires pharmacologic literacy, standardized systems, and multidisciplinary support to optimize analgesia while minimizing risk.

1. Introduction

Providing appropriate analgesia is an integral component of care in the emergency department (ED). While opioid medications have been a mainstay of pain management, this medication class possesses many adverse effects, including sedation, respiratory depression, constipation, physical dependence, and the risk of developing a life-threatening opioid use disorder [1-6]. In addition to the recent opioid epidemic, these risks have driven an increased interest in multimodal pain control that reduces opioid exposure while maintaining effective pain control [7,8].

Regional anesthesia (often referred to as "nerve blocks") is a component of multimodal pain control that involves the injection of a local anesthetic near a specific nerve or collection of nerves [5,9-11]. The effectiveness and safety of regional anesthesia is well established in the anesthesia literature. Compared with systemic analgesia, regional anesthesia has demonstrated effective analgesia and improved patient satisfaction and post-surgical functional outcomes, while also decreasing the risk of delirium, opioid requirement, length of stay, and total cost [12-26]. In patients with hip and rib fractures, regional anesthesia has also been associated with reduced mortality [27,28].

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Recently, regional anesthesia has been used outside of the surgical setting, including the ED, particularly in concert with ultrasound guidance [2,27,29-32]. In the ED setting, regional anesthesia provides rapid, safe, and effective analgesia across a wide range of clinical indications including fracture management, procedural analgesia, and other acute or chronic pain conditions [19-21,28,31,33-50]. The American College of Emergency Physicians (ACEP) recognizes ultrasound-guided nerve blocks as a core application of emergency ultrasound for acute pain management, and ultrasound-guided procedural skills—including regional anesthesia and specific peripheral nerve block techniques—are incorporated into the procedural content domains used by the American Board of Emergency Medicine (ABEM) for emergency physician training and certification [51,52].

The translation of these professional standards into routine clinical practice requires more than technical proficiency alone. Emergency clinicians must decisively select appropriate local anesthetic agents, calculate weight-based dosing across heterogeneous patient populations, determine when adjunctive agents may provide benefit or pose risk, and promptly recognize and manage rare but potentially life-threatening complications such as local anesthetic systemic toxicity (LAST). Standardized education; structured ultrasound-guided nerve block training; familiarity with pharmacokinetic principles relevant to emergency care; and systems-based safeguards such as dosing tools, order sets, and immediate access to lipid emulsion therapy are essential to safe implementation. Accordingly, this review focuses on the pharmacotherapeutic considerations most relevant to emergency clinicians and provides a practical framework to support the integration of regional anesthesia into contemporary ED practice.

2. Local anesthetics

2.1. Pharmacology and pharmacokinetics

Local anesthetics exert their effect by blocking voltage-gated sodium (Na_v) channels along neuronal membranes, preventing sodium influx and thereby inhibiting action potential initiation and propagation. Because the Na_v channel's voltage-dependent activation site is located on the intracellular surface of the neuronal membrane, local anesthetics must access the interior of the neuron to exert an effect, for which the degree of ionization, tissue pH, and onset of action are clinically important determinants of efficacy [53].

Local anesthetic molecules share three key structural components: lipophilic aromatic group, an intermediary linkage (either ester or amide), and a terminal tertiary amine (Figure 1) [54]. As with most drugs, local anesthetics are weak bases and chemically stable as hydrochloride salts. While this contributes to pharmaceutical stability, it also lowers the solution's pH to approximately 4-6 (or 3-5 when epinephrine is added) [55,56]. The resulting acidity often produces a brief burning sensation during tissue infiltration. Each agent has a characteristic pKa that determines the proportion of drug that is ionized at physiologic pH [54]. In acidic tissue environments (e.g., infection or ischemia), the equilibrium is shifted to favor the ionized form, and less active drug is available to diffuse across cellular membranes (Figure 2). Consequently, the pKa is a key determinant of onset, with higher pKa values relative to tissue pH associated with longer time to onset. Although receptor binding ultimately requires the ionized form intracellularly, reduced membrane penetration in acidic tissue environments predominates as the limiting factor leading to diminished anesthetic effectiveness.

Another important pharmacologic characteristic is lipophilicity, required to diffuse intracellularly to the Na_v channel binding site [54,57]. Agents with higher lipophilicity are generally more potent, but also more prone to toxicity. The logD reflects a drug's tendency to penetrate lipid membranes at a given pH (Table 1) [58]. Lipophilicity also confers the ability for local anesthetics to diffuse into cardiac myocytes or across the blood-brain barrier, causing unintended cardiac or central nervous system (CNS) adverse effects, respectively. Together, pKa, lipophilicity (logD), and protein binding influence clinically relevant properties such as onset, potency, and duration of action, which in turn guide agent selection for specific procedures and block types. In practice, agents with lower pKa values provide faster onset for time-sensitive procedures (e.g. laceration repair), whereas more lipophilic and highly protein-bound agents produce longer duration of anesthesia for major nerve blocks (e.g. pericapsular nerve group block for hip fracture) but may carry greater toxicity risk. Table 1 highlights

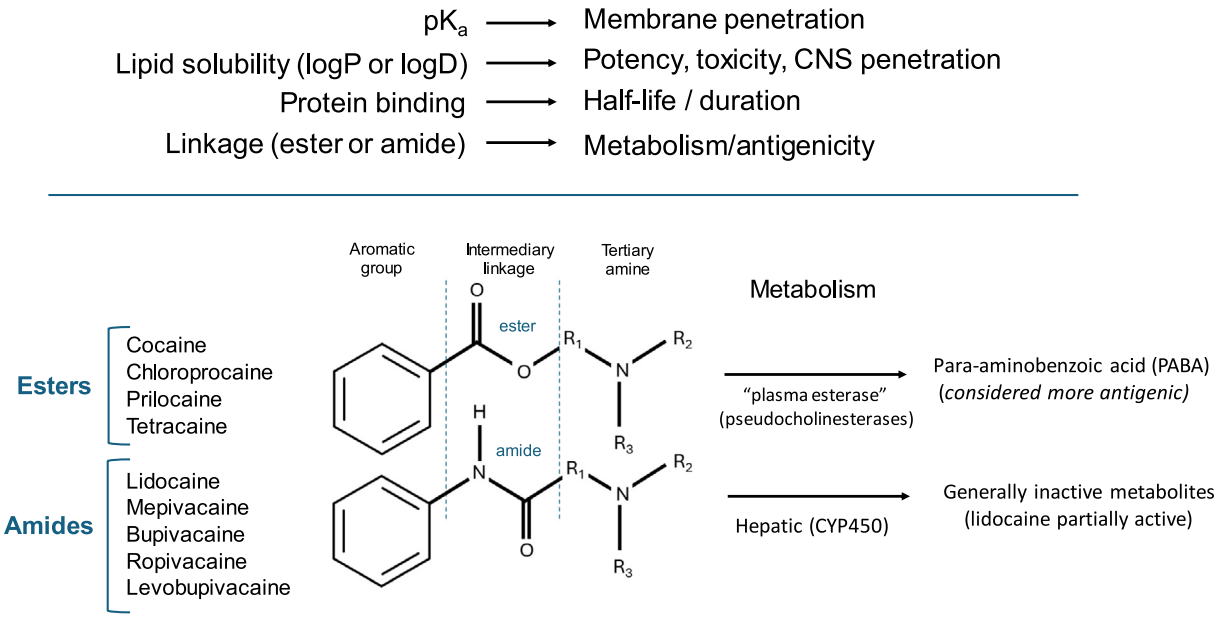

Fig. 1. Pharmacologic determinants of local anesthetics. pK_a governs ionization and membrane penetration; lipid solubility relates to potency and toxicity; protein binding influences duration; and intermediary linkage determines metabolism and potential antigenicity.

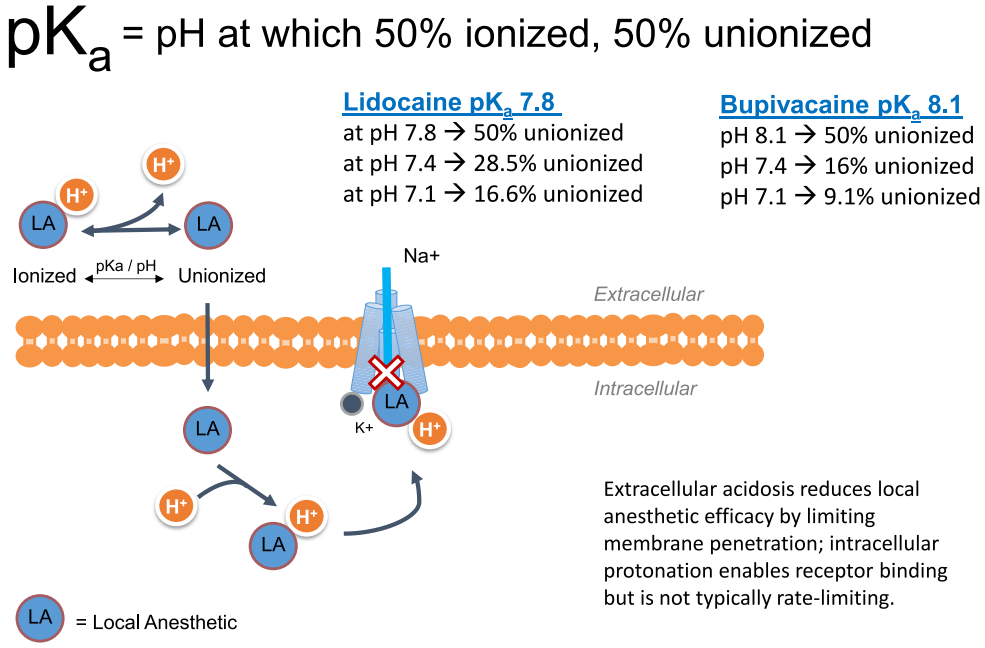

Fig. 2. Local anesthetics are weak bases that exist in equilibrium between ionized and unionized forms. The non-ionized fraction diffuses across neuronal membranes, while the ionized form binds intracellular voltage-gated sodium channels to inhibit conduction. When tissue pH falls below the drugs pK_a (e.g. infection or ischemia), the proportion of unionized drug decreases, reducing membrane penetration and clinical efficacy.

how commonly used local anesthetics vary across these properties, illustrating the relationship between pKa, lipophilicity, and expected onset and duration.

Local anesthetics are generally categorized by their intermediary linkage structure, which primarily relates to metabolic pathways. Esters are rapidly metabolized by plasma esterases, most of which form para-aminobenzoic acid (PABA). While the PABA metabolite is inactive, its high immunogenicity is thought to be responsible for hypersensitivity reactions, although true allergic reactions are rare [59,60]. Amides are metabolized hepatically, with potential accumulation in hepatic dysfunction with large repeat doses [54,61]. Local anesthetics with higher degree of protein-binding (e.g., bupivacaine) exhibit a longer duration

Table 1
Local anesthetics [54,58,152-155].

Medication	Concentration	Dose	Onset (minutes)	Duration[a]	Physiochemical properties	
					pK_a	logD[b] (pH7.4)
Esters						
Articaine	4%	20 to 136 mg (Max 7 mg/kg)	1-9	2 hours	7.8	1.7
Chloroprocaine	1%, 2%, 3%	11 mg/kg (max dose 800 mg) with epinephrine: 14 mg/kg (max 1000 mg)	6-12	60 minutes *60-90 with epi	9.1	1.15 (0.86 at 7.1)
Cocaine*	4%	3 mg/kg (topical)			8.6	1.9
Prilocaine	4%	6 mg/kg (400 mg max) (w epi 1:200K) 8 mg/kg (max 600mg) in 2 h	2	2-3 hours	7.7	1.4
Amides						
Bupivacaine	0.25%, 0.5%, 0.75%	2.5 mg/kg (max dose 175 mg) with epinephrine: 3 mg/kg (max 400 mg)	2-10 28	2-4 hours (3-8 with epinephrine)	8.1	2.6
Levobupivacaine**	0.25%, 0.5%, 0.75%	Single dose: up to 150 mg 24 hours: up to 400 mg	≤15	2-9 hours	8.1	2.8
Lidocaine	0.5%, 1%, 1.5%, 2%, 4%	4.5 mg/kg (max dose 300 mg) with epinephrine: 7 mg/kg (max dose 500 mg)	1-3	60-120 minutes (120-240 with epinephrine)	7.8	1.6
Mepivacaine	1%, 1.5%, 2%, 3%[c]	6 mg/kg (max dose 400 mg)	3-20	45-90 minutes	7.7	1.5
Ropivacaine	0.2%, 0.5%, 0.75%, 1%	3 mg/kg (max dose 300 mg)	3-20	3-15 hours	8.1	2.1
Liposomal bupivacaine	1.3%	7-20 mL (max dose 266 mg)	30-60	72-120 hours	7.8	N/A***

[a] Reported durations are typically for local blocks, and vary depending on type of regional block, which may be increased.
[b] logD greater than 0 indicates lipophilicity; > 2.0 is highly lipophilic; logD derived from pKa and logP values in PubChem database.
[c] Mepivacaine available as 1%, 1.5%, 2% in the United States; available as 3%.
* Available as topical only in United States.
** Not available in United States.
*** Once bupivacaine molecule is released from lipid matrix, follows similar chemical properties as bupivacaine.

of action at the site of administration. Lower protein-binding capability, and therefore a greater potential for toxicity, is seen in acidemia, hepatic disease, pregnancy, and infants less than 6 months of age [54,62].

2.2. Clinical application and agent selection

There are a variety of available local anesthetics (Table 1). Regional anesthesia was first documented in 1885 using cocaine; however, various undesirable effects including coronary vasospasm, sympathetic stimulation, and physical dependence led to the development of other agents [9,63]. In the ED, a local anesthetic should be selected based on the desired duration of action. A quicker recovery and shorter analgesia duration may be appropriate for shoulder, elbow, or simple fractures, while a long-bone, hip, or rib fracture or back pain may warrant longer duration of action [48,64,65]. ED clinicians should note the nuances of various agents, when an alternative may be appropriate, and how adjunctive agents mixed with the local anesthetic may enhance pharmacologic properties (Table 2). Observational data from large emergency medicine registries demonstrate that lidocaine, bupivacaine, and ropivacaine account for the vast majority of local anesthetics used in ultrasound-guided ED nerve blocks, reflecting their favorable balance of onset, duration, and safety in acute care settings [66].

Lidocaine is an amide agent commonly used in the ED, given its rapid onset of action within 1-3 minutes with an intermediate duration of action (up to 2 hours without epinephrine; Table 1). Because of its rapid onset and moderate duration, lidocaine is particularly useful for short procedural blocks in the ED, including digital blocks, superficial wound infiltration, and upper-extremity blocks used for fracture reduction or abscess drainage, where rapid analgesia and reassessment are desirable.

Longer-acting agents such as bupivacaine or ropivacaine are frequently preferred for nerve blocks used in traumatic injuries, including fascia iliaca or pericapsular nerve group (PENG) blocks for hip fracture and serratus anterior or erector spinae plane blocks for rib fractures, where sustained analgesia may reduce opioid requirements [10,27,66]. Median durations of bupivacaine and ropivacaine vary widely based on location of injection but are usually between 3 and 8 hours in superficial infiltration [55,67]. Bupivacaine's onset is reported as 2-10 minutes for more superficial blocks, but studies have demonstrated an onset between 20-30 minutes in deeper (femoral and sciatic) nerve blocks [53,55].

Levobupivacaine, the isolated S-enantiomer of bupivacaine, exhibits reduced central nervous system (CNS) and cardiotoxicity compared with racemic bupivacaine. Although not available in the United States, it demonstrates comparable efficacy with a more favorable safety profile compared to bupivacaine [68-70]. The dose and pharmacokinetic profile are similar to bupivacaine [71].

A liposomal formulation of bupivacaine provides sustained-release, extending analgesia up to 72 hours by gradually releasing the drug over time [72]. This product should never be mixed with other medications, as it may damage the lipid mechanism and provide a toxic release of bupivacaine [73]. Although perioperative studies have demonstrated potential advantages, including reduction in ED visits post-discharge, data supporting its use in the ED remain limited, and cost considerations restrict widespread adoption [74,75].

Other extended-release bupivacaine formulations, including bupivacaine–meloxicam and bupivacaine implant products, are approved in the United States but are not indicated for regional nerve blockade, being intended for postsurgical analgesia and wound implantation, respectively.

Chloroprocaine (2-chloroprocaine) is an ester compound with an excellent safety profile and ultra-short half-life (23 seconds in plasma circulation) [76]. Although this agent is historically employed in obstetrics due to its favorable safety profile in pregnancy, there may be utility in the ED setting for procedures where a very short duration and rapid neurological reassessment are desired. Chloroprocaine may also be considered in patients with a suspected amide local anesthetic allergy, as ester anesthetics undergo rapid plasma metabolism and exhibit minimal cross-reactivity with amide agents.

Prilocaine and articaine are approved for use in dental nerve blocks due to rapid onset, short-to-moderate duration of action, and favorable safety profile [77,78]. These agents are most commonly used for dental and oral nerve blocks, but their rapid onset and favorable safety profile may make them reasonable alternatives for superficial facial or oral

Table 2
Adjunct agents in peripheral nerve blocks.

Adjunctive Agent	Dose and Concentration	Impact in Care	Additional Considerations*
Epinephrine	5 mcg/mL (1:200,000)** or 10 mcg/mL (1:100,000)	Increased duration of regional analgesia by 60 minutes.	Allows for a higher dose of LA. Concern for digit ischemia in local blocks not well founded.
Sodium bicarbonate	1 mEq added to every 10 mL lidocaine or mepivacaine; 0.12 mEq added to 10 mL bupivacaine [156]	Buffering allows for quicker LA onset and reduced pain at injection site.	No commercially available products in the United States. Studies show mixed benefit. Use immediately if mixing with anesthetics due to concern for precipitation or product degradation
Dexamethasone	4-10 mg	Studies suggest maximum effect with 4-5 mg, but up to 10 mg has been used successfully. Motor/sensory block increased up to 2 hours. Analgesia increased to 4-7 hours.	Use preservative-free formulations when possible.
Clonidine	0.5 mcg/kg (max 150 mcg)	Prolongs motor and sensory block by 1.5-2h	Systemic absorption may lead to bradycardia, hypotension, and sedation.
Dexmedetomidine	0.75-12 mcg/kg (30-50 mcg maximum suggested)	Shown to extend brachial plexus block duration by 284 min. May reduce local inflammation.	Evidence on dosing limited. Bradycardia and somnolence may occur systemically; local vasoconstriction may occur (>150mcg)
Magnesium sulfate	150-200 mg	Reduces pain, nausea, and vomiting at 6 and 12h.	Generally well tolerated.
Opioids	Buprenorphine 0.1-0.3 mg	Recommended due to mixed results in peripheral blocks; buprenorphine has best evidence.	Higher rates of nausea and vomiting.

LA: local anesthetic.
* Most local anesthetic/adjunct combinations lack supportive evidence for stability and are off-label. Bedside admixtures should be used cautiously and immediately after preparation due to potential for precipitation or degradation.
** The use of ratios are no longer recommended by the Institute of Safe Medication Practices.

procedural anesthesia when available. There are limited data comparing effectiveness between specific local anesthetic agents in the ED. Table 1 includes a summary of commonly available local anesthetic formulations and pharmacological properties.

3. Combining agents

Combining different local anesthetics in a single nerve block is unnecessary and not recommended due to complexity, potential for drug incompatibility, and lack of clinical benefit [79,80]. Multiple studies have demonstrated a slightly quicker onset of action but a paradoxically lower duration of action, with no benefit in sensory or motor block quality [53,80-86]. The shorter duration of effect is thought to arise from protein displacement of competing agents, resulting in increased free plasma drug levels and thus rapid drug metabolism. Higher levels of circulating free drug also increase the risk of LAST [87].

4. Adjunctive agents

Adjunctive agents can be added to local anesthetics to enhance their pharmacologic properties, which in turn optimizes the block duration and quality of analgesia (Table 2). Extreme caution should be taken when mixing any medications in the same syringe, as such admixtures are often off-label and may carry risks of incompatibility, precipitation, or dosing error.

4.1. Epinephrine

A commonly used adjunct is epinephrine, which is added to local anesthetics for its vasoconstrictive effects, thereby reducing systemic absorption and prolonging the anesthetic effects. This allows for a higher dose of local anesthetic to be administered (note the maximum doses with and without epinephrine in Table 1). Transient sympathetic effects, including tachycardia, may occur, particularly with inadvertent intravascular absorption. Historical dogma is that epinephrine injection should be avoided in the digits, nose, and penis due to risk of ischemia; however, no evidence of necrosis has been reported [88]. Despite the Institute for Safe Medication Practice petitioning the FDA to remove epinephrine ratio-based dosing due to serious and fatal errors, ratio dosing persists in common commercial products [89]. Thus, the dose of epinephrine combined with local anesthetics commercially available is 1:100,000 or 1:200,000, equating to 10 mcg/mL or 5 mcg/mL, respectively. It is preferred to use commercially manufactured products over manually prepared admixtures, given the risk of errors and potential risk of local ischemic injury. Epinephrine is also the most studied adjunctive agent. A systematic review and meta-analysis of 70 studies (n=3644) examined epinephrine with local anesthetics for epidural, intrathecal, or locoregional anesthesia [90]. Using trial sequential analyses, it found that epinephrine extended the duration of action by 60 minutes; however, there was insufficient information to determine its impact on adverse effects. A poison center study analyzed digital injection of epinephrine auto-injectors for anaphylaxis (higher concentration and dose relative to regional anesthesia) and found that only 3% had ischemic effects documented, which were treated with a local vasodilator (e.g., topical nitroglycerin) with complete resolution of symptoms [91]. Thus, the risk of adverse effects from the addition of epinephrine to local anesthetics is likely very low.

4.2. Dexamethasone

Dexamethasone added to peripheral nerve blocks has been shown to decrease the onset and significantly increase duration of nerve blocks, while reducing post-procedure pain intensity [66,92]. Evidence indicates the most robust effect of dexamethasone is in brachial plexus blockade, where motor and sensory blockade is increased by an average of 2 hours compared to local anesthetic use alone [93,94]. The duration of analgesia has been shown to last up to 4 to 7 hours after perineural injection [95]. While intravenous administration has been studied, perineural administration is considered the standard route to limit systemic effects of dexamethasone and maximize intended local effect [96]. Dexamethasone's mechanism of action is not well understood but is thought to be related to its anti-inflammatory effects and local nociceptive C-fibers [97]. Perineural dexamethasone doses of 8-10 mg have been most frequently studied, though lower doses (4-5 mg) have been used and shown equal benefit regarding duration of sensory block and analgesia [92]. Based on animal studies, there is some concern for local neuronal cell death when dexamethasone is employed in regional blockade [98]. For this reason, it is prudent to utilize the preservative free dexamethasone phosphate (10 mg/mL) product.

4.3. Sodium bicarbonate

Sodium bicarbonate may be added to local anesthetics for two reasons. First, inflamed and infected tissues are more acidic, reducing the amount of unionized local anesthetic available to cross intracellularly and provide analgesia (Figure 2). Buffering shifts the pH, allowing for more unionized drug to be immediately available, theoretically resulting in a more rapid onset. However, studies evaluating bicarbonate alkalinization show inconsistent effects on onset. Some trials report a modest acceleration, typically 5-10 minutes earlier onset in epidural and select peripheral nerve blocks, while others demonstrate no meaningful difference depending on the local anesthetic and block location [99-103]. Although alkalinization may modestly accelerate onset in some settings, peak blood effect and overall duration generally appear unchanged across studies [104-106]. Second, local anesthetics are packaged as an acidic solution, frequently causing pain upon injection. Thus, adding sodium bicarbonate reduces local injection site pain. A 2009 meta-analysis found that in 12 studies including 1224 patients, sodium bicarbonate decreased pain on injection site by a mean of -1.17 on a visual analog scale [101]. Operationalizing buffered local anesthetics for each use is challenging given short admixture stability (often requiring immediate use after preparation) and frequent national shortages of sodium bicarbonate; thus, we suggest selective use (e.g., patients cannot tolerate local anesthetic injection or procedures requiring extensive local infiltration).

4.4. Alpha-2 adrenergic agonists

Alpha-2 adrenergic receptors are located in spinal and peripheral nerve terminals and have long served as a target for neuraxial and regional anesthesia although the exact mechanism is unclear [107]. Alpha-2 agonists, including dexmedetomidine and clonidine, are shown to extend sensory and motor block duration and improve postoperative analgesia. The vast majority of evidence is from perioperative studies, with limited ED-specific data [108,109]. Dexmedetomidine is 8-fold more selective for alpha-2 receptors than clonidine and typically more readily available and less expensive than clonidine [110]. While intravenous use of dexmedetomidine in the ED is limited by potential bradycardia and hypotension, administration of larger doses peripherally (above 150 mcg) may cause local paradoxical vasoconstriction, due to loss of alpha-2 selectivity [80]. Therefore, administering dexmedetomidine in fixed compartments (e.g. posterior popliteal block) is cautioned. However, perineural administration of 30-50 mcg dexmedetomidine has shown to prolong analgesia compared to lidocaine or bupivacaine alone in brachial plexus blockade (by approximately 4-6 hours) and reduce local inflammation in femoral blocks [111-114].

4.5. Magnesium sulfate

Magnesium sulfate as an adjunct for nerve blocks has been investigated in multiple randomized controlled trials and meta-analyses,

although virtually all available evidence derives from perioperative surgical populations rather than the ED setting. It is used for its NMDA receptor-modulating properties, which can reduce central sensitization and theoretically prolong analgesia [115]. A meta-analysis of 21 RCTs including 1323 patients, mostly in a surgical setting, found that magnesium sulfate prolonged the total duration of sensory blockade, reduced pain at 6 and 12 hours and reduced incidence of nausea and vomiting following transversus abdominis plane blockade [116]. It has also demonstrated a reduction in opioids up to 24 hours after the surgical procedure [117]. The duration of sensory and motor block vary by block type, dose, and administration technique [116,118]. Its benefits must also be balanced against potential adverse effects such as hypotension, flushing, or bradycardia when administered systemically, though perineural dosing appears generally well tolerated [115].

4.6. Opioids

The use of opioids as a supplement to local anesthetics is a longstanding practice in neuraxial anesthesia (i.e., intrathecal, epidural). However, opioids have demonstrated mixed results in various regional blocks and for this reason are not commonly employed [119,120]. Buprenorphine is the most consistently effective opioid adjuvant for peripheral nerve blocks; perineural administration combined with local anesthetic has demonstrated a relatively longer duration of analgesia than without [120]. Morphine and fentanyl may also prolong analgesia, but the effect is less pronounced than buprenorphine. However, opioid adjuncts are associated with higher rates of postoperative nausea and vomiting [121]. Studies analyzing opioids as additives to nerve blocks have been performed in the peri-operative space rather than the ED.

4.7. Additional considerations

Preservatives are common in injectable solutions and contraindicated in neuraxial anesthesia (i.e., epidurals) due to a concern for neurotoxicity [122]. Specifically, benzyl alcohol and methyl- or propylparabens have been linked to aseptic meningitis and arachnoiditis when used intrathecally [123]. While caution may be warranted in neuraxial spaces, local anesthetics or adjuvant agents need not be preservative-free for most regional anesthesia blocks in the ED.

5. Bleeding risks

Most peripheral or regional nerve blocks can be performed relatively safely in the setting of anticoagulation or antiplatelet therapy. Hematoma formation and expansion are most concerning within noncompressible sites of smaller, fixed spaces. The American Society of Regional Anesthesia (ARSA) recommends holding antithrombotic therapy in neuraxial (e.g., epidural) and deep plexus or any deep peripheral block since these sites involve the highest risk of poor outcome [124]. Specific drug- and patient-level recommendations are covered in ASRA guidance [125].

Neuraxial anesthesia should be avoided in the setting of a platelet count less than 50,000/mcL [126]. While conservative, this cutoff is often extrapolated to regional anesthesia. In practice, the decision should incorporate not only the absolute platelet count but also the trend, underlying etiology of thrombocytopenia, presence of coagulopathy, and overall clinical context.

6. Adverse effects

6.1. Local anesthetic systemic toxicity

LAST is an important consideration for all clinicians who provide regional anesthesia when administering local anesthetics. Although uncommon, LAST can be life-threatening [127].

Within the CNS, Na_v blockage can lead to neuronal excitation, resulting in sensory or vision changes, muscle activation, or seizures [127-129]. This can lead to altered mental status, coma, myocardial depression, conduction abnormalities (e.g., PR and QRS prolongation), and vascular tone instability, ultimately resulting in cardiac arrest [127-129]. Seizure-induced hypoxia and acidemia may further compound cardiovascular instability. Despite the risk, LAST is uncommon in practice, with data reporting rates ranging from 0.03 to 1.8 per 1,000 cases [130-134]. The recent National Ultrasound-Guided Nerve Block (NURVE) Registry reported a 0.4% complication rate across diverse block types, with only one case of intravenous intralipid emulsion (ILE) administration out of 2,735 ultrasound-guided nerve blocks [135]. Risk of LAST is dose-dependent, emphasizing the importance of calculating and adhering to the maximum dose (including across multiple or repeat injections). Ultrasound guidance helps to avoid accidental intravascular injection. We recommend injections be performed 3-5 mL at a time, checking for deposition in the plane and avoidance of intravascular injection.

Among anesthetic agents, bupivacaine is considered more cardiotoxic than ropivacaine, which is more cardiotoxic than lidocaine due to the former's higher affinity for and slower dissociation from inactive Na_v channels [127,129,136-138]. All patients receiving near maximum recommended doses should be placed on a cardiac monitor during the procedure to assess for cardiac dysrhythmias. Patients receiving regional anesthesia should be monitored 30-45 minutes post-procedure for findings suggestive of LAST [134].

First line treatment for LAST is ILE, in conjunction with supportive care [125,127]. Table 3 describes ILE dosing. ILE is believed to function as a "lipid shuttle", transporting local anesthetic from areas of high blood flow (e.g., CNS, heart) to organs capable of metabolizing or storing it [139,140]. This concept evolved from the earlier "lipid sink" hypothesis, which proposed passive sequestration of lipophilic drug within the intravascular lipid phase; the shuttle model instead reflects a more dynamic redistribution of drug away from target tissues. Moreover, ILE provides a free fatty acid energy substrate, which may sensitize vascular catecholamine receptors and have a direct inotropic effect in the setting of cardiovascular instability [141-144].

Rapid recognition of LAST is essential to enable timely treatment and prevent progression to cardiac arrest. However, the optimal timing for initiating ILE remains unclear [145]. Although a lower threshold for treatment is reasonable, clinicians should avoid administering ILE for nonspecific symptoms alone. Perioral paresthesia or tachycardia may occur with LAST but are also common in benign conditions such as anxiety or hyperventilation. In these cases, vigilance and readiness (e.g., ILE at the bedside) are appropriate, but treatment should be deferred unless there are electrocardiogram (ECG) changes, altered mental status, or seizure activity. Bupivacaine carries stronger recommendations for ILE administration given its unique profile and propensity for cardiotoxicity; however, increasing reports of lidocaine-associated toxicity and death since 2010 underscore that attention should not be limited to bupivacaine alone [145,146]. Sodium bicarbonate may be used for wide-complex tachyarrhythmias and atropine for bradycardia associated with LAST [137]. Early consultation with a regional poison center is encouraged for suspected cases.

6.2. Methemoglobinemia

Development of methemoglobinemia is another concern with local anesthetics. Historically, topical benzocaine is most often implicated, with one report showing the agent precipitated two-thirds of all methemoglobinemia cases [147,148]. Management involves methylene blue and poison center consultation (Table 3).

7. System design and implementation

Safe and sustainable implementation of regional anesthesia in the ED requires deliberate systems-based support in addition to individual

Table 3
Therapies for LAST and methemoglobinemia [134,137,146,157-159].

LAST	Patient weight	Bolus	Additional dosing	Considerations
Intravenous lipid emulsion 20% (20g/100mL) formulation	≥ 70 kg	100 mL over 2-3 minutes, then 250 mL over 10-15 minutes	250 mL over 10-15 min; if continued instability, repeat bolus and administer additional 500 mL over 15-20 min (max total dose: 12 mL/kg)	Use Ideal Body Weight when calculating maximum dose May decrease or terminate infusion if clinical status improves Consider alternate diagnosis or therapy when 10-12 mL/kg Adverse effects: hypertriglyceridemia, pancreatitis, fat embolism, interference in colorimetric laboratory analysis (e.g. creatinine, glucose, magnesium, bilirubin), ECMO circuit obstruction, acute lung injury.
	< 70 kg	1.5 mL/kg over 2-3 minutes	0.25 mL/kg/min over 15-20 min; if continued instability, repeat bolus and administer additional 0.5 mL/kg/min over 30 minutes	
Methemoglobinemia				
Methylene Blue	N/A	1 mg/kg over 5 minutes	May administer additional 1 mg/kg in 30-60 minutes if symptoms persist	Increased risk of hemolysis in presence of G6PD deficiency Methylene blue acts as a potent, reversible inhibitor of monoamine oxidase, preventing the breakdown of serotonin. Serotonin syndrome has been reported.

G6PD: Glucose-6-phosphate dehydrogenase; ECMO: extracorporeal circulation membrane oxygenation.

clinician proficiency. Standardized order set development may reduce practice variability while reinforcing safe pharmacologic dosing, appropriate monitoring, and ready access to rescue therapies. Well-designed order sets can integrate weight-based local anesthetic dosing calculators, default concentration selections, adjunct guidance, post-procedure monitoring recommendations, and automatic inclusion of ILE therapy when higher risk agents or larger volume blocks are selected. Such standardization promotes adherence to best practices while minimizing cognitive load.

Operationalizing regional anesthetics in clinical practice requires attention to medication selection, dosing strategies, workflow integration, and safety monitoring. Selection of the local anesthetic should balance onset time, duration of action, and toxicity risk, with commonly used agents (namely lidocaine, bupivacaine, and ropivacaine with or without epinephrine) chosen based on procedural needs and expected analgesic duration. Incorporation of adjuvants can enhance block quality or prolong analgesia, but requires careful consideration of compatibility, evidence for benefit, and potential adverse effects. Epinephrine is commonly available in solutions with other local anesthetics, while other adjunctive agents are not. Together, protocolization, interdisciplinary collaboration, and education help ensure regional anesthesia is delivered safely and consistently while maximizing analgesic benefit.

Collaboration with emergency medicine pharmacists is critical to optimizing medication safety and operational feasibility. Pharmacist involvement supports selection of appropriate local anesthetic formulations and adjunctive agents, ensures availability of preservative-free medications when indicated, and facilitates stocking and rapid access to ILE therapy. Pharmacists can also play a key role in reviewing institutional dosing thresholds, identifying high-risk medication combinations, and supporting education around safe preparation and administration of local anesthetics and adjuncts [149].

Structured training and credentialing pathways further support safe adoption of regional anesthesia in the ED [150,151]. Competency should encompass not only ultrasound-guided needle visualization and anatomical identification, but also pharmacologic principles, dosing limits, complication recognition, and post-procedure monitoring. Incorporating regional anesthesia training into established emergency ultrasound curricula, including resident, fellowship-level, and faculty education, provides a scalable framework for skill acquisition and quality assurance. Ongoing physician input, procedural tracking, and quality review can help refine protocols over time and ensure that regional anesthesia is integrated into ED practice in a manner that prioritizes patient safety, clinician confidence, and operational reliability.

8. Conclusion

Regional anesthesia represents an evolving, evidence-supported component of multimodal analgesia in emergency medicine. Appropriate local anesthetic agent selection, dosing, and administration techniques are essential to maximizing analgesic benefit while minimizing adverse effects. Key pharmacologic properties of local anesthetics, including solution pH, pKa, and lipophilicity, directly influence onset, potency, and duration of nerve blockade and should inform agent selection. The judicious use of adjuncts may further enhance block onset, duration, and quality, but should be guided by available evidence, patient-specific factors, and safety considerations. Standardized training and a multidisciplinary, systems-based approach can help optimize the safe and effective implementation of regional anesthesia in the ED.

CRediT authorship contribution statement

Lance Ray: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Michael Gottlieb:** Writing – review & editing, Writing – original draft. **Brit Long:** Writing – review & editing, Writing – original draft. **Matthew Riscinti:** Writing – review & editing, Writing – original draft. **Megan A. Rech:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

The above authors have nothing to declare relevant to this work.

References

[1] Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11:S105–20.
[2] Amini R, Kartchner JZ, Nagdev A, Adhikari S. Ultrasound-guided nerve blocks in emergency medicine practice. J Ultrasound Med. 2016;35:731–6. doi:10.7863/ultra.15.05095.
[3] Koehler RM, Okoroafor UC, Cannada LK. A systematic review of opioid use after extremity trauma in orthopedic surgery. Injury. 2018;49:1003–7. doi:10.1016/j.injury.2018.04.003.
[4] Butler MM, Ancona RM, Beauchamp GA, Yamin CK, Winstanley EL, Hart KW, et al. Emergency department prescription opioids as an initial exposure preceding addiction. Ann Emerg Med. 2016;68:202–8. doi:10.1016/j.annemergmed.2015.11.033.
[5] Guay J, Kopp S. Peripheral nerve blocks for hip fractures in adults. Cochrane Database Syst Rev. 2020;11:CD001159. doi:10.1002/14651858.CD001159.pub3.
[6] Cheatle MD. Prescription opioid misuse, abuse, morbidity, and mortality: balancing effective pain management and safety. Pain Med. 2015;16(Suppl. 1):S3–8. doi:10.1111/pme.12904.

[7] Ball CG. Surgeons as advocates for opioid control. Can J Surg. 2019;62:220–1. doi:10.1503/cjs.011419.
[8] National Center for Injury Prevention and Control (NCIPC), Centers for Disease Control and Prevention (CDC), US Department of Health and Human Services, Atlanta, Georgia. Annual surveillance report of drug-related risks and outcomes. United States. https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf; 2026. (accessed March 23, 2025).
[9] Go D, Gould M, Ganti L. History of the nerve block. Orthop Rev (Pavia). 2024;16:125260. doi:10.52965/001c.125260.
[10] Long B, Shalaby M, Gottlieb M. Managing analgesia for hip fractures. Ann Emerg Med. 2025;86:616–24. doi:10.1016/j.annemergmed.2025.04.007.
[11] Gottlieb M, Long B. Peripheral nerve block for hip fracture. Acad Emerg Med. 2021;28:1198–9. doi:10.1111/acem.14239.
[12] Blaivas M, Adhikari S, Lander L. A prospective comparison of procedural sedation and ultrasound-guided interscalene nerve block for shoulder reduction in the emergency department. Acad Emerg Med. 2011;18:922–7. doi:10.1111/j.1553-2712.2011.01140.x.
[13] Tezel O, Kaldirim U, Bilgic S, Deniz S, Eyi YE, Ozyurek S, et al. A comparison of suprascapular nerve block and procedural sedation analgesia in shoulder dislocation reduction. Am J Emerg Med. 2014;32:549–52. doi:10.1016/j.ajem.2014.02.014.
[14] Liu SS. Evidence basis for ultrasound-guided block characteristics onset, quality, and duration. Reg Anesth Pain Med. 2016;41:205–20. doi:10.1097/AAP.0000000000000141.
[15] Kapral S, Greher M, Huber G, Willschke H, Kettner S, Kdolsky R, et al. Ultrasonographic guidance improves the success rate of interscalene brachial plexus blockade. Reg Anesth Pain Med. 2008;33:253–8. doi:10.1016/j.rapm.2007.10.011.
[16] Neal JM, Brull R, Chan VWS, Grant SA, Horn J-L, Liu SS, et al. The ASRA evidence-based medicine assessment of ultrasound-guided regional anesthesia and pain medicine: executive summary. Reg Anesth Pain Med. 2010;35:S1–9. doi:10.1097/AAP.0b013e3181d22fe0.
[17] Bhoi S, Chandra A, Galwankar S. Ultrasound-guided nerve blocks in the emergency department. J Emerg Trauma Shock. 2010;3:82–8. doi:10.4103/0974-2700.58655.
[18] American College of Surgeons. Best practices guidelines for acute pain management in Trauma Patients. Released November 2020; 2026..
[19] Cogan CJ, Kandemir U. Role of peripheral nerve block in pain control for the management of acute traumatic orthopaedic injuries in the emergency department: diagnosis-based treatment guidelines. Injury. 2020;51:1422–5. doi:10.1016/j.injury.2020.04.016.
[20] Ammann S, Schoell E, Nieves Ortega R, Bingisser R. Ultrasound-guided regional anaesthesia and reduction of distal radius fractures in an emergency department. Swiss Med Wkly. 2020;150:w20288. doi:10.4414/smw.2020.20288.
[21] Jaffe TA, Shokoohi H, Liteplo A, Goldsmith A. A novel application of ultrasound-guided interscalene anesthesia for proximal humeral fractures. J Emerg Med. 2020;59:265–9. doi:10.1016/j.jemermed.2020.05.013.
[22] Raeyat Doost E, Heiran MM, Movahedi M, Mirafzal A. Ultrasound-guided interscalene nerve block vs procedural sedation by propofol and fentanyl for anterior shoulder dislocations. Am J Emerg Med. 2017;35:1435–9. doi:10.1016/j.ajem.2017.04.032.
[23] Stone MB, Price DD, Wang R. Ultrasound-guided supraclavicular block for the treatment of upper extremity fractures, dislocations, and abscesses in the ED. Am J Emerg Med. 2007;25:472–5. doi:10.1016/j.ajem.2006.08.019.
[24] Stone MB, Wang R, Price DD. Ultrasound-guided supraclavicular brachial plexus nerve block vs procedural sedation for the treatment of upper extremity emergencies. Am J Emerg Med. 2008;26:706–10. doi:10.1016/j.ajem.2007.09.011.
[25] Kaushal B, Chauhan S, Magoon R, Krishna NS, Saini K, Bhoi D, et al. Efficacy of bilateral erector spinae plane block in management of acute postoperative surgical pain after pediatric cardiac surgeries through a midline sternotomy. J Cardiothorac Vasc Anesth. 2020;34:981–6. doi:10.1053/j.jvca.2019.08.009.
[26] Cardwell TW, Zabala V, Mineo J, Ochner CN. The effects of perioperative peripheral nerve blocks on Peri- and Postoperative opioid use and pain management. Am Surg. 2022;88:2842–50. doi:10.1177/00031348211023395.
[27] Morrison RS, Dickman E, Hwang U, Akhtar S, Ferguson T, Huang J, et al. Regional nerve blocks improve pain and functional outcomes in hip fracture: a randomized controlled trial. J Am Geriatr Soc. 2016;64:2433–9. doi:10.1111/jgs.14386.
[28] Gadsden J, Warlick A. Regional anesthesia for the trauma patient: improving patient outcomes. Local Reg Anesth. 2015;8:45–55. doi:10.2147/LRA.S55322.
[29] Nagdev A, Dreyfuss A, Martin D, Mantuani D. Principles of safety for ultrasound-guided single injection blocks in the emergency department. Am J Emerg Med. 2019;37:1160–4. doi:10.1016/j.ajem.2019.03.045.
[30] Unneby A, Svensson PO, Gustafson PY, Lindgren APB-M, Bergström U, Olofsson PB. Complications with focus on delirium during hospital stay related to femoral nerve block compared to conventional pain management among patients with hip fracture - a randomised controlled trial. Injury. 2020;51:1634–41. doi:10.1016/j.injury.2020.04.013.
[31] Riddell M, Ospina M, Holroyd-Leduc JM. Use of femoral nerve blocks to manage hip fracture pain among older adults in the emergency department: a systematic review. CJEM. 2016;18:245–52. doi:10.1017/cem.2015.94.
[32] Canders CP, Krishna PK, Moheimani RS, Weaver CM. Management of an acute exacerbation of chronic neuropathic pain in the emergency department: a case to support ultrasound-guided forearm nerve blocks. J Emerg Med. 2018;55:e147–51. doi:10.1016/j.jemermed.2018.08.003.
[33] Kettner SC, Willschke H, Marhofer P. Does regional anaesthesia really improve outcome? Br J Anaesth. 2011;107(Suppl. 1):i90–5. doi:10.1093/bja/aer340.
[34] Beaudoin FL, Haran JP, Liebmann O. A comparison of ultrasound-guided three-in-one femoral nerve block versus parenteral opioids alone for analgesia in emergency department patients with hip fractures: a randomized controlled trial. Acad Emerg Med. 2013;20:584–91. doi:10.1111/acem.12154.
[35] Herring AA, Stone MB, Nagdev AD. Ultrasound-guided abdominal wall nerve blocks in the ED. Am J Emerg Med. 2012;30:759–64. doi:10.1016/j.ajem.2011.03.008.
[36] Clattenburg E, Herring A, Hahn C, Johnson B, Nagdev A. ED ultrasound-guided posterior tibial nerve blocks for calcaneal fracture analagesia. Am J Emerg Med. 2016;34(1183):e1–3. doi:10.1016/j.ajem.2015.11.002.
[37] Lyons C, Herring AA. Ultrasound-guided axillary nerve block for ED incision and drainage of deltoid abscess. Am J Emerg Med. 2017;35:1032.e3–7. doi:10.1016/j.ajem.2017.01.064.
[38] Selame LA, McFadden K, Duggan NM, Goldsmith AJ, Shokoohi H. Ultrasound-guided transgluteal sciatic nerve block for gluteal procedural analgesia. J Emerg Med. 2021;60:512–6. doi:10.1016/j.jemermed.2020.10.047.
[39] Goldsmith AJ, Liteplo AS, Shokoohi H. Ultrasound-guided serratus anterior plane block for intractable herpes zoster pain in the emergency department. J Emerg Med. 2020;59:409–12. doi:10.1016/j.jemermed.2020.04.053.
[40] Goldsmith AJ, Liteplo A, Hayes BD, Duggan N, Huang C, Shokoohi H. Ultrasound-guided transgluteal sciatic nerve analgesia for refractory back pain in the ED. Am J Emerg Med. 2020;38:1792–5. doi:10.1016/j.ajem.2020.06.001.
[41] Lewis SR, Price A, Walker KJ, McGrattan K, Smith AF. Ultrasound guidance for upper and lower limb blocks. Cochrane Database Syst Rev. 2015;2015:CD006459. doi:10.1002/14651858.CD006459.pub3.
[42] Ritcey B, Pageau P, Woo MY, Perry JJ. Regional nerve blocks for hip and femoral neck fractures in the emergency department: a systematic review. CJEM. 2016;18:37–47. doi:10.1017/cem.2015.75.
[43] Steenberg J, Møller AM. Systematic review of the effects of fascia iliaca compartment block on hip fracture patients before operation. Br J Anaesth. 2018;120:1368–80. doi:10.1016/j.bja.2017.12.042.
[44] Kreutziger J, Hirschi D, Fischer S, Herzog RF, Zbinden S, Honigmann P. Comparison of interscalene block, general anesthesia, and intravenous analgesia for out-patient shoulder reduction. J Anesth. 2019;33:279–86. doi:10.1007/s00540-019-02624-6.
[45] Ketelaars R, Stollman JT, van Eeten E, Eikendal T, Bruhn J, van Geffen G-J. Emergency physician-performed ultrasound-guided nerve blocks in proximal femoral fractures provide safe and effective pain relief: a prospective observational study in The Netherlands. Int J Emerg Med. 2018;11:12. doi:10.1186/s12245-018-0173-z.
[46] Vrablik M, Akhavan A, Murphy D, Schrepel C, Hall MK. Ultrasound-guided nerve blocks for painful hand injuries: a randomized control trial. Cureus. 2021;13:e18978. doi:10.7759/cureus.18978.
[47] Abdelhamid K, ElHawary H, Turner JP. The use of the erector spinae plane block to decrease pain and opioid consumption in the emergency department: a literature review. J Emerg Med. 2020;58:603–9. doi:10.1016/j.jemermed.2020.02.022.
[48] Abou-Setta AM, Beaupre LA, Rashiq S, Dryden DM, Hamm MP, Sadowski CA, et al. Comparative effectiveness of pain management interventions for hip fracture: a systematic review. Ann Intern Med. 2011;155:234–45. doi:10.7326/0003-4819-155-4-201108160-00346.
[49] Schnekenburger M, Mathew J, Fitzgerald M, Hendel S, Sekandarzad MW, Mitra B. Regional anaesthesia for rib fractures: a pilot study of serratus anterior plane block. Emerg Med Australas. 2021;33:788–93. doi:10.1111/1742-6723.13724.
[50] Benesch T, Mantuani D, Nagdev A. Case report: bilateral ultrasound-guided serratus anterior plane blocks for a chest wall burn. Clin Pract Cases Emerg Med. 2021;5:117–20. doi:10.5811/cpcem.2020.12.50184.
[51] American College of Emergency Physicians. Policy statement: ultrasound-guided nerve blocks. Approved by the ACEP board of directors; 2026..
[52] American Board of Emergency Medicine. Procedures list for the ABEM certifying examination; 2026..
[53] Cuvillon P, Nouvellon E, Ripart J, Boyer J-C, Dehour L, Mahamat A, et al. A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. Anesth Analg. 2009;108:641–9. doi:10.1213/ane.0b013e31819237f8.
[54] Taylor A, McLeod G. Basic pharmacology of local anaesthetics. BJA Educ. 2020;20:34–41. doi:10.1016/j.bjae.2019.10.002.
[55] Bupivacaine injection. Lake Forest, IL, USA; 2018..
[56] Martinez MN, Amidon GL. A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals. J Clin Pharmacol. 2002;42:620–43. doi:10.1177/00970002042006005.
[57] Whitman Z, Thompson J. Chapter 5: local anaesthetics. Smith and aitkenhead's textbook of anaesthesia. 8th ed. Elsevier; 2026. p. 90–8.
[58] Wiedmer SK, Sohn J-T. Lipophilicity of drugs, including local anesthetics, and its association with lipid emulsion resuscitation. Korean J Anesthesiol. 2024;77:170–2. doi:10.4097/kja.23825.
[59] Speca SJ, Boynes SG, Cuddy MA. Allergic reactions to local anesthetic formulations. Dent Clin N Am. 2010;54:655–64. doi:10.1016/j.cden.2010.06.006.
[60] Becker DE, Reed KL. Local anesthetics: review of pharmacological considerations. Anesth Prog. 2012;59:90–101. quiz 102–3. https://doi.org/10.2344/0003-3006-59.2.90.
[61] Peck T, Harris B. Chapter 10: analgesics. Pharmacology for anaesthesia and intensive care. 5th ed. New York, NY: Cambridge University Press; 2026. p. 131.
[62] El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: current perspectives. Local Reg Anesth. 2018;11:35–44. doi:10.2147/LRA.S154512.
[63] The ophthalmological congress in Heidelberg: Muriate of cocaine as a local anesthetic to the cornea–no radiating muscular fibers in the Iris–actual cautery in superficial corneal ulcerations–optico-ciliary neurectomy–is cataract the result of chronic bright's disease?–professor Arlt and his recent work in glaucoma. 1884;26(15):1866. 1.

[64] Thomson CJ, Lalonde DH. Randomized double-blind comparison of duration of anesthesia among three commonly used agents in digital nerve block. Plast Reconstr Surg. 2006;118:429–32. doi:10.1097/01.prs.0000227632.43606.12.
[65] Hartmannsgruber MW, Silverman DG, Halaszynski TM, Bobart V, Brull SJ, Wilkerson C, et al. Comparison of ropivacaine 0.2% and lidocaine 0.5% for intravenous regional anesthesia in volunteers. Anesth Analg. 1999;89:727–31. doi:10.1097/00000539-199909000-00037.
[66] Brown J, Milgrim F, Driver L, Meeker MA, Tucker R, Le N-N, et al. Efficacy and safety of adjunct medications in ED ultrasound-guided nerve blocks: a national ultrasound-guided NeRVE (NURVE) block registry study. Acad Emerg Med. 2025;32:1299–308. doi:10.1111/acem.70128.
[67] Naropin (Ropivacaine) Injection. Lake Zurich, IL: Fresenius Kabi; 2018..
[68] Bajwa SJS, Kaur J. Clinical profile of levobupivacaine in regional anesthesia: a systematic review. J Anaesthesiol Clin Pharmacol. 2013;29:530–9. doi:10.4103/0970-9185.119172.
[69] Frawley GP, Downie S, Huang GH. Levobupivacaine caudal anesthesia in children: a randomized double-blind comparison with bupivacaine. Paediatr Anaesth. 2006;16:754–60. doi:10.1111/j.1460-9592.2006.01841.x.
[70] Burlacu CL, Buggy DJ. Update on local anesthetics: focus on levobupivacaine. Ther Clin Risk Manag. 2008;4:381–92. doi:10.2147/tcrm.s1433.
[71] Levobupivacaine solution for injection. Buckinghamshire, UK: Martindale Pharma; Ethypharm Group Company.; 2026..
[72] Chahar P, Cummings KC. Liposomal bupivacaine: a review of a new bupivacaine formulation. J Pain Res. 2012;5:257–64. doi:10.2147/JPR.S27894.
[73] Exparel (bupivacaine liposome injectable suspension) Prescribing Information. SanDiego, CA: Pacira Pharmaceuticals, Inc.; 2021..
[74] Pal S, Beins M, Dobson A, Kim S, Kim S, Heath S, et al. Effects of liposomal bupivacaine (LB) and provider experience with LB on service utilization, clinical outcomes, and medicare expenditures among fee-for-service (FFS) beneficiaries. J Med Econ. 2025;28:848–58. doi:10.1080/13696998.2025.2510814.
[75] Berven S, Wang MY, Lin JH, Kakoty S, Lavelle W. Effects of liposomal bupivacaine on opioid use and healthcare resource utilization after outpatient spine surgery: a real-world assessment. Spine J. 2024;24:1890–9. doi:10.1016/j.spinee.2024.05.005.
[76] Nescaine (chloroprocaine HCl injection, USP). Lake Zurich, IL: Fresenius Kabi.; 2018..
[77] Septocaine (articaine) product insert. Louisville, CO: Novocol Pharmaceutical of Canada Inc.; 2018..
[78] Citanest plain dental (prilocaine) product insert. Woodbridge, ON, CA: Dentsply Canada; 2015..
[79] Hoerner E, Stundner O, Fiegl H, Gasteiger L. Crystallization of short-acting and intermediate-acting local anesthetics when mixed with adjuvants: a semiquantitative light microscopy analysis. Reg Anesth Pain Med. 2023;48:508–12. doi:10.1136/rapm-2023-104398.
[80] Nestor CC, Ng C, Sepulveda P, Irwin MG. Pharmacological and clinical implications of local anaesthetic mixtures: a narrative review. Anaesthesia. 2022;77:339–50. doi:10.1111/anae.15641.
[81] Sepehripour S, Dheansa BS. Is there an advantage in onset of action with mixing lignocaine and bupivacaine? J Plast Reconstr Aesthet Surg. 2017;70:1782. doi:10.1016/j.bjps.2017.06.009.
[82] Ribotsky BM, Berkowitz KD, Montague JR. Local anesthetics. Is there an advantage to mixing solutions? J Am Podiatr Med Assoc. 1996;86:487–91. doi:10.7547/87507315-86-10-487.
[83] Powell MF, Jarzombek KW, Venhuizen KJ, Tubinis MD, Morgan CJ, Frölich MA. Comparing bupivacaine, lidocaine, and a combination of bupivacaine and lidocaine for labor epidural activation: a prospective, randomized, double-blind study. Asian J Anesthesiol. 2019;57:55–60. doi:10.6859/aja.201906_57(2).0004.
[84] Maben D, Suresh A, Desai AK, Shetty S, Juturu U, Anand J. Efficacy of lidocaine vs combination of lidocaine and bupivacaine in management of maxillofacial trauma: a clinical comparative study. Clin Oral Investig. 2023;27:6613–7. doi:10.1007/s00784-023-05267-w.
[85] Nishiyama T. Comparison of the motor and sensory block by ropivacaine and bupivacaine in combination with lidocaine in interscalene block. Mediev Archaeol. 2012;66:315–7. doi:10.5455/medarh.2012.66.315-317.
[86] Almasi R, Rezman B, Kriszta Z, Patczai B, Wiegand N, Bogar L. Onset times and duration of analgesic effect of various concentrations of local anesthetic solutions in standardized volume used for brachial plexus blocks. Heliyon. 2020;6:e04718. doi:10.1016/j.heliyon.2020.e04718.
[87] Hoda W, Pandey K. Time to rethink mixing local anaesthetics: a practical update for modern regional anaesthesia. Indian J Anaesth. 2025;69:243–4. doi:10.4103/ija.ija_1110_24.
[88] Schnabl SM, Ghoreschi FC, Scheu A, Kofler L, Häfner H-M, Breuninger H. Use of local anesthetics with an epinephrine additive on fingers and penis - dogma and reality. J Dtsch Dermatol Ges. 2021;19:185–96. doi:10.1111/ddg.14434.
[89] Single entity injectable drug products. FDA; 2026. https://www.fda.gov/drugs/information-drug-class/single-entity-injectable-drug-products (accessed January 4, 2026).
[90] Tschopp C, Tramèr MR, Schneider A, Zaarour M, Elia N. Benefit and harm of adding epinephrine to a local anesthetic for neuraxial and locoregional anesthesia: a meta-analysis of randomized controlled trials with trial sequential analyses. Anesth Analg. 2018;127:228–39. doi:10.1213/ANE.0000000000003417.
[91] Muck AE, Bebarta VS, Borys DJ, Morgan DL. Six years of epinephrine digital injections: absence of significant local or systemic effects. Ann Emerg Med. 2010;56:270–4. doi:10.1016/j.annemergmed.2010.02.019.
[92] Pehora C, Pearson AM, Kaushal A, Crawford MW, Johnston B. Dexamethasone as an adjuvant to peripheral nerve block. Cochrane Database Syst Rev. 2017;11:CD011770. doi:10.1002/14651858.CD011770.pub2.
[93] Movafegh A, Razazian M, Hajimaohamadi F, Meysamie A. Dexamethasone added to lidocaine prolongs axillary brachial plexus blockade. Anesth Analg. 2006;102:263–7. doi:10.1213/01.ane.0000189055.06729.0a.
[94] Albrecht E, Renard Y, Desai N. Intravenous versus perineural dexamethasone to prolong analgesia after interscalene brachial plexus block: a systematic review with meta-analysis and trial sequential analysis. Br J Anaesth. 2024;133:135–45. doi:10.1016/j.bja.2024.03.042.
[95] Xuan C, Yan W, Wang D, Li C, Ma H, Mueller A, et al. The facilitatory effects of adjuvant pharmaceutics to prolong the duration of local anesthetic for peripheral nerve block: a systematic review and network meta-analysis. Anesth Analg. 2021;133:620–9. doi:10.1213/ANE.0000000000005640.
[96] Desai N, Pararajasingham S, Onwochei D, Albrecht E. Comparison of intravenous versus perineural dexamethasone as a local anaesthetic adjunct for peripheral nerve blocks in the lower limb: A meta-analysis and systematic review. Eur J Anaesthesiol. 2024;41:749–59. doi:10.1097/EJA.0000000000002038.
[97] Dawson RL, McLeod DH, Koerber JP, Plummer JL, Dracopoulos GC. A randomised controlled trial of perineural vs intravenous dexamethasone for foot surgery. Anaesthesia. 2016;71:285–90. doi:10.1111/anae.13346.
[98] Dani C, Vestri V, Bertini G, Pratesi S, Rubaltelli FF. Toxicity of corticosteroids and catecholamines for mice neuronal cell cultures: role of preservatives. J Matern Fetal Neonatal Med. 2007;20:325–33. doi:10.1080/14767050701227992.
[99] Burns CA, Ferris G, Feng C, Cooper JZ, Brown MD. Decreasing the pain of local anesthesia: a prospective, double-blind comparison of buffered, premixed 1% lidocaine with epinephrine versus 1% lidocaine freshly mixed with epinephrine. J Am Acad Dermatol. 2006;54:128–31. doi:10.1016/j.jaad.2005.06.043.
[100] Hobeich P, Simon S, Schneiderman E, He J. A prospective, randomized, double-blind comparison of the injection pain and anesthetic onset of 2% lidocaine with 1:100,000 epinephrine buffered with 5% and 10% sodium bicarbonate in maxillary infiltrations. J Endodont. 2013;39:597–9. doi:10.1016/j.joen.2013.01.008.
[101] Hanna MN, Elhassan A, Veloso PM, Lesley M, Lissauer J, Richman JM, et al. Efficacy of bicarbonate in decreasing pain on intradermal injection of local anesthetics: a meta-analysis. Reg Anesth Pain Med. 2009;34:122–5. doi:10.1097/AAP.0b013e31819a12a6.
[102] Torres-Rojas K, Chumpitaz-Cerrate V, Chávez-Rimache L, Núñez-Díaz D, Pérez-Jimenez V. Comparison of the anesthetic effect of alkalized lidocaine versus non-alkalized lidocaine administered at a slow rate in mandibular primary molars. J Dent Res Dent Clin Dent Prospects. 2023;17:47–53. doi:10.34172/joddd.2023.37014.
[103] Candido KD, Winnie AP, Covino BG, Raza SM, Vasireddy AR, Masters RW. Addition of bicarbonate to plain bupivacaine does not significantly alter the onset or duration of plexus anesthesia. Reg Anesth. 1995;20:133–8.
[104] Capogna G, Celleno D, Laudano D, Giunta F. Alkalinization of local anesthetics. Which block, which local anesthetic? Reg Anesth. 1995;20:369–77.
[105] Quinlan JJ, Oleksey K, Murphy FL. Alkalinization of mepivacaine for axillary block. Anesth Analg. 1992;74:371–4. doi:10.1213/00000539-199203000-00010.
[106] Chow MY, Sia AT, Koay CK, Chan YW. Alkalinization of lidocaine does not hasten the onset of axillary brachial plexus block. Anesth Analg. 1998;86:566–8. doi:10.1097/00000539-199803000-00024.
[107] Eisenach JC, De Kock M, Klimscha W. alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology. 1996;85:655–74. doi:10.1097/00000542-199609000-00026.
[108] Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Clonidine as an adjuvant to local anesthetics for peripheral nerve and plexus blocks: a meta-analysis of randomized trials. Anesthesiology. 2009;111:406–15. doi:10.1097/ALN.0b013e3181aae897.
[109] Chen Z, Liu Z, Feng C, Jin Y, Zhao X. Dexmedetomidine as an adjuvant in peripheral nerve block. Drug Des Devel Ther. 2023;17:1463–84. doi:10.2147/DDDT.S405294.
[110] Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. Anesthesiology. 2000;93:1345–9. doi:10.1097/00000542-200011000-00030.
[111] Cai H, Fan X, Feng P, Wang X, Xie Y. Optimal dose of perineural dexmedetomidine to prolong analgesia after brachial plexus blockade: a systematic review and Meta-analysis of 57 randomized clinical trials. BMC Anesthesiol. 2021;21:233. doi:10.1186/s12871-021-01452-0.
[112] Dai W, Tang M, He K. The effect and safety of dexmedetomidine added to ropivacaine in brachial plexus block: a meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018;97:e12573. doi:10.1097/MD.0000000000012573.
[113] Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth. 2013;110:915–25. doi:10.1093/bja/aet066.
[114] Li J, Wang H, Dong B, Ma J, Wu X. Adding dexmedetomidine to ropivacaine for femoral nerve block inhibits local inflammatory response. Minerva Anestesiol. 2017;83:590–7. doi:10.23736/S0375-9393.17.11430-6.
[115] Dahake JS, Verma N, Bawiskar D. Magnesium sulfate and its versatility in anesthesia: a comprehensive review. Cureus. 2024;16:e56348. doi:10.7759/cureus.56348.
[116] Zeng J, Chen Q, Yu C, Zhou J, Yang B. The use of magnesium sulfate and peripheral nerve blocks: an updated meta-analysis and systematic review. Clin J Pain. 2021;37:629–37. doi:10.1097/AJP.0000000000000944.
[117] Pulitanò R, Giudice M, La Verde F, Di Sabatino E, Carassiti M, Pascarella G. Ropivacaine and magnesium sulfate in sciatic nerve block at the popliteal level: randomized double-blind study. Minerva Anestesiol. 2024;90:1090–7. doi:10.23736/S0375-9393.24.18126-6.
[118] Kirksey MA, Haskins SC, Cheng J, Liu SS. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic qualitative review. PloS One. 2015;10:e0137312. doi:10.1371/journal.pone.0137312.
[119] Murphy DB, McCartney CJ, Chan VW. Novel analgesic adjuncts for brachial plexus block: a systematic review. Anesth Analg. 2000;90:1122–8. doi:10.1097/00000539-200005000-00023.

[120] Schnabel A, Reichl SU, Zahn PK, Pogatzki-Zahn EM, Meyer-Frießem CH. Efficacy and safety of buprenorphine in peripheral nerve blocks: a meta-analysis of randomised controlled trials. Eur J Anaesthesiol. 2017;34:576–86. doi:10.1097/EJA.0000000000000628.
[121] Schubert A-K, Seneviratne V, Stolz J, Wiesmann T, Wulf H, Eberhart L, et al. The effect of adjuvants added to local anaesthetics for single-injection upper extremity peripheral regional anaesthesia: a systematic review with network meta-analysis of randomised trials. Eur J Anaesthesiol. 2023;40:672–90. doi:10.1097/EJA.0000000000001860.
[122] Kempenaers R, Roofthooft E, Van de Velde M. Adjuncts for neuraxial anaesthesia in obstetrics. BJA Educ. 2025;25:219–25. doi:10.1016/j.bjae.2025.01.006.
[123] Hetherington NJ, Dooley MJ. Potential for patient harm from intrathecal administration of preserved solutions. Med J Aust. 2000;173:141–3. doi:10.5694/j.1326-5377.2000.tb125570.x.
[124] Kopp SL, Vandermeulen E, McBane RD, Perlas A, Leffert L, Horlocker T. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (fifth edition). Reg Anesth Pain Med. 2025. doi:10.1136/rapm-2024-105766. rapm-2024-105766.
[125] Neal JM, Neal EJ, Weinberg GL. American society of regional anesthesia and pain medicine local anesthetic systemic toxicity checklist: 2020 version. Reg Anesth Pain Med. 2021;46:81–2. doi:10.1136/rapm-2020-101986.
[126] Bauer ME, Arendt K, Beilin Y, Gernsheimer T, Perez Botero J, James AH, et al. The society for obstetric anesthesia and perinatology interdisciplinary consensus statement on neuraxial procedures in obstetric patients with thrombocytopenia. Anesth Analg. 2021;132:1531–44. doi:10.1213/ANE.0000000000005355.
[127] Long B, Chavez S, Gottlieb M, Montrief T, Brady WJ. Local anesthetic systemic toxicity: a narrative review for emergency clinicians. Am J Emerg Med. 2022;59:42–8. doi:10.1016/j.ajem.2022.06.017.
[128] Di Gregorio G, Neal JM, Rosenquist RW, Weinberg GL. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. Reg Anesth Pain Med. 2010;35:181–7. doi:10.1097/aap.0b013e3181d2310b.
[129] Zink W, Graf BM. The toxicity of local anesthetics: the place of ropivacaine and levobupivacaine. Curr Opin Anaesthesiol. 2008;21:645–50. doi:10.1097/ACO.0b013e32830c214c.
[130] Sites BD, Taenzer AH, Herrick MD, Gilloon C, Antonakakis J, Richins J, et al. Incidence of local anesthetic systemic toxicity and postoperative neurologic symptoms associated with 12,668 ultrasound-guided nerve blocks: an analysis from a prospective clinical registry. Reg Anesth Pain Med. 2012;37:478–82. doi:10.1097/AAP.0b013e31825cb3d6.
[131] Liu SS, Ortolan S, Sandoval MV, Curren J, Fields KG, Memtsoudis SG, et al. Cardiac arrest and seizures caused by local anesthetic systemic toxicity after peripheral nerve blocks: should we still fear the reaper? Reg Anesth Pain Med. 2016;41:5–21. doi:10.1097/AAP.0000000000000329.
[132] Mörwald EE, Zubizarreta N, Cozowicz C, Poeran J, Memtsoudis SG. Incidence of local anesthetic systemic toxicity in orthopedic patients receiving peripheral nerve blocks. Reg Anesth Pain Med. 2017;42:442–5. doi:10.1097/AAP.0000000000000544.
[133] Rubin DS, Matsumoto MM, Weinberg G, Roth S. Local anesthetic systemic toxicity in total joint arthroplasty: incidence and risk factors in the united states from the national inpatient sample 1998-2013. Reg Anesth Pain Med. 2018;43:131–7. doi:10.1097/AAP.0000000000000684.
[134] Neal JM, Barrington MJ, Fettiplace MR, Gitman M, Memtsoudis SG, Mörwald EE, et al. The third American society of regional anesthesia and pain medicine practice advisory on local anesthetic systemic toxicity: executive summary 2017. Reg Anesth Pain Med. 2018;43:113–23. doi:10.1097/AAP.0000000000000720.
[135] Goldsmith A, Driver L, Duggan NM, Riscinti M, Martin D, Heffler M, et al. Complication rates after ultrasonography-guided nerve blocks performed in the emergency department. JAMA Netw Open. 2024;7:e2444742. doi:10.1001/jamanetworkopen.2024.44742.
[136] Groban L, Deal DD, Vernon JC, James RL, Butterworth J. Cardiac resuscitation after incremental overdosage with lidocaine, bupivacaine, levobupivacaine, and ropivacaine in anesthetized dogs. Anesth Analg. 2001;92:37–43. doi:10.1097/00000539-200101000-00008.
[137] Lavonas EJ, Akpunonu PD, Arens AM, Babu KM, Cao D, Hoffman RS, et al. 2023 American heart association focused update on the management of patients with cardiac arrest or life-threatening toxicity due to poisoning: an update to the American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2023;148:e149–84. doi:10.1161/CIR.0000000000001161.
[138] Block A, Covino BG. Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth. 1981;6:55–61. doi:10.1136/rapm-00002370-198104000-00003.
[139] Fettiplace MR, Lis K, Ripper R, Kowal K, Pichurko A, Vitello D, et al. Multi-modal contributions to detoxification of acute pharmacotoxicity by a triglyceride microemulsion. J Control Release. 2015;198:62–70. doi:10.1016/j.jconrel.2014.11.018.
[140] Shalaby M, Sahni R, Hamilton R. Local anesthetic systemic toxicity: awareness, recognition, and risk mitigation in the emergency department. Clin Exp Emerg Med. 2024;11:121–6. doi:10.15441/ceem.24.231.
[141] Stepniakowski KT, Goodfriend TL, Egan BM. Fatty acids enhance vascular alpha-adrenergic sensitivity. Hypertension. 1995;25:774–8. doi:10.1161/01.hyp.25.4.774.
[142] Corman SL, Skledar SJ. Use of lipid emulsion to reverse local anesthetic-induced toxicity. Ann Pharmacother. 2007;41:1873–7. doi:10.1345/aph.1K244.
[143] Stehr SN, Ziegeler JC, Pexa A, Oertel R, Deussen A, Koch T, et al. The effects of lipid infusion on myocardial function and bioenergetics in l-bupivacaine toxicity in the isolated rat heart. Anesth Analg. 2007;104:186–92. doi:10.1213/01.ane.0000248220.01320.58.
[144] Silveira L, Hirabara SM, Alberici LC, Lambertucci RH, Peres CM, Takahashi HK, et al. Effect of lipid infusion on metabolism and force of rat skeletal muscles during intense contractions. Cell Physiol Biochem. 2007;20:213–26. doi:10.1159/000104168.
[145] American College of Medical Toxicology. ACMT position statement: guidance for the use of intravenous lipid emulsion. J Med Toxicol. 2017;13:124–5. doi:10.1007/s13181-016-0550-z.
[146] Fettiplace M, Weinberg G, Nixon H, Barabanova A, Chiang C, Gitman M. The impact of local anesthetic systemic toxicity advisories on reporting to the National Poison Data System (NPDS). Reg Anesth Pain Med. 2025. doi:10.1136/rapm-2025-106464. rapm-2025-106464.
[147] Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. Anesth Analg. 2009;108:837–45. doi:10.1213/ane.0b013e318187c4b1.
[148] Belzer A, Krasowski MD. Causes of acquired methemoglobinemia - A retrospective study at a large academic hospital. Toxicol Rep. 2024;12:331–7. doi:10.1016/j.toxrep.2024.03.004.
[149] Morgan SR, Acquisto NM, Coralic Z, Basalyga V, Campbell M, Kelly JJ, et al. Clinical pharmacy services in the emergency department. Am J Emerg Med. 2018;36:1727–32. doi:10.1016/j.ajem.2018.01.056.
[150] Graglia S, Harmon D, Klein B. The development, implementation, and evolution of an emergency medicine ultrasound-guided regional anesthesia curriculum. West J Emerg Med. 2024;25:117–21. doi:10.5811/westjem.59793.
[151] Rauschenbach A, Paetow G, Musial H, Laudenbach A, Parsons-Moss D, Knack S, et al. Implementation of regional anesthesia education for emergency medicine residents and faculty. AEM Educ Train. 2025;9:e70007. doi:10.1002/aet2.70007.
[152] Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs. 2000;59:551–79. doi:10.2165/00003495-200059030-00013.
[153] PubChem. https://pubchem.ncbi.nlm.nih.gov/; 2026. (accessed December 15, 2025).
[154] Carbocaine (mepivacaine hydrochloride injection, USP). Lake Forest, IL, USA: Hospira; 2018..
[155] Scandonest (mepivacaine) 3% solution for injection. Maidstone, Kent, United Kingdom: Septodont Limited.; 2020..
[156] Plohal A, Dutchover EP, Root J, Kurilla B, Balas R. Changing the buffer in buffered lidocaine. J Infus Nurs. 2022;45:245–51. doi:10.1097/NAN.0000000000000481.
[157] Provayblue (methylene blue) injection. Shirley, NY; 2024..
[158] Gillman PK. CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity. J Psychopharmacol. 2011;25:429–36. doi:10.1177/0269881109359098.
[159] Top WMC, Gillman PK, de Langen CJ, Kooy A. Fatal methylene blue associated serotonin toxicity. Neth J Med. 2014;72:179–81.