

Narrative Review

Prolonging Peripheral Nerve Blocks in Adults: A Narrative Review of Adjunct Medications for Single-Injection Techniques

Sachin “Sunny” Jha, MD

From: SJMD Solutions, Indian
Harbour Beach, FL

Address Correspondence:
Sachin Sunny Jha, MD
SJMD Solutions
1201 NW 16th St, Miami, FL 33125
E-mail:
sunny@sjmdsolutions.com

Disclaimer: There was no external
funding in the preparation of this
article.

Conflict of interest: Each author
certifies that he or she, or a
member of his or her immediate
family, has no commercial
association (i.e., consultancies,
stock ownership, equity interest,
patent/licensing arrangements,
etc.) that might pose a conflict of
interest in connection with the
submitted article.

Article received: 11-26-2025

Revised article received:

12-24-2025

Accepted for publication:

03-02-2026

Free full article:
www.painphysicianjournal.com

Background: Single-injection peripheral nerve blocks (PNBs) are a cornerstone of multimodal perioperative analgesia. However, the duration of commonly used long-acting local anesthetics is finite; many patients experience abrupt and sometimes severe “rebound pain” as the block resolves. This phenomenon is particularly prominent after painful orthopedic procedures and may increase early opioid consumption and reduce patient satisfaction.

Objectives: To review the effectiveness and safety of pharmacologic adjuncts used to prolong adult single-injection PNBs and to provide practical, clinically oriented recommendations for their use.

Study Design: Narrative review.

Methods: I conducted a focused narrative review of randomized controlled trials, observational studies, and systematic reviews or meta-analyses evaluating adjunct medications administered with single-injection PNBs in adults. The agents considered were dexamethasone, dexmedetomidine, clonidine, morphine, fentanyl, buprenorphine, magnesium sulfate, midazolam, and ketamine. The outcomes of interest were sensory block duration and analgesia, postoperative opioid consumption, rebound pain, and adverse events.

Results: Dexamethasone, given intravenously or perineurally, consistently prolongs analgesia by approximately 6–8 hours and reduces early opioid use. Buprenorphine, administered perineurally, often extends analgesia to 24–48 hours but increases postoperative nausea. Dexmedetomidine modestly prolongs a block’s duration and improves a block’s quality, but is associated with dose-dependent bradycardia, hypotension, and sedation. Clonidine yields smaller gains in a block’s duration with similar hemodynamic and sedative concerns to dexmedetomidine. Magnesium sulfate and midazolam produce modest and more variable benefits. Ketamine has inconsistent effects on a block’s duration but may help mitigate hyperalgesia in select patients. Conventional opioids (morphine, fentanyl) provide little incremental benefit as perineural adjuncts; they also increase opioid-typical adverse effects.

Limitations: This is a narrative rather than a systematic review; heterogeneity among studies in block type, local anesthetic formulation, dosing, and outcome definitions precludes pooled quantitative estimates.

Conclusions: Dexamethasone and buprenorphine have the strongest and most consistent evidence for clinically meaningful prolongation of single-injection PNBs in adults and may be considered first-line adjuncts in appropriate patients. Dexmedetomidine, clonidine, magnesium, midazolam, and ketamine may be useful in some situations when their specific benefit-risk profiles are acceptable. Conventional opioids offer little advantage as perineural adjuncts and are not recommended for routine use. Evidence-based selection of adjuncts within a multimodal analgesic strategy can improve postoperative analgesia, reduce opioid exposure, and potentially attenuate rebound pain.

Key words: Peripheral nerve block, single-injection nerve block, adjuvant medications, perineural dexamethasone, buprenorphine, alpha-2 adrenergic agonists, regional anesthesia, postoperative analgesia, prolonged analgesia, multimodal analgesia

Pain Physician 2026; 29:307-315

Peripheral nerve blocks (PNBs) are an essential component of multimodal perioperative analgesia for a wide range of surgical procedures. When compared with opioid-centered strategies alone, PNBs are associated with superior postoperative pain control, reduced opioid requirements, and, in many settings, improved functional recovery and patient satisfaction (1,2). Single-injection PNB techniques are widely used because they are technically straightforward, do not require specialized ambulatory equipment, and can be used in both inpatient and outpatient practice environments (1,2).

The main limitation of single-injection PNBs is that long-acting local anesthetics have a finite sensory blockade duration. Once the block's anesthetic effect ends, some patients experience a pronounced increase in pain intensity that exceeds what might be expected. This "rebound pain" is particularly evident after painful orthopedic procedures such as shoulder, knee, and foot or ankle surgery and is associated with higher opioid use and lower patient satisfaction scores (3-5).

Continuous perineural catheter techniques can maintain analgesia for several days, but they require pumps, catheters, and personnel for placement, education, and follow-up. Catheter dislodgement, leakage, infection, and logistical barriers limit the routine use of continuous techniques, especially in ambulatory settings (1,2,6). For many institutions and patient populations, enhancing the performance of single-injection blocks is a more feasible and scalable strategy.

Over the past 2 decades, numerous pharmacologic adjuncts have been investigated to prolong a PNB's duration, improve its block quality, and reduce rebound pain. These adjuncts include corticosteroids (most notably dexamethasone), α_2 -adrenergic agonists (dexmedetomidine and clonidine), opioids (morphine, fentanyl, and buprenorphine), magnesium sulfate, benzodiazepines such as midazolam, and N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine (2,4,7,8). Early studies were small and heterogeneous, but subsequent randomized controlled trials and meta-analyses have clarified the magnitude of benefit and safety profiles for many of these agents (2,7,8).

The objective of this narrative review is to summarize the current evidence on commonly used adjunct medications for prolonging single-injection PNBs in adults. The review focuses on mechanism of action, clinical efficacy, typical dosing strategies, and adverse-effect profiles, and provides pragmatic recommenda-

tions informed by existing reviews and expert guidance in regional anesthesia and pain medicine (1,2,4,6-8).

METHODS

This review is narrative in design and does not follow a formal systematic review or meta-analysis protocol. The original source manuscript was developed using a targeted search of major biomedical databases to identify adult human studies evaluating adjunct medications administered intravenously or perineurally in conjunction with single-injection PNBs. Study designs included randomized controlled trials, nonrandomized comparative studies, observational cohorts, and systematic reviews or meta-analyses (1,2,4,6-8).

Eligible studies examined adjuncts administered at or near the time of block placement and reported outcomes related to block characteristics (duration of sensory and/or motor block, onset time), postoperative analgesia (time to first analgesic request, pain scores in the first 24–48 hours, opioid consumption), rebound pain, and adverse events (including neurotoxicity, hemodynamic instability, infection, respiratory depression, nausea, vomiting, and sedation). Neuraxial studies, pediatric populations, and systemic infusions administered independently of a PNB were excluded unless they provided information on mechanistic or safety considerations relevant to perineural use.

Because of substantial heterogeneity in block types; local anesthetic formulation and concentration; adjunct dosing; surgical procedure; and outcome definitions, quantitative pooling was not attempted. Instead, results from key randomized controlled trials and meta-analyses are summarized qualitatively, and the overall strength of evidence for each adjunct is estimated with reference to existing high-quality reviews (1,2,4,6-8).

Rebound Pain and Rationale for Adjunct Use

Rebound pain refers to the abrupt onset of moderate to severe pain as a PNB's anesthetic effect diminishes, often after a period of near-complete analgesia. Recent prospective work has identified younger age, high preoperative pain scores, and highly nociceptive procedures—such as shoulder arthroscopy—as important risk factors for more severe rebound pain (3,6,7). In such patients, rebound pain may result in increased opioid requirements, sleep disruption, and unplanned health care resources contact in the early postoperative period (3-5).

The mechanisms underlying rebound pain are in-

completely understood. Observational and experimental data suggest that ongoing nociceptive input during the period of dense block may contribute to peripheral and central sensitization, which is unmasked as soon as the block recedes (3-5). Inflammatory mediators accumulate in the surgical field, lowering nociceptor thresholds and amplifying afferent input. Central sensitization within dorsal horn and supraspinal structures may further enhance perceived pain intensity once sensory transmission resumes (5,8). Psychological factors, including patient expectations and the contrast between profound numbness and subsequent pain, likely contribute to the subjective experience as well.

Adjunct medications are used in this context with 2 main goals. The first is to prolong the period of effective analgesia so that peak nociceptive input occurs later in the postoperative course, when patients may be more prepared with systemic analgesics and less vulnerable to distress. The second is to modulate peripheral and central sensitization through anti-inflammatory, antinociceptive, or antihyperalgesic mechanisms, potentially blunting the intensity of rebound pain even if the duration of dense block itself does not increase dramatically (2,4,6-8).

Dexamethasone

Dexamethasone is a synthetic long-acting glucocorticoid that has become one of the most widely used adjuncts for PNBs. Its analgesic effects are mediated by both peripheral and central mechanisms. Peripherally, dexamethasone down-regulates the production of inflammatory mediators such as prostaglandins and bradykinin, reduces local edema, and may inhibit ectopic discharge from injured or inflamed nerves (4,7-9). Centrally, glucocorticoids modulate gene transcription of receptors and mediators involved in nociceptive processing, effects that outlast measurable plasma concentrations (4,6,9-11).

Multiple randomized trials and meta-analyses have confirmed that dexamethasone, whether administered perineurally or intravenously, prolongs the duration of sensory block and postoperative analgesia across a variety of block types and surgical procedures (9-11). In meta-analyses of brachial plexus, femoral, adductor canal, and sciatic blocks performed with long-acting local anesthetics, dexamethasone typically extends analgesia by approximately 6–8 hours beyond control blocks, often yielding total analgesic durations of 20–24 hours (9-11). Patients administered dexamethasone consistently report lower pain scores in the first postoperative day

and require fewer opioids compared with those administered a local anesthetic alone (9-12).

Early studies suggested that perineural administration might be superior to intravenous dosing. However, more recent randomized trials and quantitative syntheses comparing the 2 routes have shown minimal or no clinically important difference in block duration or analgesic outcomes for most upper and lower extremity blocks (13-17). Several randomized trials in interscalene and brachial plexus blocks, as well as pooled analyses, indicate that perineural and intravenous dexamethasone produce similar improvements in analgesia duration, time to rescue analgesic, and overall opioid consumption (13-17). These findings support the use of intravenous administration when there are concerns about off-label perineural use or when preservative-free formulations are not readily available.

Typical dexamethasone doses range from 4 mg to 8 mg. Dose-response data suggest that 4 mg may achieve most of the prolongation, with a plateau between 4 and 8 mg and little additional benefit at higher doses (9-12,15-17). The time of administration appears less critical, assuming the drug is given in close temporal proximity to block placement; effects are preserved when dexamethasone is administered intravenously at induction rather than at the conclusion of surgery (13-16).

The safety profile of single-dose perioperative dexamethasone administration is favorable. Transient postoperative hyperglycemia is the most common concern, particularly in patients with diabetes or impaired glucose tolerance, but clinically significant complications are rare (9-12,16,17). Available data do not demonstrate increased wound infection, delayed healing, or neurotoxicity when preservative-free formulations are used in recommended doses (6,8-12,15-17). Because dexamethasone is inexpensive, widely available, and supported by multiple high-quality meta-analyses, it can be considered a first-line adjunct for prolonging single-injection PNBs in adults, especially when overnight analgesia is desired and continuous catheter placement is impractical.

Dexmedetomidine

Dexmedetomidine is a highly selective α_2 -adrenergic agonist with sedative, anxiolytic, and analgesic properties. As a PNB adjunct, dexmedetomidine exerts both local and systemic effects. Locally, it induces vasoconstriction in perineural tissues, slowing the systemic uptake of a local anesthetic, and it hyperpolarizes neuronal

membranes by activating G-protein-coupled inwardly rectifying potassium channels and modulating hyperpolarization-activated cation currents (18-20). Systemically, its actions in the locus coeruleus and dorsal horn reduce sympathetic outflow and facilitate descending inhibitory pathways, diminishing nociceptive transmission (18-20).

Several randomized trials and meta-analyses reported that perineural dexmedetomidine added to long-acting local anesthetics prolongs sensory block duration and analgesia by approximately 4–5 hours compared with local anesthetic alone (18,19). These studies span brachial plexus, femoral, and sciatic blocks. They consistently report improved block quality, shorter onset times, and reduced early postoperative opioid consumption (18-21). A dose-response relationship has been suggested, with greater prolongation at higher perineural doses, although gains diminish beyond 50 µg–60 µg (18-21).

Recent work focusing on dose optimization indicates that perineural doses of 25 µg–50 µg often provide a favorable balance between an extended block duration and hemodynamic stability (21). Higher doses (≥ 1 µg/kg) are associated with more frequent bradycardia and hypotension, particularly in patients who are elderly or volume-depleted (18-21). When dexmedetomidine is administered intravenously as a bolus or infusion during block placement, it can also prolong analgesia but tends to produce more systemic sedation and hemodynamic effects than perineural administration at comparable overall doses (18-20).

In most clinical series, dexmedetomidine's main adverse effects are bradycardia, hypotension, and mild to moderate sedation (18-22). These events are usually manageable with standard treatments such as atropine, intravenous fluids, or vasopressors. Respiratory depression is rare, which makes dexmedetomidine attractive as an adjunct for patients at high risk for opioid-induced ventilatory impairment (18-20,22). Preclinical data do not demonstrate neurotoxicity at clinically relevant concentrations; some studies even suggest neuroprotective properties, though the clinical significance of this observation remains uncertain (20).

Dexmedetomidine is a reasonable second-line adjunct in adults when moderate block duration prolongation is desired and mild sedation and cardiovascular effects are acceptable. It may be particularly useful for patients undergoing highly painful procedures who are at increased risk of respiratory compromise with systemic opioids. Caution is warranted in patients with significant cardiac conduction disease, baseline brady-

cardia, or labile hemodynamics; close monitoring of heart rate and blood pressure is advisable whenever dexmedetomidine is used (18-22).

Clonidine

Clonidine, a partial α_2 -adrenergic agonist with a long elimination half-life, has a long history of use as an adjunct in neuraxial and peripheral regional anesthesia. Its mechanisms of action as a PNB adjunct are like those of dexmedetomidine but less selective, involving peripheral vasoconstriction, hyperpolarization of peripheral nerve fibers, and modulation of nociceptive neuropeptide release, as well as central sympatholytic and antinociceptive effects after systemic absorption (23-26).

Randomized trials evaluating clonidine (typically 50 µg–150 µg perineural) as an adjunct to intermediate- and long-acting local anesthetics in brachial plexus and lower extremity blocks showed modest prolongation of sensory block and analgesia, generally on the order of one to 2 hours (23,24). Some studies report slightly faster onset and improved block quality, but the magnitude of benefit is smaller than that seen with dexamethasone or dexmedetomidine (23-25). Meta-analyses combining peripheral and neuraxial data support a small but statistically significant reduction in early postoperative pain scores and opioid consumption using clonidine adjuncts, with more pronounced effects when added to intermediate-acting agents (25,26).

The adverse-effect profile of clonidine is dominated by sedation, hypotension, and bradycardia, which reflects its central sympatholytic activity and relatively prolonged half-life (23-26). These events are more likely to occur with higher doses, in elderly patients, and in those with baseline hemodynamic instability. Nevertheless, clonidine has an extensive clinical safety record for both neuraxial and peripheral applications; there is no convincing evidence of neurotoxicity when preservative-free formulations are used at typical perineural doses (25,26).

Given its modest efficacy and relatively frequent hemodynamic and sedative adverse effects, clonidine is best regarded as a second-line adjunct. It may be appropriate when dexamethasone and dexmedetomidine are unavailable or contraindicated, or when only limited prolonged analgesia is needed and hemodynamic stability can be carefully monitored. Doses of 50 µg–100 µg are commonly recommended to balance benefit and risk in adult patients (23-26).

Conventional Opioids: Morphine and Fentanyl

The discovery of peripheral μ -opioid receptors on nociceptive fibers raised the possibility that perineural-administered opioids might provide local analgesia while minimizing systemic side effects. Animal models showed that peripheral nerve injections of opioids can reduce inflammatory pain behaviors, especially in inflamed tissue. These findings prompted clinical studies of morphine and fentanyl as adjuncts to PNBs (4,7,27,28).

However, contemporary human data have been disappointing. Studies of perineural-administered morphine (2 mg–5 mg) in axillary and other limb blocks reveal, at best, small and inconsistent extensions in time to first analgesic request and no robust increase in block duration compared with systemic opioid use (27–29). Fentanyl, which is highly lipophilic and rapidly absorbed, has similarly inconsistent effects on block duration, and any benefit often resembles that of a short systemic bolus rather than a prolonged local action (4,30–33). A recent meta-analysis of fentanyl as a brachial plexus adjunct found no clinically meaningful benefit in terms of analgesic duration once study heterogeneity and bias were accounted for (32).

At the same time, perineural-administered morphine and fentanyl have the usual spectrum of opioid-related adverse effects, including sedation, pruritus, nausea, vomiting, and respiratory depression (27–33). Potential neuraxial spread or central uptake, especially when morphine is injected near the spinal canal, raises concern for delayed respiratory depression (27–29,31). Because any desired systemic opioid effect can be achieved more safely and predictably with intravenous or oral dosing, and because more effective and better-tolerated adjuncts are available, conventional opioids are not recommended as routine perineural adjuncts for single-injection PNBs in adults (4,7,27–33).

Buprenorphine

Buprenorphine is a partial μ -opioid receptor agonist and κ -receptor antagonist with very high receptor affinity and slow dissociation, producing prolonged analgesia after single doses. When administered perineurally, buprenorphine likely exerts both peripheral and central effects, acting on opioid receptors in the nerve vicinity and, after absorption, within the central nervous system (34–37).

Randomized controlled trials of perineural-administered buprenorphine (typically 0.15 mg–0.3 mg)

added to bupivacaine or ropivacaine for brachial plexus and sciatic blocks have reported some of the longest extensions in analgesia observed with any adjunct. Analgesic durations of 24 hours–48 hours are common; many patients require little or no rescue opioids in the first postoperative day (34–36). A recent meta-analysis of buprenorphine added to PNBs confirms these findings, showing clinically significant and statistically significant reductions in postoperative pain scores and opioid consumption compared with local anesthetic alone (37).

The main drawback of buprenorphine is an increased incidence of postoperative nausea and vomiting. Across trials, patients receiving perineural-administered buprenorphine had higher rates of nausea than controls, although these events are usually manageable with standard antiemetic prophylaxis and treatment (34–37). Sedation and respiratory depression appear less common than with equianalgesic doses of full μ -agonists, but careful monitoring is prudent, particularly in patients with significant comorbid respiratory or central nervous system disease (35–37). Current evidence does not demonstrate neurotoxicity when preservative-free buprenorphine is used perineurally at clinical doses (36,37).

Buprenorphine is especially attractive in ambulatory surgery and for patients undergoing highly painful procedures for whom prolonged analgesia from a single block can prevent the need for continuous catheters. Shoulder surgery; major foot and ankle reconstruction; and complex joint procedures are typical examples. In such settings, routine antiemetic prophylaxis and clear patient counseling regarding analgesia's expected duration are advisable. Buprenorphine use requires additional consideration for patients already receiving buprenorphine for opioid use disorder or chronic pain, for whom μ -opioid receptor occupancy and risk of causing withdrawal must be considered.

Magnesium Sulfate

Magnesium sulfate acts as a physiological NMDA receptor antagonist and calcium channel blocker. These properties make it an ideal adjunct for attenuating central sensitization and postoperative hyperalgesia. Both intravenous- and perineural-administered magnesium sulfate have been investigated in conjunction with regional anesthesia (38–40).

A recent meta-analysis of perineural-administered magnesium sulfate as a PNB adjunct concluded that it modestly prolongs sensory block and reduces early

postoperative pain intensity and opioid requirements across various block types (38). In most randomized trials, perineural-administered magnesium sulfate doses from 50 mg up to 150 mg added to long-acting local anesthetics prolonged analgesia from about one hour up to 2 hours and slightly improved early pain scores compared with local anesthetic alone (39,40). The magnitude of benefit is smaller than that seen with dexamethasone or buprenorphine but is relatively consistent across studies (38-40).

Perineural-administered magnesium sulfate appears to have a favorable safety profile. Adjunct doses rarely produce clinically significant changes in serum magnesium, and symptomatic hypermagnesemia is unlikely in patients with normal renal function. Clinical reports have not identified neurologic deficits attributable to perineural-administered magnesium, and pre-clinical data do not suggest neurotoxicity at clinically relevant concentrations (38-40).

Magnesium sulfate can be considered a secondary adjunct for adult PNBs, particularly when first-line agents are contraindicated or unavailable, or when there is a specific concern about central sensitization and hyperalgesia. Its modest efficacy and good safety profile make it a reasonable option where incremental prolongation is desired but high-potency agents, such as buprenorphine or α_2 -agonists, are not preferred.

Midazolam

Midazolam is a short-acting benzodiazepine that enhances γ -aminobutyric acid A (GABA_A) receptor-mediated inhibitory neurotransmission. Experimental work suggests that benzodiazepines may modulate neuronal excitability in dorsal root ganglia and peripheral nerves, leading to potential perineural analgesic effects. These observations prompted evaluation of midazolam as a PNB adjunct (41,42).

Clinical data are limited. In randomized trials, perineural-administered midazolam (1 mg–5 mg) added to long-acting local anesthetics for brachial plexus or lower extremity blocks modestly prolonged analgesia (often from 2 hours up to 3 hours) and reduced early postoperative pain scores compared with local anesthetic alone (41,42). Some investigations reported synergistic effects when midazolam is combined with certain local anesthetics, but sample sizes were small (41).

Sedation is the most common adverse effect and may be desirable in some settings but problematic for ambulatory patients for whom rapid cognitive recovery

is important. Respiratory depression is uncommon at the perineural-administered doses used in these studies, especially when systemic sedatives and opioids are minimized (41,42). Historical concerns about neurotoxicity stem primarily from intrathecal-administered benzodiazepines at high doses with older, preservative-containing formulations. Contemporary PNB trials using preservative-free midazolam have not identified convincing neurotoxicity signals, but the total number of trial patients and the duration of follow-up remain are limited (42).

Given the modest evidence base and residual concern regarding neural safety, midazolam should not be considered a first-line PNB adjunct. It may be reserved for select patients when other agents are unsuitable and where mild, adjunctive sedation is acceptable. When used, preservative-free formulations should be chosen, and the total benzodiazepine dosage from all perioperative sources should be considered.

Ketamine

Ketamine is a dissociative anesthetic and potent NMDA receptor antagonist. It has established roles for systemic perioperative analgesia and chronic pain management. Its potential as a PNB adjunct arises from its actions on NMDA receptors, voltage-gated ion channels, and local inflammatory mediators, which may reduce both nociception and hyperalgesia (43-45).

Randomized trials of perineural-administered ketamine (typically 25 mg–50 mg) added to ropivacaine or bupivacaine in brachial plexus, ankle, or foot blocks have yielded mixed results. Some studies showed modest analgesia prolongations and reductions in early postprocedure opioid consumption, whereas others showed little or no benefit in block duration or pain scores (43,44). In several reports, ketamine seemed to influence pain intensity and opioid use more than objective block duration, suggesting that its primary benefit may lie in attenuating central sensitization rather than simply extending sensory blockade (43-45).

At the low perineural-administered doses studied, psychomimetic adverse effects, such as hallucinations and dysphoria, occurred infrequently, particularly in patients with prior psychiatric disease or when systemic ketamine was also administered (43-45). Mild increases in heart rate and blood pressure are possible. Available data have not reported neurotoxicity at clinical perineural-administered doses, although the total number of patients studied was relatively small (43-45).

Given inconsistent clinical efficacy and the avail-

ability of more reliable adjuncts, ketamine should not be used routinely as a PNB adjunct in adults. It may be considered in highly selected patients—such as those at particular risk of central sensitization, chronic postsurgical pain, or opioid-induced hyperalgesia—especially when systemic ketamine is already part of the perioperative analgesic plan.

Synthesis and Practical Considerations

When the evidence across agents is considered together, a practical hierarchy for adult single-injection PNB adjuncts emerges. Dexamethasone has robust support from multiple randomized trials and meta-analyses that showed clinically meaningful analgesia prolongation, reduced opioid consumption, and a favorable safety profile with either perineural or intravenous administration (6-11,13-17). Buprenorphine provides some of the longest extensions in postoperative analgesia, often into the second postprocedure day, and is particularly valuable for painful ambulatory procedures, albeit at the cost of increased nausea (34-37).

Dexmedetomidine has a moderate effect on prolonging a block's duration, improvement in block quality, and opioid-sparing effects, but is limited by dose-dependent bradycardia, hypotension, and sedation (18-22). It is especially useful when respiratory stability is a priority and mild sedation is acceptable. Clonidine provides more modest benefits with a similar hemodynamic and sedative profile and is best reserved for scenarios in which other agents are unavailable or contraindicated (23-26).

Magnesium sulfate and midazolam provide smaller increments in block duration compared to the other adjuncts, but may be helpful secondary options in carefully selected patients when first-line agents are not suitable (38-42). Ketamine has a good mechanistic rationale and may be useful in patients at high risk for central sensitization or chronic pain; however, supporting clinical data for its use as a PNB adjunct are relatively sparse and heterogeneous (43-45). Conventional opioids, such as morphine and fentanyl, have little incremental benefit in terms of block duration yet carry the full spectrum of opioid-related adverse effects and therefore should not be used as routine perineural adjuncts (27-33).

Adjunct selection must be individualized. Factors to consider include expected pain intensity and duration for the planned procedure; the feasibility of continuous perineural catheter techniques; inpatient vs ambulatory context; patient comorbidities such as diabetes, cardiovascular disease, and sleep-disordered

breathing; existing opioid tolerance; and institutional formulary and regulatory constraints (1,2,4,6-8). For example, a patient who is healthy and ambulatory who undergoes shoulder arthroscopy might be well served by an interscalene block with a long-acting local anesthetic plus intravenous-administered dexamethasone, whereas a young patient who undergoes major ankle reconstruction could be an ideal candidate for a sciatic block supplemented with perineural buprenorphine. In a frail older adult who has significant cardiovascular disease, dexamethasone alone may be preferred over α_2 -agonists to minimize hemodynamic risk.

Combination strategies, such as dexamethasone paired with a low-dose α_2 -agonist or magnesium sulfate, are used in some practices but remain incompletely studied. Potential additive benefits must be weighed against the possibility of cumulative adverse effects such as hyperglycemia, bradycardia, hypotension, and off-label neurotoxicity concerns (4,6-8,18-22,38-40). Until more robust data are available, combination regimens should be used cautiously, with careful patient selection and close monitoring.

Future Directions and Conclusions

Further research is needed to refine adjunct use for single-injection PNBs in adults. High-quality head-to-head trials comparing leading agents—such as dexamethasone, buprenorphine, and dexmedetomidine—within specific block types and surgical procedures would help define optimal choices in common clinical scenarios. Dose-finding studies to determine ceiling effects and safe upper limits, particularly for buprenorphine and α_2 -agonists, are a priority. Trials evaluating combining adjuncts and their cumulative toxicity are also warranted. Long-term observational data are needed to assess potential neurocognitive or neuropathic consequences of repeated perineural exposure to adjuncts. Finally, comparative effectiveness and cost-utility analyses of adjunct-based strategies vs continuous catheter techniques would inform implementation in resource-constrained settings (1,2,4,6-8,9-11,38).

In conclusion, pharmacologic adjuncts can substantially enhance the effectiveness of single-injection PNBs in adults. Among currently available agents, dexamethasone and buprenorphine stand out as first-line options. They provide robust and clinically important analgesia prolongation with acceptable safety profiles. Dexmedetomidine and clonidine offer useful alternatives when their sedative and cardiovascular effects are acceptable, while magnesium sulfate,

midazolam, and ketamine have more limited, but potentially valuable, roles in selected patients. Conventional opioids offer little advantage as perineural-administered adjuncts and are best reserved for systemic rescue therapy. Thoughtful, evidence-based

selection and dosing of adjuncts, integrated into a comprehensive multimodal analgesic strategy, can improve postoperative pain control, reduce opioid exposure, and mitigate rebound pain across a broad spectrum of surgical procedures.

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