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Perioperative Use of Benzodiazepines in Orthopedic Surgery: A Brief Narrative Review

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Keywords: benzodiazepines, orthopedic anesthesia, regional anesthesia, perioperative sedation, anxiolysis, amnesia, enhanced recovery after surgery, ERAS, outpatient orthopedic surgery

<https://doi.org/10.52965/001c.158573>

Orthopedic Reviews

Vol. 18, 2026

Benzodiazepines are frequently administered in orthopedic anesthesia for anxiolysis, sedation, amnesia, and seizure prophylaxis. Their role continues to evolve with the growing use of regional anesthesia, outpatient joint procedures, and enhanced recovery after surgery (ERAS) pathways. This narrative review examines the pharmacology, mechanisms of action, clinical indications, contraindications, and key clinical studies of benzodiazepines commonly used in the operating room in the United States, with a specific focus on their application in orthopedic surgical practice.

INTRODUCTION

Orthopedic surgery represents one of the highest-volume surgical specialties in the United States, with millions of procedures performed annually. Advances in regional anesthesia, multimodal analgesia, and enhanced recovery after surgery (ERAS) protocols have reshaped perioperative anesthetic goals, emphasizing early mobilization, participation in physical therapy, and rapid cognitive recovery.^{1,2}

Historically, benzodiazepines were routinely administered as premedication to reduce perioperative anxiety and facilitate anesthetic induction. However, growing evidence linking benzodiazepine exposure to postoperative delirium, prolonged sedation, and delayed functional recovery, particularly among elderly orthopedic patients, has prompted a more selective and individualized approach to their use.^{3,4}

Despite these concerns, benzodiazepines continue to play an important role in contemporary orthopedic anesthesia. They may be beneficial for facilitating neuraxial anesthesia and peripheral nerve block placement, improving tolerance of tourniquet use, and managing perioperative anxiety in appropriately selected patients. Additionally, the development of newer agents such as remimazolam, with more favorable pharmacokinetic profiles, may better align benzodiazepine use with modern ERAS-driven orthopedic practice.⁵

MECHANISM OF ACTION

Benzodiazepines exert their clinical effects through modulation of the gamma-aminobutyric acid type A (GABA-A) receptor. GABA is the principal inhibitory neurotransmitter receptor in the central nervous system. GABA-A receptors are ligand-gated chloride channels composed of multiple

subunits (typically two α , two β , and one γ subunit), with benzodiazepines binding at the interface between the α and γ subunits. This binding does not directly activate the receptor; rather, benzodiazepines act as positive allosteric modulators, increasing the affinity of the receptor for endogenous GABA and enhancing chloride influx when GABA is present.⁶

The resulting hyperpolarization of neuronal membranes leads to decreased neuronal excitability and produces dose-dependent anxiolytic, sedative, amnestic, anticonvulsant, and muscle-relaxant effects. Importantly, benzodiazepines exhibit a ceiling effect on respiratory depression when used alone, a property that historically contributed to their widespread use in anesthetic practice. However, synergistic respiratory depression occurs when benzodiazepines are combined with opioids or other sedatives, a common scenario in orthopedic anesthesia.⁷

Subunit specificity partially explains the clinical effects of benzodiazepines. $\alpha 1$ -containing GABA-A receptors are primarily responsible for sedation and anterograde amnesia, while $\alpha 2$ and $\alpha 3$ subunits mediate anxiolysis and muscle relaxation. This pharmacologic profile is particularly relevant in orthopedic surgery, where anxiolysis and amnesia during neuraxial or peripheral nerve block placement are desired, but excessive sedation may impair intraoperative communication and postoperative recovery.^{6,8}

Benzodiazepines have no intrinsic analgesic properties and may paradoxically worsen postoperative pain outcomes by interfering with sleep architecture and increasing delirium risk. In orthopedic populations, especially older adults undergoing hip fracture repair or total joint arthroplasty, these effects may hinder early mobilization and rehabilitation, key determinants of functional postoperative recovery.^{3,4}

Table 1. Pharmacokinetic Characteristics

Agent	IV Onset	Half-Life	Metabolism	Active Metabolites
Midazolam	30–60 s	1.7–3.5 h	CYP3A4	Yes
Lorazepam	3–5 min	11–22 h	Glucuronidation	No
Diazepam	2–5 min	20–50 h	CYP2C19/3A4	Yes
Remimazolam	Rapid	~5–10 min	Esterase	No

MIDAZOLAM

Midazolam was synthesized in the early 1970s by Hoffmann-La Roche and introduced into clinical practice in the late 1970s as the first water-soluble benzodiazepine. This chemical modification allowed for reliable intravenous administration without the need for propylene glycol, distinguishing it from earlier agents such as diazepam.⁷

Midazolam has a rapid onset (30–60 seconds intravenous) and a relatively short elimination half-life (1.7–3.5 hours), with hepatic metabolism via cytochrome P450 3A4 to active hydroxylated metabolites. These properties make midazolam the most commonly used benzodiazepine in United States operating rooms.⁹

In orthopedic anesthesia, midazolam is frequently administered for anxiolysis and amnesia during neuraxial anesthesia, peripheral nerve block placement, and monitored anesthesia care for upper and lower extremity procedures. It is particularly useful during tourniquet application and positioning, where patient discomfort and anxiety may otherwise compromise procedural success.

Midazolam is inexpensive, widely available in generic formulations, and routinely stocked in perioperative areas. Its low cost and predictable effects have reinforced its continued dominance despite growing concerns regarding postoperative cognitive outcomes.

LORAZEPAM

Lorazepam was developed in the early 1960s and introduced into clinical use in 1977. Unlike midazolam and diazepam, lorazepam undergoes direct hepatic glucuronidation rather than oxidative metabolism, rendering its pharmacokinetics less dependent on hepatic enzyme activity.¹⁰

Lorazepam has a slower onset and longer duration of action (elimination half-life 11–22 hours) compared with midazolam. While this makes it effective for sustained anxiolysis and seizure prophylaxis, it limits its usefulness for intraoperative orthopedic anesthesia, where rapid recovery is desired.^{10,11}

In contemporary orthopedic practice, lorazepam is therefore infrequently used intraoperatively and is more commonly encountered in trauma settings, postoperative agitation management, or intensive care unit sedation.

Although inexpensive and widely available, its prolonged sedative effects and well-established association with postoperative delirium have contributed to declining routine use in elective orthopedic surgery.

DIAZEPAM

Diazepam, introduced in 1963, was the first benzodiazepine to gain widespread clinical adoption and rapidly replaced barbiturates for anxiolysis and sedation. It played a foundational role in the early development of modern anesthetic practice.⁷

Diazepam has a rapid onset but an exceptionally long elimination half-life (20–50 hours), with multiple active metabolites, including desmethyldiazepam. These pharmacokinetic characteristics result in prolonged sedation and psychomotor impairment, particularly in elderly patients.^{7, 12}

In contemporary orthopedic anesthesia, diazepam has largely been abandoned for intraoperative use. Its role is now limited to chronic outpatient management of muscle spasm or anxiety rather than perioperative administration.

Although inexpensive, diazepam's unfavorable recovery profile renders it poorly suited to modern orthopedic anesthetic goals emphasizing early ambulation and discharge.

REMIMAZOLAM

Remimazolam is a novel ultra-short-acting benzodiazepine developed in the early 2000s and approved for procedural sedation in the United States in 2020. It was designed by combining the benzodiazepine core structure with an ester linkage, allowing for rapid metabolism by tissue esterases.¹³

Remimazolam exhibits rapid onset, predictable clearance, and context-insensitive recovery, closely resembling propofol while retaining benzodiazepine reversibility with flumazenil. Unlike midazolam, it does not produce active metabolites and is largely independent of hepatic or renal function.^{13,14}

Early studies suggest that remimazolam may be particularly advantageous for ambulatory orthopedic surgery and procedures performed under regional anesthesia, where rapid cognitive recovery is essential. However, orthopedic-specific outcome data remain limited.

Widespread adoption of remimazolam is limited by high acquisition costs, restricted formulary access, clinician unfamiliarity, and the absence of large, orthopedic-specific randomized trials assessing delirium, postoperative mobilization, and hospital length of stay. Accordingly, current utilization is largely restricted to academic institutions and ambulatory procedural environments.

Table 2. Orthopedic-Specific Clinical Use

Agent	Neuraxial	Peripheral Nerve Block	Ambulatory Surgery	Geriatric Patients
Midazolam	Yes	Yes	Yes	Use with caution
Lorazepam	Limited	Limited	No	Avoid
Diazepam	No	No	No	Avoid
Remimazolam	Emerging	Emerging	Yes	Insufficient data

POSTOPERATIVE OUTCOMES AND DELIRIUM

Orthopedic patients, particularly older adults undergoing hip fracture repair or joint arthroplasty, are at increased risk of postoperative delirium. Benzodiazepine exposure has consistently been identified as an independent risk factor, with observational studies demonstrating approximately a 1.5–2.5-fold increase in delirium incidence and longer hospital length of stay among exposed patients. This association persists after adjustment for comorbidity burden, anesthesia type, and surgical complexity.^{3,4,15,16}

In light of these findings, routine or indiscriminate administration of benzodiazepines in orthopedic anesthesia should be avoided. Instead, their use should be selective and guided by clear clinical indications, patient-specific risk factors, and procedural requirements. Factors such as advanced age, baseline cognitive impairment, frailty, polypharmacy, and prior history of delirium should prompt heightened caution. When benzodiazepines are considered necessary, clinicians should employ the lowest effective dose, choose agents with favorable pharmacokinetic profiles, and integrate their use within a broader multimodal and ERAS-aligned anesthetic strategy to minimize adverse cognitive and functional outcomes.

CONCLUSION

Benzodiazepines remain an important, albeit increasingly selective component of anesthetic management in orthopedic surgery. Historically administered routinely for premedication and intraoperative anxiolysis, their role has evolved alongside broader shifts toward regional anesthesia, ambulatory surgery, and ERAS pathways. In contemporary orthopedic practice, the benefits of benzodiazepines, namely anxiolysis, amnesia, facilitation of neuraxial and peripheral nerve block placement, and management of intraoperative discomfort, must be carefully balanced against well-documented risks, particularly in older and medically complex patients.

Among available agents, midazolam continues to be the most widely utilized benzodiazepine in the operating room

due to its rapid onset, short duration, and favorable pharmacokinetic profile. Its use remains common during neuraxial anesthesia, peripheral nerve block placement, and monitored anesthesia care for upper and lower extremity procedures. However, growing evidence linking benzodiazepine exposure to postoperative delirium, delayed cognitive recovery, and prolonged hospitalization has prompted more judicious dosing strategies, especially in geriatric orthopedic populations undergoing hip fracture repair or joint arthroplasty.

Longer-acting agents such as lorazepam and diazepam have largely fallen out of favor in routine orthopedic anesthesia because of their prolonged sedative effects and association with delayed functional recovery. Their use is now generally limited to specific clinical contexts, such as seizure management or intensive care unit sedation, rather than elective orthopedic surgery. In contrast, newer agents such as remimazolam represent a promising development, offering rapid onset, predictable metabolism, and faster recovery profiles that may better align with ambulatory orthopedic procedures and ERAS principles. While early clinical studies suggest favorable safety and efficacy, further orthopedic-specific outcome data are needed before widespread adoption can be recommended.

Ultimately, optimal use of benzodiazepines in orthopedic anesthesia requires individualized patient assessment, consideration of surgical complexity, and alignment with perioperative goals emphasizing early mobilization and cognitive preservation. As orthopedic surgical volumes continue to rise and patient populations age, anesthesiologists must remain attentive to evolving evidence and emerging pharmacologic options. Future research should focus on procedure-specific outcomes, delirium mitigation strategies, and comparative effectiveness of benzodiazepines versus alternative anxiolytic and sedative agents within modern orthopedic care pathways.

Submitted: January 18, 2026 EDT. Accepted: January 22, 2026 EDT. Published: March 12, 2026 EDT.

REFERENCES

1. Grossi P. Enhanced Recovery After Surgery (ERAS) Protocols in Orthopaedic Surgery: Opioids or Not Opioids? *J Pain Res.* 2025;18:1683-1695. doi:[10.2147/JPR.S496891](https://doi.org/10.2147/JPR.S496891). PMID:40176785
2. Neuman MD, Feng R, Carson JL, et al. Spinal Anesthesia or General Anesthesia for Hip Surgery in Older Adults. *N Engl J Med.* 2021;385(22):2025-2035. doi:[10.1056/NEJMoa2113514](https://doi.org/10.1056/NEJMoa2113514). PMID:34623788
3. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc.* 2001;49(5):516-522. doi:[10.1046/j.1532-5415.2001.49108.x](https://doi.org/10.1046/j.1532-5415.2001.49108.x). PMID:11380742
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-922. doi:[10.1016/S0140-6736\(13\)60688-1](https://doi.org/10.1016/S0140-6736(13)60688-1). PMID:23992774
5. Antonik LJ, Goldwater DR, Kilpatrick GJ, et al. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics. *Anesth Analg.* 2012;115(2):274-283. doi:[10.1213/ANE.0b013e31823f0c28](https://doi.org/10.1213/ANE.0b013e31823f0c28). PMID:22190555
6. Rudolph U, Möhler H. GABA-based therapeutic approaches: GABAA receptor subtype functions. *Curr Opin Pharmacol.* 2006;6(1):18-23. doi:[10.1016/j.coph.2005.10.003](https://doi.org/10.1016/j.coph.2005.10.003). PMID:16376150
7. Reves JG, Fragen RJ, Vinik HR, et al. Midazolam: pharmacology and uses. *Anesthesiology.* 1985;62(3):310-324. doi:[10.1097/00000542-198503000-00017](https://doi.org/10.1097/00000542-198503000-00017). PMID:3156545
8. Sieghart W. Structure and pharmacology of gamma-aminobutyric acidA receptor subtypes. *Pharmacol Rev.* 1995;47(2):181-234. doi:[10.1016/S0031-6997\(25\)06840-1](https://doi.org/10.1016/S0031-6997(25)06840-1). PMID:7568326
9. Greenblatt DJ, Ehrenberg BL, Gunderman J, et al. Pharmacokinetic and electroencephalographic study of intravenous diazepam, midazolam, and placebo. *Clin Pharmacol Ther.* 1989;45(4):356-365. doi:[10.1038/clpt.1989.41](https://doi.org/10.1038/clpt.1989.41). PMID:2702793
10. Greenblatt DJ, Schillings RT, Kyriakopoulos AA, et al. Clinical pharmacokinetics of lorazepam. I. Absorption and disposition of oral 14C-lorazepam. *Clin Pharmacol Ther.* 1976;20(3):329-341. doi:[10.1002/cpt1976203329](https://doi.org/10.1002/cpt1976203329). PMID:8232
11. Young CC, Prielipp RC. Benzodiazepines in the intensive care unit. *Crit Care Clin.* 2001;17(4):843-862. doi:[10.1016/S0749-0704\(05\)70183-4](https://doi.org/10.1016/S0749-0704(05)70183-4). PMID:11762264
12. Shader RI, Greenblatt DJ. The use of benzodiazepines in clinical practice. *Br J Clin Pharmacol.* 1981;11 Suppl 1(Suppl 1):5S-9S. doi:[10.1111/j.1365-2125.1981.tb01832.x](https://doi.org/10.1111/j.1365-2125.1981.tb01832.x). PMID:6133535
13. Pambianco DJ, Borkett KM, Riff DS, et al. A phase IIb study comparing the safety and efficacy of remimazolam and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc.* 2016;83(5):984-992. doi:[10.1016/j.gie.2015.08.062](https://doi.org/10.1016/j.gie.2015.08.062). PMID:26363333
14. Sieber FE, Neufeld KJ, Gottschalk A, et al. Effect of Depth of Sedation in Older Patients Undergoing Hip Fracture Repair on Postoperative Delirium: The STRIDE Randomized Clinical Trial. *JAMA Surg.* 2018;153(11):987-995. doi:[10.1001/jamasurg.2018.2602](https://doi.org/10.1001/jamasurg.2018.2602). PMID:30090923
15. Deiner S, Westlake B, Dutton RP. Patterns of surgical care and complications in elderly adults. *J Am Geriatr Soc.* 2014;62(5):829-835. doi:[10.1111/jgs.12794](https://doi.org/10.1111/jgs.12794). PMID:24731176
16. Antonik LJ, Goldwater DR, Kilpatrick GJ, et al. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part I. Safety, efficacy, and basic pharmacokinetics. *Anesth Analg.* 2012;115(2):274-283. doi:[10.1213/ANE.0b013e31823f0c28](https://doi.org/10.1213/ANE.0b013e31823f0c28). PMID:22190555