Agency Mission: To protect and promote the welfare of the people of Kansas.

**Kansas Board of Nursing**
**Landon State Office Building, Room 509**
**APRN Committee Agenda**
**March 24, 2026**

**NOTE: The audience may attend in person or via Zoom. Link to access meeting to follow agenda.**

**Time: 2:00 p.m. – 3:00 p.m.**

Committee Members:
Melissa Oropeza, DNP, APRN-BC, CGRN, Chair
Amy Hite, EdD(c), DNP, EdS, APRN, FNP-BC, V-Chair
Tosha Fields, MSN, RN, LNHA, LNC
Karen "Kelly" Fritz, MSN, APRN, CNM
Kimyatta Brent, DNP, MS, CRNA
Abigail Lehman, MSN, APRN, FNP-BC, WCC
Tracy Clark, DNP, APRN, FNP-C, ACHPN – K-TRACS

Staff: Carol Moreland, MSN, RN – Executive Administrator
Jill Simons – Executive Assistant

I. Quorum (minimum of 4 members present) – Yes or No

II. Call to Order

III. Review of on-site packet

IV. Additions/Revisions to the agenda

V. Announcements

VI. Approval of minutes – December 9, 2025

**Consent Item Agenda**
1. APRN Programs approved for Licensure

VII. Unfinished Business
1. Prescription Monitoring Program (PMP) Committee Report
2. Update on CNM-I Regulations
   a. K.A.R. 100-28b-8
   b. K.A.R. 100-28b-9
3. Update on revision of K.A.R. 60-9-106
4. Five-year Combined Statute and Regulation Review
   a. K.S.A. 65-1131
   b. K.S.A. 65-1154
   c. K.S.A. 65-1155
   d. K.A.R. 60-11-116

VIII. New Business

a. Ketamine Guidelines & Any New Legislation – KANA *(from Practice Committee)*
b. APRNs Ordering X-rays – KAPN *(from Practice Committee)*
c. Legal Review and Statement on KDHE Request *(from Practice Committee)*
d. APRNs Sign Off on KSHSAA Form *(from Practice Committee)*

IX. Agenda for June 2026 Committee meeting

X. Adjourn

**Committee Responsibilities:**
**To review and recommend revisions to statutes and regulations for approval of APRN and RNA programs in collaboration with the Education Committee.**

**Please note: Additional items which have come to the attention of the Board or Committee will be handled as time permits. Agenda is subject to change based upon items to come before the Board. Handouts or copies of materials brought to the Board or Committee for discussion by Committee Members or visitors must be submitted to staff 30 calendar days prior to start of the meeting. Any items received after the 30th calendar day may be addressed at the meeting at the discretion of the President of the Board or Chairperson of the Committee.**

**You are invited to a Zoom webinar!**
**When: Mar 24, 2026 02:00 PM Central Time (US and Canada)**
**Topic: Kansas State Board of Nursing - APRN Committee**

**Join from PC, Mac, iPad, or Android:**
**https://us02web.zoom.us/j/89861974526?pwd=pWapZ8AyxRZc7xflxSwcTrErNPb3PU.1**
**Passcode:KsbnAPComm**

**Phone one-tap:**
**+16699006833,,89861974526#,,,,*9516315353# US (San Jose)**
**+17193594580,,89861974526#,,,,*9516315353# US**

**Join via audio:**
**+1 669 900 6833 US (San Jose)**
**+1 719 359 4580 US**
**+1 253 205 0468 US**
**+1 253 215 8782 US (Tacoma)**
**+1 346 248 7799 US (Houston)**
**+1 669 444 9171 US**
**+1 507 473 4847 US**
**+1 564 217 2000 US**
**+1 646 876 9923 US (New York)**
**+1 646 931 3860 US**
**+1 689 278 1000 US**
**+1 301 715 8592 US (Washington DC)**
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**Carol Moreland [KSBN]**

**From:** Warran Wiebe [KSBHA]
**Sent:** Tuesday, January 20, 2026 12:39 PM
**To:** Carol Moreland [KSBN]; Derenda Mitchell [KSBHA]
**Cc:** Susan Gile [KSBHA]; LeeAnn Hunter-Roach [KSBHA]
**Subject:** RE: CNM-I Council

Carol:

Forwarding your email below to Derenda Mitchell, KSBHA General Counsel.

Derenda is the Board attorney that primarily works with the CNM-I Council.

Thank you.

Warran

Warran D. Wiebe
Deputy General Counsel

Kansas State Board of Healing Arts
800 SW Jackson, Suite 700
Topeka, KS 66612

(785) 296-3288
warran.wiebe@ks.gov
https://ksbha.ks.gov



Kansas

**State Board of Healing Arts**

**From:** Carol Moreland [KSBN] <carol.moreland@ks.gov>
**Sent:** Wednesday, January 14, 2026 10:20 AM
**To:** Warran Wiebe [KSBHA] <warran.wiebe@ks.gov>; Susan Gile [KSBHA] <susan.gile@ks.gov>
**Subject:** CNM-I Council

Good morning,

KSBN is to submit the names of four licensed nurse midwives that will represent KSBN on the CNM-I council. Here are their names and email addresses:

1. Amber Clark, CNP, CNM clark.amber@live.com
2. Jamie Harrington, CNP, CNM (former CNM-I and former birth center owner) midwifeformoms@gmail.com
3. Veronica Mullet, CNM, (also former CNM-I and current homebirth practice owner) veronica.s.mullet@gmail.com
4. Kelly Fritz, MSN, CNM KELFritzCNM@gmail.com

Please let me know if there is anything else you need from me regarding this.

Kansas
State Board of Nursing

***The mission of the Board of Nursing is to protect and promote the welfare of the people of Kansas.***

**Carol Moreland, MSN, RN**
*Executive Administrator*

**Kansas State Board of Nursing**
*900 SW Jackson, Suite 1051*
*Topeka, KS 66612*

**1-785-296-5752**
carol.moreland@ks.gov

**ksbn.kansas.gov**

**e-Notify** - This will allow you to receive real-time automated license and discipline notifications.
- Enroll yourself in e-Notify as an individual/institution/employer here

**Kansas State Board of Nursing (KSBN)**
**Statute and Regulation Review Form**

**STATUTE or RULE AND REGULATION**

**Number:** K.S.A. 65-1131
**Article Title:** Kansas Nurse Practice Act
**Title:** Definitions.
**Type (new, amended):** Amended
**Effective Date (history):** 1949
**Authorizing KSA(s) and/or Related KAR(s):**
**Implementing KSA(s) and/or Related KAR(s):**
History: L. 1949, ch. 331, § 1; L. 1963, ch. 314, § 1; L. 1975, ch. 316, § 1; L. 1978, ch. 240, § 1; L. 1980, ch. 186, § 1; L. 1983, ch. 206, § 6; L. 2011, ch. 114, § 39; L. 2018, ch. 42, § 2; July 1, 2019.

**KSBN OVERSIGHT STRUCTURE**
**KSBN Oversite Committee:** APRN
**Staff Review Owner:** Executive Administrator
**Date Last Reviewed by Committee**:
**Review Year Cycle Number**: Year 1. 2026
**Quarter of Review:** Q1

**PURPOSE:** Briefly describe the public purpose of the statute, rule and regulation. (*limited to 400 characters)*

Definitions relating to "Advanced practice registered nurse."

**Section 1. Environmental Assessment**

Is KSBN operating in good faith and reasonable compliance with this statute, rule or regulation? **Yes.**

Is the statute, rule or regulation in agreement with current healthcare practice? **Yes.**

How does this statute, rule or regulation compare with other states, model legislation, or healthcare accreditation standards? **This statute is comparable to most states.**

Have there been any changes in the National Licensure Compact, case law, statutes, rules or regulations that might impact this statute, rule or regulation? **No.**

***If changes are needed in statute, rule or regulation, what are the key elements of the substance of the revisions that need to be made?**

**Section 2. NECESSITY (Primarily for Rules and Regulations)**

***Is the statute necessary for the implementation and administration of state law, or could it be revoked?** (*necessary/ could be revoked)* Necessary.

Does the statute serve an identifiable public purpose in support of state law? *yes/no* **Yes.**

Is the statute broader than necessary to meet its public purpose? (*yes/no)* **No.**

**Section 3. TIES TO FEDERAL PROGRAMS (Typically not applicable to KSBN)**

***Is the rule and regulation federally required for state participation in a federal program or authority?** (*yes/no*) **No. NA.**

Is the rule and regulation necessary for federal delegation of enforcement authority to the State? (*yes/no*) **No. NA.**

If the rule and regulation is federally required, the state and federal program names and the federal agency name (*yes/no*) **No. NA.**

Could federal moneys be in jeopardy under current law if the rule and regulation were repealed? (*yes/no*) **No. NA.**

If federal moneys could be in jeopardy, the approximate amount received for the most recent fiscal year. (*yes/no*) **No. NA.**

**Section 4. POTENTIAL FOR REVOCATION (Primarily for Rules and Regulations)**

Briefly describe how revocation would affect Kansans. (*limited to 600 characters*)

**Removal of this statue would severely limit if not prevent KSBN from implementing other statutes in the KNPA. Definitions are needed for all stakeholders to know what the statute means.**

If the rule and regulation is not in active use, would revocation require a change to the authorizing or implementing statute? (*in active use/ yes/ no*) **This statute is in active use.**

***If the rule and regulation is not in active use and revocation would require a change to the authorizing or implementing statute, which change(s)?** (*limited to 400 characters*) **This statute is in active use.**

**ADDITIONAL INFORMATION**

Additional information necessary to understanding the necessity of this rule and regulation (*limited to 1,200 characters*)

**SUMMARY OF REVIEW**

Based on the summary of the information above, this KSBN Committee recommends

_____ no changes with review for another 5 years, or

_____ the Board develop a plan for revision and adoption as defined by Kansas laws.

Revisions need to address the key elements summarized in the Environmental Assessment.

Committee Reviewing:

Committee Chair: Date of Meeting:

Date Presented to Board: Board Chair:

https://ksrevisor.gov/statutes/chapters/ch65/065_011_0013.html

Proposed Changes:

65-1113. Definitions. When used in this act and the act of which this section is amendatory:
(a) "Board" means the board of nursing.
(b) "Diagnosis" in the context of nursing practice means that identification of and discrimination between physical and psychosocial signs and symptoms essential to effective execution and management of the nursing regimen and shall be construed as distinct from a medical diagnosis.
(c) "Treatment" means the selection and performance of those therapeutic measures essential to effective execution and management of the nursing regimen, and any prescribed medical regimen.
(d) Practice of nursing. (1) The practice of professional nursing as performed by a registered professional nurse for compensation or gratuitously, except as permitted by K.S.A. 65-1124, and amendments thereto, means the process in which substantial specialized knowledge derived from the biological, physical, and behavioral sciences is applied to: the care, diagnosis, treatment, counsel and health teaching of persons who are experiencing changes in the normal health processes or who require assistance in the maintenance of health or the prevention or management of illness, injury or infirmity; administration, supervision or teaching of the process as defined in this section; and the execution of the medical regimen as prescribed by a person licensed to practice medicine and surgery or a person licensed to practice dentistry.
(2) The practice of nursing as a licensed practical nurse means the performance for compensation or gratuitously, except as permitted by K.S.A. 65-1124, and any amendments thereto, of tasks and responsibilities defined in paragraph (1), which tasks and responsibilities are based on acceptable educational preparation within the framework of supportive and restorative care under the direction of a registered professional nurse, a person licensed to practice medicine and surgery or a person licensed to practice dentistry.
(e) A "professional nurse" means a person who is licensed to practice professional nursing as defined in subsection (d)(1).
(f) A "practical nurse" means a person who is licensed to practice practical nursing as defined in subsection (d)(2).
(g) "Advanced practice registered nurse" or "APRN" means a professional nurse who holds a license from the board to function as a professional nurse in an advanced role, and this advanced role shall be defined by rules and regulations adopted by the board in accordance with K.S.A. 65-1130, and amendments thereto.
(h) "Continuing nursing education" means learning experiences intended to build upon the educational and experiential bases of the registered professional and licensed practical nurse for the enhancement of practice, education, administration, research or theory development to the end of improving the health of the public.

History: L. 1949, ch. 331, § 1; L. 1963, ch. 314, § 1; L. 1975, ch. 316, § 1; L. 1978, ch. 240, § 1; L. 1980, ch. 186, § 1; L. 1983, ch. 206, § 6; L. 2011, ch. 114, § 39; L. 2018, ch. 42, § 2; July 1, 2019.

Law Review and Bar Journal References:
"Guideline for Joint Policy Statement on Nursing Service," 69 J.K.M.S. 66, 67 (1968).
"Medico-Legal Aspects of the Student Health Service," John E. Howe and Barry McGrath, 69 J.K.M.S. 421, 424, 425, 444 (1968).
"A New Kansas Approach to an Old Fraud," consumer protection, Polly Higdon Wilhardt, 14 W.L.J. 623 (1975).
"Physician's Assistant and Nurse Practitioner Laws: A Study of Health Law Reform," Philip C. Kissam, 24 K.L.R. 1, 4, 13 (1975).
"The Roles of the Office and Hospital Nurse," Wayne T. Stratton, 90, No. 3, Kan.Med. 66 (1989).
"Reconsidering the Regulation of Health Professionals in Kansas," Lisa E. Bartra, 5 Kan. J.L. & Pub. Pol'y, No. 3, 155, 156, 160, 166, 167, 170-173 (1996).

Attorney General's Opinions:
Examination, licensure and regulation of nursing; nonprohibited acts. 86-76.
Physicians' assistants; advanced registered nurse practitioners; persons authorized to issue prescription orders. 86-125.
Rules and regulations; statutory procedure; uniform determination of death act. 90-81.
Administration of over the counter medications by nurses to school students. 90-119.
Insurance coverage for services rendered in treatment of alcoholism, drug abuse or nervous or mental conditions. 90-130.
Regulation of nursing; acts which are not prohibited; auxiliary patient care services. 91-45.
Delegation of performance of medical procedures (IVFT) by licensed practitioners of healing arts; board of nursing authority to interpret law, legal opinions. 95-84.

CASE ANNOTATIONS
1. Applied; order of board suspending license of nurse for unprofessional conduct under K.S.A. 65-1120 held arbitrary and unreasonable. Kansas State Board of Nursing v. Burkman, 216 Kan. 187, 531 P.2d 122.
2. Nursing act does not apply to midwifery; section not unconstitutionally vague. State Bd. of Nursing v. Ruebke, 259 Kan. 599, 625, 913 P.2d 142 (1995).
3. Employee did not engage in statutorily protected opposition to alleged disability discrimination. Conrad v. Board of Johnson County Com'rs, 237 F. Supp. 2d 1204, 1262 (2002).
4. Kansas Nurse Practice Act cannot be basis for retaliatory discharge claim. Goodman v. Wesley Med. Center, 276 Kan. 586, 78 P.3d 817 (2003).

**Kansas State Board of Nursing (KSBN)**
**Statute and Regulation Review Form**

**STATUTE or RULE AND REGULATION**

**Number:** K.S.A. 65-1154
**Article Title:** Kansas Nurse Practice Act
**Title:** Application; fees; deposit of moneys.
**Type (new, amended):** Amended
**Effective Date (history):** 1986
**Authorizing KSA(s) and/or Related KAR(s):**
**Implementing KSA(s) and/or Related KAR(s):**
History: L. 1986, ch. 183, § 4; L. 1992, ch. 135, § 5; L. 1996, ch. 179, § 4; L. 2011, ch. 114, § 48; January 1, 2012.

**KSBN OVERSIGHT STRUCTURE**
**KSBN Oversite Committee:** APRN
**Staff Review Owner:** Executive Administrator
**Date Last Reviewed by Committee**:
**Review Year Cycle Number**: Year 1. 2026
**Quarter of Review:** Q1

**PURPOSE:** Briefly describe the public purpose of the statute, rule and regulation. (*limited to 400 characters)*

Application; fees; deposit of moneys.

**Section 1. Environmental Assessment**

Is KSBN operating in good faith and reasonable compliance with this statute, rule or regulation? **Yes.**

Is the statute, rule or regulation in agreement with current healthcare practice? **Yes.**

How does this statute, rule or regulation compare with other states, model legislation, or healthcare accreditation standards? **This statute is comparable to most states.**

Have there been any changes in the National Licensure Compact, case law, statutes, rules or regulations that might impact this statute, rule or regulation? **No.**

***If changes are needed in statute, rule or regulation, what are the key elements of the substance of the revisions that need to be made?**

**Section 2. NECESSITY (Primarily for Rules and Regulations)**

***Is the statute necessary for the implementation and administration of state law, or could it be revoked?** (*necessary/ could be revoked)* Necessary.

Does the statute serve an identifiable public purpose in support of state law? *yes/no* **Yes.**

Is the statute broader than necessary to meet its public purpose? (*yes/no)* **No.**

**Section 3. TIES TO FEDERAL PROGRAMS (Typically not applicable to KSBN)**

***Is the rule and regulation federally required for state participation in a federal program or authority?** (*yes/no*) **No. NA.**

Is the rule and regulation necessary for federal delegation of enforcement authority to the State? (*yes/no*) **No. NA.**

If the rule and regulation is federally required, the state and federal program names and the federal agency name (*yes/no*) **No. NA.**

Could federal moneys be in jeopardy under current law if the rule and regulation were repealed? (*yes/no*) **No. NA.**

If federal moneys could be in jeopardy, the approximate amount received for the most recent fiscal year. (*yes/no*) **No. NA.**

**Section 4. POTENTIAL FOR REVOCATION (Primarily for Rules and Regulations)**

Briefly describe how revocation would affect Kansans. (*limited to 600 characters)*

**Removal of this statue would severely limit if not prevent KSBN from implementing other statutes in the KNPA.**

If the rule and regulation is not in active use, would revocation require a change to the authorizing or implementing statute? (*in active use/ yes/ no)* **This statute is in active use.**

***If the rule and regulation is not in active use and revocation would require a change to the authorizing or implementing statute, which change(s)?** (*limited to 400 characters)* **This statute is in active use.**

**ADDITIONAL INFORMATION**

Additional information necessary to understanding the necessity of this rule and regulation (*limited to 1,200 characters)*

**SUMMARY OF REVIEW**

Based on the summary of the information above, this KSBN Committee recommends

_____ no changes with review for another 5 years, or

_____ the Board develop a plan for revision and adoption as defined by Kansas laws.

Revisions need to address the key elements summarized in the Environmental Assessment.

Committee Reviewing:

Committee Chair: Date of Meeting:

Date Presented to Board: Board Chair:

https://ksrevisor.gov/statutes/chapters/ch65/065_011_0054.html

Proposed Changes:

65-1154. Application; fees; deposit of moneys. Upon application to the board by any licensed professional nurse in this state and upon satisfaction of the standards and requirements established under this act and K.S.A. 65-1130, and amendments thereto, the board shall grant an authorization to the applicant to perform the duties of a registered nurse anesthetist and be licensed as an advanced practice registered nurse. An application to the board for an authorization, for an authorization with temporary authorization, for biennial renewal of authorization, for reinstatement of authorization and for reinstatement of authorization with temporary authorization shall be upon such form and contain such information as the board may require and shall be accompanied by a fee to assist in defraying the expenses in connection with the administration of the provisions of this act. The fee shall be fixed by rules and regulations adopted by the board in an amount fixed by the board under K.S.A. 65-1118, and amendments thereto. There shall be no fee assessed for the initial, renewal or reinstatement of the advanced practice registered nurse license as long as the registered nurse anesthetist maintains authorization. The executive administrator of the board shall remit all moneys received to the state treasurer as provided by K.S.A. 74-1108, and amendments thereto.

History: L. 1986, ch. 183, § 4; L. 1992, ch. 135, § 5; L. 1996, ch. 179, § 4; L. 2011, ch. 114, § 48; January 1, 2012.

**Kansas State Board of Nursing (KSBN)**
**Statute and Regulation Review Form**

**STATUTE or RULE AND REGULATION**

**Number:** K.S.A. 65-1155
**Article Title:** Kansas Nurse Practice Act
**Title:** Expiration of authorizations to practice; renewal; lapsed authorization; reinstatement fee
**Type (new, amended):** Amended
**Effective Date (history):** 1986
**Authorizing KSA(s) and/or Related KAR(s):**
**Implementing KSA(s) and/or Related KAR(s):**
History: L. 1986, ch. 183, § 5; L. 1988, ch. 242, § 3; L. 1993, ch. 194, § 16; L. 2007, ch. 99, § 3; July 1.

**KSBN OVERSIGHT STRUCTURE**
**KSBN Oversite Committee:** APRN
**Staff Review Owner:** Executive Administrator
**Date Last Reviewed by Committee:**
**Review Year Cycle Number:** Year 1. 2026
**Quarter of Review:** Q1

**PURPOSE:** Briefly describe the public purpose of the statute, rule and regulation. (*limited to 400 characters)* Expiration of authorizations to practice; renewal; lapsed authorization; reinstatement fee

**Section 1. Environmental Assessment**

Is KSBN operating in good faith and reasonable compliance with this statute, rule or regulation? **Yes.**

Is the statute, rule or regulation in agreement with current healthcare practice? **Yes.**

How does this statute, rule or regulation compare with other states, model legislation, or healthcare accreditation standards? **This statute is comparable to most states.**

Have there been any changes in the National Licensure Compact, case law, statutes, rules or regulations that might impact this statute, rule or regulation? **No.**

***If changes are needed in statute, rule or regulation, what are the key elements of the substance of the revisions that need to be made?**

**The Board approved a policy at the December 10, 2025 meeting that provided direction to the KSBN Investigative Committee that might influence implementation of this regulation.**

**Section 2. NECESSITY (Primarily for Rules and Regulations)**

***Is the statute necessary for the implementation and administration of state law, or could it be revoked?** (*necessary/ could be revoked)* Necessary.

Does the statute serve an identifiable public purpose in support of state law? *yes/no* **Yes.**

Is the statute broader than necessary to meet its public purpose? (*yes/no)* **No.**

**Section 3. TIES TO FEDERAL PROGRAMS (Typically not applicable to KSBN)**

***Is the rule and regulation federally required for state participation in a federal program or authority?** (*yes/no)* **No. NA.**

Is the rule and regulation necessary for federal delegation of enforcement authority to the State? (*yes/no)* **No. NA.**

If the rule and regulation is federally required, the state and federal program names and the federal agency name (*yes/no)* **No. NA.**

Could federal moneys be in jeopardy under current law if the rule and regulation were repealed? (*yes/no)* **No. NA.**

If federal moneys could be in jeopardy, the approximate amount received for the most recent fiscal year. (*yes/no)* **No. NA.**

**Section 4. POTENTIAL FOR REVOCATION (Primarily for Rules and Regulations)**

Briefly describe how revocation would affect Kansans. (*limited to 600 characters)*

**Removal of this statue would severely limit if not prevent KSBN from implementing other statutes in the KNPA.**

If the rule and regulation is not in active use, would revocation require a change to the authorizing or implementing statute? (*in active use/ yes/ no)* **This statute is in active use.**

***If the rule and regulation is not in active use and revocation would require a change to the authorizing or implementing statute, which change(s)?** (*limited to 400 characters)* **This statute is in active use.**

**ADDITIONAL INFORMATION**

Additional information necessary to understanding the necessity of this rule and regulation (*limited to 1,200 characters)*

**SUMMARY OF REVIEW**

Based on the summary of the information above, this KSBN Committee recommends

_____ no changes with review for another 5 years, or

_____ the Board develop a plan for revision and adoption as defined by Kansas laws.

Revisions need to address the key elements summarized in the Environmental Assessment.

Committee Reviewing:

Committee Chair: Date of Meeting:

Date Presented to Board: Board Chair:

https://ksrevisor.gov/statutes/chapters/ch65/065_011_0055.html

Proposed Changes:

65-1155. Expiration of authorizations to practice; renewal; lapsed authorization; reinstatement fee.

(a) All authorizations to practice under this act, whether initial or renewal, shall expire every two years. The biennial authorizations to practice as a registered nurse anesthetist shall expire at the same time as the license to practice as a registered nurse. The board shall send a notice for renewal of the authorization to practice to every registered nurse anesthetist at least 60 days prior to the expiration date of such person's authorization to practice. To renew such authorization to practice the registered nurse anesthetist shall file with the board, before the date of expiration of such authorization to practice, a renewal application together with the prescribed biennial renewal fee. Upon satisfaction of the requirements of subsection (a) of K.S.A. 65-1159, and amendments thereto, the board shall grant the renewal of an authorization to practice as a registered nurse anesthetist to the applicant.

(b) Any person who fails to secure the renewal of an authorization to practice prior to the expiration of the authorization may secure a reinstatement of such lapsed authorization by making application on a form provided by the board. Such reinstatement shall be granted upon receipt of proof that the applicant is competent and qualified to act as a registered nurse anesthetist, has satisfied all of the requirements and has paid the board a reinstatement fee as established by the board by rules and regulations in accordance with K.S.A. 65-1118, and amendments thereto.

History: L. 1986, ch. 183, § 5; L. 1988, ch. 242, § 3; L. 1993, ch. 194, § 16; L. 2007, ch. 99, § 3; July 1.

**Kansas State Board of Nursing (KSBN)**
**Statute and Regulation Review Form**

**STATUTE or RULE AND REGULATION**

Number: K.A.R. 60-11-116
Article Title: Kansas Nurse Practice Act
Title: Advanced Practice Registered Nurses (APRN). Reinstatement of inactive or lapsed license.
Type (new, amended): Amended
Effective Date (history): 1949
Authorizing KSA(s) and/or Related KAR(s) :
Implementing KSA(s) and/or Related KAR(s):

History: Authorized by K.S.A. 2019 Supp. 65-1117 and K.S.A. 65-1129; implementing K.S.A. 2019 Supp. 65-1117 and K.S.A. 65-1132; effective Sept. 2, 1991; amended March 22, 2002; amended May 18, 2012; amended Aug. 21, 2020.

**KSBN OVERSIGHT STRUCTURE**
**KSBN Oversite Committee:** APRN
**Staff Review Owner:** Executive Administrator
**Date Last Reviewed by Committee**:
**Review Year Cycle Number**: Year 1. 2026
**Quarter of Review:** Q1

**PURPOSE:** Briefly describe the public purpose of the statute, rule and regulation. (*limited to 400 characters)*

Advanced Practice Registered Nurses (APRN). Reinstatement of inactive or lapsed license.

**Environmental Assessment**

Is KSBN operating in good faith and reasonable compliance with this statute, rule or regulation? **Yes.**

Is the statute, rule or regulation in agreement with current healthcare practice? **Yes.**

How does this statute, rule or regulation compare with other states, model legislation, or healthcare accreditation standards?

**This statute is comparable to most states. The NCSBN Model statutes suggests a change in language away from "discipline" to the consideration of "Board action."**

Have there been any changes in the National Licensure Compact, case law, statutes, rules or regulations that might impact this statute, rule or regulation?

**There has been some recent feedback from the legislature and the media to KSBN in reference to "lapsed practice" and how it relates to reinstatements. The Board approved a policy at the December 10, 2025, meeting that provided direction to the KSBN Investigative Committee that might influence implementation of this regulation.**

*If changes are needed in statute, rule or regulation, what are the key elements of the substance of the revisions that need to be made?

**NECESSITY (Primarily for Rules and Regulations)**

*Is the rule and regulation necessary for the implementation and administration of state law, or could it be revoked? (*necessary/ could be revoked)* ***No***

Does the rule and regulation serve an identifiable public purpose in support of state law? ***Yes***

Is the rule and regulation broader than necessary to meet its public purpose? ***Yes***

**TIES TO FEDERAL PROGRAMS (Typically not applicable to KSBN)**

*Is the rule and regulation federally required for state participation in a federal program or authority? ***No***
Is the rule and regulation necessary for federal delegation of enforcement authority to the State? ***No***
If the rule and regulation is federally required, the state and federal program names and the federal agency name ***No***
Could federal moneys be in jeopardy under current law if the rule and regulation were repealed? ***No***
If federal moneys could be in jeopardy, the approximate amount received for the most recent fiscal year. ***No***

**POTENTIAL FOR REVOCATION (Primarily for Rules and Regulations)**

Briefly describe how revocation would affect Kansans. (*limited to 600 characters)*

*APRN Committee on 12/11/24:*

*"This regulation is needed for all four APRN roles especially if a provider decides they would like to work within the state of Kansas. We need to be ready to help those individuals return to the healthcare workforce. It gives clear guidelines as to what is expected by the KSBN for all four roles to return to the healthcare workforce. Revocation would be short sided to have an option for those healthcare workers to come back to the healthcare workforce especially in a time of shortage we need to have options for those who want to work in Kansas."*

If the rule and regulation is not in active use, would revocation require a change to the authorizing or implementing statute? **In active use.**

*If the rule and regulation is not in active use and revocation would require a change to the authorizing or implementing statute, which change(s)? (*limited to 400 characters)* **In active use.**

**ADDITIONAL INFORMATION**

Additional information necessary to understanding the necessity of this rule and regulation (*limited to 1,200 characters)*

**SUMMARY OF REVIEW**

Based on the summary of the information above, this KSBN Committee recommends

_____ no changes with review for another 5 years, or

_____ the Board develop a plan for revision and adoption as defined by Kansas laws.

Revisions need to address the key elements summarized in the Environmental Assessment.

Committee Reviewing:

Committee Chair: Date of Meeting:

Date Presented to Board: Board Chair:

https://sos.ks.gov/publications/pubs_kar_Regs.aspx?KAR=60-11-116

**60-11-116. Reinstatement of inactive or lapsed license.**

(a) Each nurse anesthetist whose Kansas APRN license is inactive or has lapsed and who wants to obtain a reinstatement of APRN licensure shall meet the same requirements as those in K.A.R. 60-13-110.

(b) Any nurse practitioner, clinical nurse specialist, or nurse-midwife whose Kansas APRN license is inactive or has lapsed may, within five years of its expiration date, reinstate the license by submitting proof that the individual has met either of the following requirements:

(1) Obtained 30 hours of continuing nursing education related to the advanced practice registered nurse role within the preceding two-year period; or
(2) been licensed in another jurisdiction and, while licensed in that jurisdiction, has accumulated 1,000 hours of advanced practice registered nurse practice within the preceding five-year period.

(c) Any nurse practitioner, clinical nurse specialist, or nurse-midwife whose Kansas APRN license is inactive or has lapsed for more than five years beyond its expiration date may reinstate the license by submitting evidence of having attained either of the following:

(1) A total of 1,000 hours of advanced practice registered nurse practice in another jurisdiction within the preceding five-year period and 30 hours of continuing nursing education related to the advanced practice registered nurse role; or
(2) completion of a refresher course approved by the board.

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# Ketamine Therapy for Psychiatric Disorders and Chronic Pain Management

*Practice Considerations*

## Introduction

Ketamine hydrochloride is approved by the U.S. Food and Drug Administration (FDA) for the induction and maintenance of anesthesia.[1] Esketamine nasal spray, the s-enantiomer of ketamine, is FDA-approved for the treatment of treatment-resistant depression (TRD) in adults and depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.[2-6] Because several decades of research have shown that ketamine has antidepressive properties it has been incorporated into the treatment and management of psychiatric disorders (e.g., TRD, MDD, bipolar disorder, and post-traumatic stress disorder [PTSD], schizophrenia, anxiety, obsessive-compulsive disorder) and through ketamine's analgesic properties it has been incorporated into the treatment and management of chronic pain management (e.g., postsurgical pain, complex regional pain syndrome [CRPS], neuropathic pain, cancer pain).[5-30] Ketamine is not a singular treatment agent or a first-line therapy for psychiatric disorders or chronic pain management; therefore, it may be considered by the patient's interdisciplinary team after treatment resistance or as an adjunct treatment in the plan of care.[16]

## Purpose

These practice considerations discuss ketamine infusion clinics and the role of Certified Registered Nurse Anesthetists (CRNAs), also known as nurse anesthesiologists or nurse anesthetists, in the delivery of ketamine infusion therapy for patients with psychiatric disorders or chronic pain or esketamine for patients with TRD and MDD.

## Audience

These practice considerations are written for all members of the interdisciplinary team who treat patients with psychiatric disorders or chronic pain.

## Interdisciplinary Patient-Centered Care

A patient-centered, interdisciplinary team approach with consistent, clear communication to coordinate the care management plan is necessary to address the patient's complex clinical conditions and optimize the patient's outcome. CRNAs have the knowledge, skills, and abilities to treat and manage acute and chronic pain, administer all forms of ketamine, and manage any associated side effects or complications.[31] Throughout their careers, CRNAs may incorporate new techniques and technologies into their practice in accordance with their personal experience and competencies, professional and individual scope of practice, federal, state, and local law, and facility policy.[31,32]

Collaboration between psychiatric clinicians, including psychiatric-mental health nurses, and ketamine infusion providers is recommended for diagnosis of psychiatric disorders, referral for evaluation and treatment, and management of patient issues.[6,26,33] These professionals complement each other's skills and knowledge in the assessment, management, and delivery of ketamine infusion therapy for appropriate psychiatric disorders with a focus on improved patient safety, outcomes, and general well-being.[33] The CRNA's role in ketamine infusion therapy may include, but is not limited to, reviewing healthcare records; obtaining a health history; conducting a pre-infusion assessment and evaluation; ordering and evaluating diagnostic tests; ordering or prescribing medications; initiating, maintaining, titrating, and discontinuing the infusion;





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monitoring the patient; conducting post-infusion assessment and evaluation; and managing infusion-related adverse events or complications.[31,33,34]

Similarly, CRNAs collaborate with other clinical providers, including primary care providers, orthopedists, neurologists, psychiatrists, social workers, radiologists, physical therapists, or other pain specialists to provide chronic pain management services.[35] CRNAs may receive referrals from other clinicians or serve as the sole provider of chronic pain management services. CRNAs provide patient-centered chronic pain management and treatment, working toward the common goal of decreasing the patient's pain and improving the patient's quality of life and functionality.[35] When working in collaboration with a patient's primary care provider or other referring clinician, CRNAs may share certain responsibilities of chronic pain management.[35] The CRNA reviews and may add relevant findings (e.g., history and physical, diagnostic results) to information provided by a referring clinician to administer chronic pain management services safely.[35] More detail on CRNA chronic pain management delivery is found in the American Association of Nurse Anesthesiology (AANA) *Chronic Pain Management Guidelines*.

Continued screening, monitoring, and follow-up of patients with psychiatric disorders or chronic pain are important throughout treatment and management. The interdisciplinary team should engage in ongoing staff education and review outcomes and metrics for continuous quality improvement and research to improve processes and patient outcomes.

**Ketamine Infusion Clinics**

Ketamine infusion clinics are becoming more available. These clinics should establish clear standard operating procedures, protocols, and policies supporting positive treatment outcomes and patient safety.[6,9,36] Even when using a sub-anesthetic ketamine dose, considerations include minimizing the potential for adverse events through premedication, individualized patient therapy, and monitoring of vital signs and general condition during the peri-infusion period. The involvement of psychiatric mental health providers in the treatment and monitoring of patients receiving IV ketamine for psychiatric disorders is important because of the potential for psychiatric side effects, including but not limited to dissociation, agitation, and out-of-body experiences.[33,37] When developing or joining a ketamine infusion service, CRNAs should participate in the creation, review, and periodic updating of evidence-based policies and procedures and evaluation of the availability of necessary routine and emergency monitors, supplies, and equipment.[6] Within the facility, clinicians should be able to monitor cardiovascular, hemodynamic, and respiratory function; electrocardiography and measurement of oxygen saturation are essential.[26,28]

The AANA *Ketamine Infusion Therapy Considerations Checklist* was developed for CRNAs and other clinicians who are interested in integrating ketamine infusion therapy into their practice. This document provides an overview of practice and policy considerations for the use of ketamine infusions as an adjunct treatment for the treatment and management of psychiatric disorders or chronic pain. Additional information on office-based and ambulatory surgical center practice is located at *www.aana.com/FacilityConsiderations*.

**Plan of Care**

The selection of appropriate candidates for ketamine treatment requires careful consideration of the risks and benefits of the treatment in the context of the severity of the patient's condition, duration of current episode, previous treatment history, and urgency for treatment.[28,37] Appropriate patient selection requires an assessment of other medical, psychological, or social factors that may alter the risk-to-benefit ratio of the treatment and affect the patient's capacity to



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provide informed consent.[28] Exclusion criteria for treatment may include current or past history of psychosis, dementia, current or recent delirium, history of intracranial pressure, uncontrolled hypertension, severe cardiac decompensation, pregnancy, positive urine drug screen or current or previous abuse of ketamine, allergy to ketamine, and/or previous serious adverse effects from ketamine.[37,38]

Ketamine is associated with few drug-drug interactions, and no contraindications are currently known to exist when combined with antidepressants, benzodiazepines, or other psychotropic medications.[39] Depression and obesity are often co-occurring conditions.[40] Additionally, many psychiatric medications have weight gain and metabolic dysregulation as common side effects.[40,41] Several studies have shown that a higher BMI and weight categorization as obese were associated with a greater acute improvement from a single dose administration of IV ketamine.[40]

For patients who are predisposed to psychosis or schizophrenia, ketamine use has a markedly increased risk of provoking psychotic and schizophrenic symptoms.[27,42] In patients with TRD, a higher number of therapeutic failures and severity of the disease may predict reduced response and remission at 24 hours and 7 days, respectively, after a single ketamine infusion or esketamine nasal spray infusion.[43]

Clinicians should engage the patient in shared decision-making to plan and manage patient and caregiver expectations. These discussions should include realistic expectations of when symptoms may improve, the series of infusions that may be necessary for improvement, and the potential for nonresponse and treatment-emergent adverse events.[44] Through the informed consent process, the patient is made aware of the risks and benefits of proposed treatment and provided information that ketamine infusions for his or her condition are considered an off-label use of the product.[45] Alternative therapies and their benefits and risks should also be explained to the patient.[45]

The dose, frequency, and length of ketamine infusion treatment are individualized to each patient's condition, needs, and responsiveness to therapy with input from the psychiatric clinician in the case of psychiatric disorders and other members of the interdisciplinary team. A clear monitoring plan should be in place to avoid or manage adverse events.[6,28,46] Serial infusions appear to be more effective than a single infusion for psychiatric or chronic pain conditions.[7,47-50] Ongoing patient evaluation and communication between the patient and clinicians, both psychiatric-mental health providers in the case of psychiatric disorders and ketamine infusion providers, will help direct the continued course of treatment.

**Pharmacological Overview**

Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist. Ketamine's interaction with the NMDA receptor is important in analgesia because these receptors play a key role in central sensitization.[7,26] Ketamine has different binding sites such as opioid, monoaminergic, cholinergic, nicotinic and muscarinic receptors. The NMDA receptor, as a glutamate-dependent mechanism, is responsible for principle pharmacologic properties of ketamine.[8] Subanesthetic doses disrupt the NMDA receptor functions. At low doses, these alterations may include increased glutamate transmission and secondarily increased brain-derived neurotrophic factor.[51] This ultimately may activate a complex signaling pathway for improved neural synaptic activity, notably in the pre-frontal cortex, which can improve psychiatric functions.[51] Ketamine undergoes hepatic metabolism and renal excretion and has an elimination half-life of 2-4 hours.[7,26] Although subanesthetic doses administered once or in a



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series of infusions have been shown to be safe, the safety profile of prolonged ketamine use has not been established.[6,28,52]

Table 1 summarizes the pharmacologic properties and administration considerations for IV ketamine and esketamine.

Table 1. IV Ketamine and Esketamine Comparison Chart

| | IV Ketamine | Esketamine |
|---|---|---|
| FDA Approved Indications | • Sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation.[1]<br>• Induction of anesthesia prior to the administration of other general anesthetic agents.[1]<br>• Supplement to other anesthetic agents.[1] | • Treatment-resistant depression (TRD) in adults.[2]<br>• Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.[2] |
| Route of Administration | • IV | • Nasal spray |
| Route of Administration | • Non-selective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor.[1] | • Non-selective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor.<br>• The mechanism by which esketamine exerts its antidepressant effect is unknown. The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor with less affinity.[2] |
| Dosage for Psychiatric Disorders | • 0.5 mg/kg for 40 min.[6,12-14,16,17,19,20,22,26,28,29,43] | • Dosage for Treatment Resistant Depression[2]<br>Induction Phase: Weeks 1 to 4: Administer twice per week: Day 1 starting dose: 56 mg; Subsequent doses: 56 mg or 84 mg<br>Maintenance Phase: Weeks 5 to 8: Administer once weekly: 56 mg or 84 mg |



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| | | |
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| | Week 9 and after: Administer every 2 weeks or once weekly* | 56 mg or 84 mg |

** Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.*

| | | |
|---|---|---|
| **Absorption** | • 100% bioavailable.<br>• Rapidly attains maximum plasma concentrations.[53] | • The mean absolute bioavailability is approximately 48% following nasal spray administration. [2]<br>• The time to reach maximum esketamine plasma concentration is 20 to 40 minutes after the last nasal spray of a treatment session. [2] |
| **Distribution** | • Quick distribution to the central nervous system.<br>• Following IV administration, the ketamine concentration has an initial slope (alpha phase) lasting about 45 minutes with a half-life of 10 to 15 minutes. This first phase corresponds clinically to the anesthetic effect of the drug.[1]<br>• Ketamine undergoes hepatic metabolism and renal excretion and has an elimination half-life of 2-4 hours.[7,26]<br>• Steady-state volume of distribution is 3-5 L/kg.[54]<br>• Central compartment volume of ketamine is 70 L, and the distribution volume at steady state is 200 L or 2.3 L/kg.[55]<br>• Plasma protein binding is approximately 10-50%.[54,55] | • The mean steady-state volume of distribution of esketamine administered by the intravenous route is 709 L.[2]<br>• Plasma protein binding of esketamine is approximately 43% to 45%.[2] |
| **Metabolism** | • Metabolized via N-dealkylation to the active metabolite norketamine primarily by CYP2B6 and CYP3A4 and to a lesser extent by other CYP enzymes. Norketamine | • Esketamine is primarily metabolized to noresketamine metabolite via cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19. |



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| | undergoes hydroxylation of the cyclohexone ring to form hydroxynorketamine compounds via CYP-dependent pathways, which are conjugated with glucuronic acid and subsequently undergo dehydration of the hydroxylated metabolites to form the cyclohexene derivative dehydroxynorketamine.[1] | Noresketamine is metabolized via CYP-dependent pathways and certain subsequent metabolites undergo glucuronidation.[2] |
| **Excretion/Elimination** | • Following intravenous administration, the ketamine concentration decreases due to a combination of redistribution from the CNS to slower equilibrating peripheral tissues and hepatic biotransformation to norketamine. The redistribution half-life of ketamine from the CNS to slower equilibrating peripheral tissues (beta phase) is 2.5 hours.[1]<br>• Ketamine undergoes hepatic metabolism and renal excretion and has an elimination half-life of 2-4 hours.[7,26]<br>• Metabolites are excreted in the urine and detectable for up to 5 days. | • After $C_{max}$ is reached following intranasal administration, the decline in plasma esketamine concentrations is biphasic, with rapid decline for the initial 2 to 4 hours and a mean terminal half-life ($t_{1/2}$) that ranges from 7 to 12 hours.[2]<br>• The mean clearance of esketamine is approximately 89 L/hour following intravenous administration.[2] |
| **Post-Administration Monitoring** | • Although the minimum adequate duration is unknown for monitoring adults with TRD receiving intravenous ketamine, a period of up to 2 hours should be considered.[6,26,56] | • 2 hours before discharge.[6,26,56] |
| **Side Effects** | • Common side effects of IV ketamine include nausea, agitation/anxiety, psychotomimetic symptoms, dissociative psychiatric symptoms, headache, confusion, inebriation, blurred vision, dizziness, euphoria, elevated blood pressure, elevated | • The most common adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant):[2,4,16]<br>o TRD: dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk. |



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| | heart rate, and increased libido.[6,7,14,16,17,20,27,29,47,52,57,58] | o Treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior: dissociation, dizziness, sedation, increased blood pressure, hypoesthesia, vomiting, euphoric mood, and vertigo. |
| **Contraindications** | • Patients for whom a significant elevation of blood pressure would constitute a serious hazard.[1]<br>• Patients with known hypersensitivity to ketamine or to any excipient.[1] | • Patients with unstable or poorly controlled hypertension or pre-existing aneurysmal vascular disorders may be at increased risk for adverse cardiovascular or cerebrovascular effects.[4] |
| **Other Considerations** | • Ketamine has minimal effect on the central respiratory drive if given slowly, although rapid IV injection may cause transient apnea.[59]<br>• Ketamine can have deleterious effects on liver and urinary tract function.[6,27,48]<br>• There may be a greater risk of ketamine-induced liver injury when infusions are prolonged or repeated over a short timeframe.[6,27,48]<br>• Patients with a history of psychosis may be more vulnerable to the effects of ketamine, and may require slower infusions (e.g., 40-60 minutes).[13,60]<br>• Those with a history of dissociation may expect stronger intra-infusion dissociative experience but can also expect the ketamine-induced dissociation to resolve after infusion.[20]<br>• Ketamine rapidly passes through the placental barrier.[61,62] | • Esketamine rapidly passes through the placental barrier.[63] |



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**Abuse/Addiction Properties**

Ketamine abuse and misuse are widely recognized problems throughout the world, and while low, rates are continuing to increase.[64-71] Prolonged patient use in the outpatient setting could produce physiological and psychological dependence on ketamine.[64] The number and frequency of treatments should be limited to the minimum necessary to achieve clinical response.[28] Appropriate patient screening, such as a urine toxicology screen, may be warranted before the initiation of ketamine treatment, and caution should be taken when administering ketamine infusions due to the risk of abuse, addiction, and complications of long-term use.[11,28,37,38,52,72] Proper drug storage and disposal measures are recommended to prevent drug diversion and misuse.[7,37,73]

**Use for Psychiatric Disorders**

Because major psychiatric disorders such as MDD are among the most disabling mental, neurologic, and substance use-related illnesses, new therapeutic approaches are being considered to treat or delay the onset of these disorders.[60] Ketamine infusions have been used as an adjunct to psychiatric treatment and can offer substantial short-term resolution of symptoms, although long-term resolution has not been demonstrated.[5,16,17,36,74,75] IV low-dose ketamine can induce rapid and robust, although temporary, antidepressive effects, even in treatment-resistant patients who do not respond to electroconvulsive therapy.[8,10,14,16,36,58,64,72,76] The dosage commonly found in literature for ketamine infusions for psychiatric disorders is 0.5 mg/kg over a 40 minute infusion titrated based on patient response.[6,12-14,16,17,19,20,22,26,28,29,43] Some research has noted a dose-response relationship, where a higher dosage leads to increased time to relapse for TRD, but more research is needed on this specific topic.[17,77]

Some studies have concluded that ketamine infusion may provide acute symptom improvement of suicidal ideation within 24 hours of treatment, although in a meta-analysis, Dean et al. found no difference in suicidal ideation scores between ketamine and placebo at any time point.[16,21,75,78,79] Dean et al. also note short-term effectiveness of esketamine for treatment of depression, but recommend further studies exploring long-term outcomes.[16] The authors indicate no differences in suicidality between esketamine over placebo at any time point.[16]

Ketamine can effectively ameliorate symptoms of patients suffering from PTSD.[7,18,39] In a randomized controlled trial in individuals with chronic PTSD, repeated IV ketamine infusions administered over 2 weeks were associated with a clinically significant improvement in PTSD symptoms compared with repeated psychoactive placebo control medication.[18]

Mental health disorders in the adolescent population continue to rise, with 16.39% of adolescents (12-17 years old) reporting suffering from at least one major depressive episode in the past year and 11.5% of adolescents experiencing severe major depression.[80] While ketamine infusion therapy has been reported to have utility in the adolescent population, further research regarding safety and efficacy is needed to make a conclusive recommendation.[81-89] Adolescence is a critical period for neurodevelopment, therefore additional considerations include the effects of ketamine on the developing brain as well as other medications the patient may be receiving, such as mood stabilizers or atypical psychotics.[87]

**Use for Chronic Pain Treatment**

Chronic pain is most effectively treated using a patient-centered, interdisciplinary, multimodal approach, recognizing the complexity of chronic pain, accounting for the diverse needs of the patient, and offering an individualized multimodal treatment strategy.[30,35] Ketamine may be





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used for short-term pain relief in patients with chronic pain, including ischemic limb pain, refractory chronic pain, phantom limb pain, fibromyalgia, and other neuropathic conditions.[7,18,24,25,27,30,39,48,57,74,90-97] A 2017 Cochrane review concluded that the evidence is insufficient to assess the benefits and harms of ketamine as an adjuvant to opioids for the relief of refractory cancer pain.[98] Through a systematic review and meta-analysis, Sun, et al. concluded that perioperative IV ketamine may reduce the incidence of chronic postsurgical pain in patients, especially 3-6 months post-surgery.[96]

Ketamine has also been shown to alleviate other unintended effects (e.g., depression) in the context of chronic pain and other chronic illnesses.[8,91] Preliminary evidence supports the efficacy of ketamine in treating comorbid depression and chronic pain and comorbid depression and acute pain.[99] As part of a multimodal approach, ketamine is not considered as the first or second choice in treatment for neuropathic pain, irrespective of the cause.[30] Ketamine is often reserved for cases where other treatments have failed due to its potential side effects and the need for careful monitoring.

Ketamine may have a role as an adjunct for cancer pain and may be a treatment option for patients who cannot tolerate opioids or those with problems with opioid responsiveness. [7,98,100] Ketamine can reduce the incidence and severity of opioid side effects, which is an important factor in patient compliance.[30] Ketamine treatment in chronic pain patients may counteract opioid-induce hyperalgesia and improves pain management while simultaneously reducing a patient's required total daily morphine equivalent.[90] In some instances, this may improve quality of life and improve respiratory and hemodynamic stability.[90]

IV ketamine therapy for CRPS can provide clinically effective pain reduction for less than 3 months.[24,93,94] In a systematic review, Chitneni, et al. concluded that patients who received ketamine infusion for treatment-resistant CRPS reported adequate pain relief with treatment, therefore ketamine infusion may be a useful treatment for patients with no significant pain relief from other conservative measures.[101] Esketamine infusions can also provide clinically effective pain relief in CRPS patients with refractory pain.[25]

The effect of IV ketamine among chronic pain patients may vary widely.[95] IV ketamine may be associated with improvement in pain scores observed during the infusion, quantified as early as 48 hours after the infusion, and lasting for ≥2 weeks when high-dose regimens are used.[95] While IV ketamine has shown short-term pain relief benefits for chronic pain conditions, there is a lack of consensus on the optimal treatment protocols for prolonged ketamine infusion in chronic pain management.[30] Large-scale studies with standardized assessments, different infusion protocols, and long-term follow-up periods are needed to establish its long-term effectiveness, dose-response relationship, and safety profile.[95-97]

**Barriers to Care**

Access to ketamine infusion therapy for psychiatric disorders and chronic pain management is hindered by several barriers. One barrier is the limited availability of trained providers and specialized clinics offering this treatment, especially in rural or underserved areas. Another factor is that ketamine must be administered via IV infusion in a clinical setting, which may limit accessibility.[16] Because ketamine is a schedule III drug and requires specific monitoring, as described above, it should be administered by a trained professional in a clinical setting. Additionally, the cost of ketamine infusion therapy can be prohibitive for many patients, as it may not be covered by insurance, and out-of-pocket expenses can be substantial. Notably, the U.S. Department of Veterans Affairs and the U.S. Department of Defense provide coverage for patients with suicidal ideation and major depressive disorder. Their guidelines suggest offering

ketamine infusion as an adjunctive treatment for short-term reduction in suicidal ideation.[79] Stigma and misinformation surrounding ketamine may also deter individuals from seeking this treatment, despite its potential benefits.

CRNAs, as highly skilled anesthesia professionals, play a crucial role in overcoming many of these challenges. CRNAs have the expertise to safely administer all forms of ketamine, making their involvement a valuable solution. Additionally, their ability to provide anesthesia services independently in various healthcare settings can increase the availability of this therapy, especially in underserved or remote areas. CRNAs' holistic approach to patient care, including their strong focus on patient education and emotional support, can help reduce the stigma surrounding ketamine treatment and improve patient acceptance.

**Conclusion**

Ketamine and esketamine are both effective and safe in short-term clinical trials in adults with psychiatric disorders.[29] More research on long-term effects is needed as the clinical use of ketamine infusion therapy for psychiatric disorders and chronic pain management continues to evolve.[29] While there is supportive evidence demonstrating positive results from ketamine therapy, there are still challenges for clinical application that require consideration, discussion, and further research.[16] Clinicians, including CRNAs, should continue to monitor and contribute to the development of the related science, as well as engage in publication of new clinical findings and research on this topic.

**Disclaimer**

These practice considerations are solely for general informational purposes. Certified registered nurse anesthetists (CRNAs) practice in accordance with professional ethics, scope and standards of practice, sound professional judgment, the best available evidence, the best interests of the patient, and applicable law. AANA recommends obtaining legal and expert assistance regarding requirements for ketamine infusion therapy, including review of all applicable federal, state, and local laws and regulations specific to your practice.

The dosages listed in this document are intended to serve as a guide to patient care, rather than a one-size-fits all approach. Every patient is unique. Each anesthesia professional is responsible for independently confirming the correct dosage of medication before administration, based on an assessment and evaluation of the patient, the plan of care, the patient's clinical needs, and any relevant facility policies and procedures. AANA and our content experts are not responsible for incorrect dosage administration, and each anesthesia professional assumes full responsibility for how the information in this document is used.

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# AANA and APNA Joint Position Statement on Ketamine Infusion Therapy for Psychiatric Disorders

Ketamine infusion therapy has been shown to have antidepressive properties and is increasingly becoming used to treat psychiatric disorders, including major depressive disorder (MDD), bipolar disorder, treatment-resistant depression, and post-traumatic stress disorder (PTSD). The American Association of Nurse Anesthetists (AANA) and the American Psychiatric Nurses Association (APNA) support a patient-centered, interdisciplinary approach to managing patients who suffer from psychiatric disorders and may benefit from ketamine infusion therapy. Each organization recognizes the professional scope of practice and expertise of certified registered nurse anesthetists (CRNAs), psychiatric mental health registered nurses (PMH RNs), and psychiatric mental health advanced practice registered nurses (PMH APRNs). PMH RNs and PMH APRNs are collectively referred to as PMH Nurses. These professionals complement each other's skills and knowledge in the assessment, management, and delivery of ketamine infusion therapy for appropriate psychiatric disorders with a focus on improved patient safety, outcomes, and general well-being.

CRNAs, PMH RNs, and PMH APRNs practice in accordance with professional ethics, scope and standards of practice, sound professional judgment, available evidence, interests of the patient, and applicable law. When adding new activities to their practice, CRNAs, PMH RNs, and PMH APRNs evaluate that the new practice is in accordance with professional scope and standards of practice, applicable law, and facility policy.[1,2]

**Certified Registered Nurse Anesthetists (CRNAs)**
CRNAs, as anesthesia professionals, are educated and trained to administer ketamine for sedation and general anesthesia as well as ketamine infusion therapy for psychiatric disorders and chronic pain management.[3]

When administering ketamine for the treatment of psychiatric disorders, CRNAs collaborate with healthcare professionals whose practice includes focusing on and diagnosing mental health and psychiatric disorders within their professional and state scope of practice (e.g., PMH APRNs). As part of the collaboration, CRNAs may obtain a referral to provide ketamine infusion therapy for psychiatric disorders.

The CRNA's role in ketamine infusion therapy may include, but is not limited to, reviewing healthcare records, obtaining a health history and assessment, performing a history and physical, conducting pre-infusion assessment and evaluation, ordering and evaluating diagnostic tests, ordering or prescribing medications, initiating the infusion, monitoring the patient, conducting post-infusion assessment and evaluation, and managing infusion-related adverse events or complications.[3]

**Psychiatric Mental Health Registered Nurses (PMH RN) and Advanced Practice Registered Nurses (PMH APRN)**

PMH Nurses are educated and specialize in promoting mental health through the assessment, diagnosis, and treatment of behavioral problems, mental disorders, and comorbid conditions across the lifespan.[4]

PMH Nurses support individuals with treatment-resistant mental health disorders by: promoting and fostering health and safety; assessing dysfunction and areas of individual strength; maximizing individual strengths; preventing further disability; and assisting individuals to achieve personal recovery goals by managing symptoms and gaining, re-gaining, or improving coping abilities and living skills.[4]

PMH APRNs work with individuals who may benefit from ketamine infusion therapy by collecting and synthesizing comprehensive health data and analyzing that data to determine diagnoses, problems, and areas of focus for care and treatment, including level of risk. PMH APRNs incorporate knowledge of pharmacological, biological, and complementary interventions with applied clinical skills. PMH APRNs utilize prescriptive authority, referrals, and procedures, treatments and therapies in accordance with applicable law.[4]

PMH Nurses structure and maintain safe, therapeutic, recovery-oriented environments in collaboration with healthcare consumers, families, and other healthcare clinicians.[4] PMH Nurses collaborate with CRNAs who, within their scope of practice, administer ketamine infusion therapy for mental health disorders.[3]

## Supporting Resources

- Ketamine Infusion Therapy for Psychiatric Disorders and Chronic Pain Management, Practice Considerations (AANA)
- Ketamine Infusion Therapy Checklist (AANA login required)
- Ketamine Infusion Therapy (APNA)

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SPECIAL ARTICLE

OPEN

# Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists

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**Background:** Over the past 2 decades, the use of intravenous ketamine infusions as a treatment for chronic pain has increased dramatically, with wide variation in patient selection, dosing, and monitoring. This has led to a chorus of calls from various sources for the development of consensus guidelines.

**Methods:** In November 2016, the charge for developing consensus guidelines was approved by the boards of directors of the American Society of Regional Anesthesia and Pain Medicine and, shortly thereafter, the American Academy of Pain Medicine. In late 2017, the completed document was sent to the American Society of Anesthesiologists' Committees on Pain Medicine and Standards and Practice Parameters, after which additional modifications were made. Panel members were selected by the committee chair and both boards of directors based on their expertise in evaluating clinical trials, past research experience, and clinical experience in developing protocols and treating patients with ketamine. Questions were developed and refined by the committee, and the groups responsible for addressing each question consisted of modules composed of 3 to 5 panel members in addition to the committee chair. Once a preliminary consensus was achieved, sections were sent to the entire panel, and further revisions were made. In addition to consensus guidelines, a comprehensive narrative review was performed, which formed part of the basis for guidelines.

**Results:** Guidelines were prepared for the following areas: indications; contraindications; whether there was evidence for a dose-response relationship, or a minimum or therapeutic dose range; whether oral ketamine or another *N*-methyl-D-aspartate receptor antagonist was a reasonable treatment option as a follow-up to infusions; preinfusion testing requirements; settings and personnel necessary to administer and monitor treatment; the use of preemptive and rescue medications to address adverse effects; and what constitutes a positive treatment response. The group was able to reach consensus on all questions.

**Conclusions:** Evidence supports the use of ketamine for chronic pain, but the level of evidence varies by condition and dose range. Most studies evaluating the efficacy of ketamine were small and uncontrolled and were either unblinded or ineffectively blinded. Adverse effects were few and the rate of serious adverse effects was similar to placebo in most studies, with higher dosages and more frequent infusions associated with greater risks. Larger studies, evaluating a wider variety of conditions, are needed to better quantify efficacy, improve patient selection, refine the therapeutic dose range, determine the effectiveness of nonintravenous ketamine alternatives, and develop a greater understanding of the long-term risks of repeated treatments.

(*Reg Anesth Pain Med* 2018;43: 521–546)

## INTRODUCTION AND JUSTIFICATION

Chronic pain and depression are both leading causes of years lost to disability worldwide, as they are typically refractory to conventional treatments.[1] There is considerable overlap between chronic pain and depression in terms of coprevalence

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and treatment, with many therapies typically used to treat one being effective for the other.[2] One such treatment that intersects with both conditions is ketamine, which has generated enormous interest among health care providers, patients and their caregivers, and patient advocacy groups. Systematic and evidence-based reviews have found ketamine to be effective for both chronic pain and depression, and recent years have witnessed a dramatic increase in research and publications, clinical use, and publicity as determined by Internet traffic.[3] But because ketamine has been clinically available for almost 50 years, it has not been subject to the same scrutiny by the US Food and Drug Administration (FDA) or postmarketing surveillance as drugs that remain on patent protection. In fact, a recent symposium on its use compared its unbridled rise in clinical use as analogous to the "Wild West."[4]

Ketamine is classified by most pharmacological sources as an "anesthetic agent," being able to induce general anesthesia and ablate protective airway reflexes. Consequently, most hospitals prohibit its use as a "bolus" by nonanesthesiologists, and many require an anesthetist to oversee its use in any context. Yet, similar to other drugs used in anesthesia, the physiological effects are dose related, which has led to variations in policies. The surge in use; lack of large-scale, methodologically sound studies to guide treatment; and absence of treatment standards, to include safe-use recommendations, strongly portend the need for guidelines to inform safe practice. Previous consensus guidelines have been published on the use of ketamine for mood disorders, but these guidelines did not discuss mechanisms, address safe use, or provide guidance for pain management.[5] The objectives of this consensus statement are to provide an overview on the literature supporting ketamine for chronic pain, depression, and posttraumatic stress disorder (PTSD); determine appropriate patient selection for the use of ketamine infusions to treat acute and chronic pain; establish a framework for standardization of use during intravenous (IV) infusions; and establish safety parameters regarding monitoring, personnel, and dosing, which can be used for the treatment of chronic pain and psychiatric disorders. These recommendations are based on the US Preventive Services Task Force grading of evidence, updated in July 2012.[6]

## METHODS OF DEVELOPMENT

This was a joint effort undertaken by the American Society of Regional Anesthesia and Pain Medicine (ASRA) and the American Academy of Pain Medicine (AAPM), which commenced in November 2016; the boards of directors of these groups approved the documents in December 2017 and February 2018, respectively. In December 2017, on direction from the American Society of Anesthesiologists (ASA) president, the preliminary draft document was sent to the chairpersons of the ASA's Committees on Pain Medicine and Standards and Practice Parameters, who consulted with select members of the those committees. After incorporating minor revisions, the ASA Administrative Council approved the guidelines for both acute and chronic pain.

The Ketamine Guidelines Committee was charged with preparing guidelines on the use of ketamine as an analgesic that would enhance patient selection and safe practice, guide institutional protocol development, serve as a resource for information, and function as a template for regulatory bodies and payers. Members were selected by ASRA and AAPM, as well as the chair of the ASRA Guidelines Committee, who was selected by the 2 organizations as chairperson of the Consensus Guidelines Committee on Ketamine for Pain Management. Committee members were chosen based on their expertise and experience with the use of ketamine to treat pain; evaluating the literature; statistical background; and developing protocols to govern its oversight. The various sections of the review portion of the manuscript, as well as for the questions and answers that comprised the chronic pain guidelines, were separated into modules composed of 3 to 5 authors and the committee chair, with 1 panel member designated as "lead." These questions were selected by the committee chair based on input from the Guidelines Committee and refined by the group based on discussion during conference calls and e-mail correspondence. The answers to the questions were composed by the author modules based on consensus, with discrepancies resolved by the chair and his designee(s). All sections of the review portion and the acute and chronic pain guidelines were then reviewed by the entire committee and revised by consensus as needed through discussion. A consensus was originally deemed to be greater than 75% panel agreement with dissenting opinions noted, but we were able to reach complete concurrence on all issues considered.

Search engines used during composition of the various sections included MEDLINE, EMBASE, Google Scholar, and Cochrane Database of Systematic Reviews, as well as by examination of the reference sections of all manuscripts. Articles considered for inclusion were animal and experimental studies, systematic and other types of reviews, meta-analyses, clinical trials, and, for certain sections in which high-grade evidence was lacking (eg, treatment, complications), case reports and series. Key words used for the review section included "ketamine," "*N*-methyl-D-aspartate receptor," "central sensitization," whereas those used to address the specific guideline topics were tailored to the individual questions (eg, dose-response, dextromethorphan, intranasal, complex regional pain syndrome [CRPS]). Protocols from various institutions including academic, private practice, military, and Veterans Administration were also reviewed to gauge community standards. Conclusions for each question were graded from A to D or as insufficient, according to the US Preventive Services Task Force grading of evidence guidelines, with the level of certainty rated as high, medium, or low.[6] This system, which has been modified for use by the American Society of Interventional Pain Physicians in guidelines for pain treatment therapies,[7] was chosen over several others because of the wide range and greater flexibility it affords.[8,9] For example, unlike other systems, it allows for high-grade recommendations in the absence of systematic reviews or consistent level I studies (ie, which would be beneficial for recommendations concerning safety issues such as monitoring or rescue therapy for refractory cases).

## DISCUSSION

### History

Ketamine, originally labeled as CI-581, is a chemical derivative of phencyclidine. It was first administered to 20 volunteers from a prison population in 1964 and produced dissociative anesthesia, providing effective analgesia in doses ranging from 1 to 2 mg/kg.[10] As early as 1958, phencyclidine (CI-395) was administered to humans under a different name and was reported to cause increased blood pressure and nystagmus while maintaining respiration.[11]

The story of ketamine began with 2 scientists from Parke-Davis (now a subsidiary of Pfizer, Detroit, Michigan). A medicinal chemist, V. Harold Maddox, discovered a new chemical organic Grignard reaction, which led to the synthesis of phencyclidine (later given the clinical investigation number CI-395) on March 26, 1956.[12] Parke-Davis pharmacologist Graham Chen and his associates obtained the compound from Maddox in 1958. In animal studies, it caused an excited drunken state in rodents, but a cataleptoid immobilized state in pigeons. They extended the

studies to a large variety of animals and concluded that the pharmacology of this compound was unusually complex.[13]

After sufficient animal toxicity testing, phencyclidine was given to humans undergoing surgery. John E. Gajewski, MD, at Parke-Davis was responsible for its clinical development. Phencyclidine proved to be a relatively safe anesthetic in humans, as it had been with monkeys. However, some patients developed severe and prolonged postsurgery emergence delirium.[14] The first human was given ketamine via an IV subanesthetic dose on August 3, 1964. Guenter Corssen, MD, an anesthesiologist at the University of Alabama at Birmingham and author on that pivotal first manuscript,[10] subsequently increased the dose in a stepwise fashion from no effect to "conscious but spaced out" and finally to a dose sufficient to produce general anesthesia. The findings were described as "remarkable!" The overall incidence of adverse effects was approximately 1 in 3 volunteers, and frank emergence delirium was minimal. Most of the subjects described strange experiences such as a feeling of floating in outer space and having no feeling in their arms or legs. Encouraged by its anesthetic effect, Parke-Davis filed for FDA approval of the drug and carried out further clinical studies. Ketamine was approved by the FDA in 1970. During the Vietnam War, it became a widely used anesthetic in theaters of operation where concerns about hemodynamic instability are paramount in wounded service members and has now been in clinical use for more than 50 years.

## Epidemiology of Chronic Pain

Chronic pain is a worldwide epidemic. Among the leading causes of years lost to disability worldwide in 2013, 4 of the top 10 (low-back pain, neck pain, migraine, musculoskeletal disorders), including the perennial top cause—low-back pain—are pain related.[1] In the United States and other industrialized countries, the impact of chronic pain is even more pronounced, with 3 of the top 4 causes constituting chronic pain conditions (eg, low-back and neck pain and musculoskeletal disorders).[15] The socioeconomic burden due to chronic pain is enormous and cannot be overestimated. In a 2010 report, the Institute of Medicine estimated that chronic pain afflicts 1 of 3 Americans, costing between $560 billion and $635 billion annually.[16] In Europe, the reported burden of chronic pain is nearly equally steep, with the point prevalence estimated to be 25% to 30%.[17]

## Classification of Chronic Pain and the Effects of Ketamine for Nonneuropathic Pain

There are numerous ways to classify and categorize chronic pain, but perhaps the most meaningful is by "type" or "location" (eg, neuropathic, nociceptive, central, peripheral, or mixed), as this informs treatment at every level of care. For example, nonsteroidal anti-inflammatory drugs are widely considered to be ineffective for neuropathic pain, whereas ketamine and gabapentinoids are generally acknowledged to be less effective for nonneuropathic pain than they are for neuropathic pain.[18] However, clinical reality is different than theoretical constructs based on animal studies, and drugs previously considered to be useful for only 1 type of pain (eg, ketamine for neuropathic pain, nonsteroidal anti-inflammatory drugs for nonneuropathic pain) have been shown in clinical trials to be efficacious for other types.[19–23] Many experts consider the distinction between different pain types to be a continuum, rather than discrete classification categories.[18] Although the preponderance of preclinical evidence supporting an antinociceptive effect for ketamine has been conducted using peripheral neuropathic and central pain models,[24–26] there are a handful of studies demonstrating an analgesic benefit in inflammatory and other nonneuropathic animal models.[27,28]

Pain categorization is important for determining diagnostic workup, guiding treatment decisions, and predicting outcomes. Among chronic pain patients, between 15% and 25% are estimated to have a predominantly neuropathic etiology.[29–31] For CRPS type I, which fails to meet the most recent International Association for the Study of Pain definition of neuropathic pain[32] but is the most common indication for ketamine treatment, the estimated prevalence rates vary between 20 and 30 per 100,000 person years.[33,34] Yet, these statistics may belie the true burden of neuropathic pain, as studies have shown that neuropathic pain may be associated with a poorer quality of life than comparable degrees of nonneuropathic pain.[35] A recent review found the strongest evidence for IV ketamine to be for the treatment of neuropathic pain and CRPS, although the nonneuropathic pain condition they compared them to was fibromyalgia.[36] In addition to fibromyalgia being a particularly challenging condition to treat, the studies cited also utilized lower dosages. Anecdotal evidence also supports intermediate-term benefit for ketamine infusions for nonneuropathic pain conditions such as refractory headaches and back pain.[37]

## Mechanisms of Action

Ketamine exerts its analgesic, antidepressant, and psychomimetic effects via myriad pathways. Its primary mechanism is as a noncompetitive antagonist at the phencyclidine binding site of *N*-methyl-D-aspartate (NMDA) receptors residing in the central nervous system (CNS), particularly in the prefrontal cortex and hippocampus,[38] where it decreases the frequency of channel opening and duration of time spent in the active, open state.[39] The NMDA receptor is a ligand-gated channel whose major endogenous agonist is glutamate, the predominant excitatory neurotransmitter in the CNS. When this receptor is inhibited, decreased neuronal activity ensues. Activation of the NMDA channel plays a major role in cognition, chronic pain, opioid tolerance, and mood regulation and is considered the principal receptor involved in phenomena of central sensitization and windup.[38,40–43] Although some studies suggest a role for peripheral mechanisms in the analgesic effect of ketamine,[44] reviews have mostly found topical ketamine to be ineffective.[45]

Yet, NMDA-receptor antagonism is not the sole mechanism for its analgesic and antidepressant effects. In high doses, ketamine activates a variety of opioid receptors (mu > kappa > sigma), although the observation that its pain-relieving effects are not reversed by naloxone indicates this is not the major source of antinociception.[46,47] Ketamine also acts on a multitude of other non-NMDA pathways that play integral roles in pain and mood regulation, including antagonistic effects on nicotinic and muscarinic cholinergic receptors, the blockade of sodium and potassium (ie, hyperpolarization-activated cyclic nucleotide–gated [HCN]) channels, activation of high-affinity $D_2$ dopamine receptors and L-type voltage-gated calcium channels, facilitation of γ-aminobutyric acid A (GABA-A) signaling, and the enhancement of descending modulatory pathways.[48–51] Collectively, these other pathways may explain why ketamine may be beneficial in nonneuropathic pain conditions and provide a rationale for its use as a topical analgesic agent.[18,38,52,53]

The recent surge in opioid use and overdoses has led to a rise in non–opioid-based treatment options. In preclinical studies, ketamine has been shown to reduce opioid tolerance and hyperalgesia.[24,54] Although a recent meta-analysis demonstrated a small effect size for ketamine and other NMDA-receptor antagonists in reducing opioid consumption and improving analgesia in the perioperative setting,[55] the results of clinical studies have not been uniformly positive, which may in part be due to the multitude of factors that contribute to postsurgical pain and opioid consumption.[55–57]

The antidepressant effects of ketamine have generated intense interest in recent years in the psychiatric community. Given the high coprevalence rate of chronic pain and depression and other psychiatric morbidities, as well as the requirement of some institutions for patients being administered ketamine to be monitored by anesthesia providers, this has important ramifications for pain medicine providers.[58] Despite the recent surge in use in the context of mood disorders, there is a relative paucity of clinical data compared with its use as an anesthetic and analgesic agent, but the mood-enhancing effects appear to emerge in approximately 4 hours, after most of the drug has been cleared from circulation, and persist for up to 2 weeks, long after the acute analgesic effects dissipate.[59] Similar to its use as an analgesic, a variety of routes of administration have been successfully used for treatment of depression, including oral, intramuscular, and intranasal.[38,60–62]

Several mechanisms have been postulated to explain the rapid-acting antidepressant effects of ketamine. These include: (1) blockade of interneuronal and excitotoxic extrasynaptic NMDA receptors; (2) disinhibition of pyramidal cells leading to a glutamate surge; (3) activation of prosynaptogenic AMPA (α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid) receptors; (4) activation of synaptogenic intracellular signaling, including TORC1 (mammalian target of rapamycin complex 1) and brain-derived neurotrophic factor pathways; (5) increased GABA-B levels; and (6) inhibition of brain glycogen synthase kinase 3 (GSK-3B).[63–68] Inhibition of GSK-3 is a mechanism shared by the mood-stabilizing drug lithium, and the use of adjunct GSK-3B inhibitors such as lithium may augment and prolong ketamine's antidepressant effects.[69] Clinical trials and anecdotal experience have demonstrated efficacy not only for depression, but also for the treatment and prevention of PTSD.[70,71] Yet despite these other physiological effects, similar to its anticociceptive properties, the primary mechanism for its psychiatric effects is believed to be via the NMDA receptor. In preclinical and clinical studies, ketamine's antidepressant effects appear to follow a glutamate surge that leads to a cascade of events resulting in synaptogenesis and subsequent reversal of the negative effects of chronic stress and depression, particularly within the prefrontal cortex.[59] For PTSD, the potential beneficial effects of ketamine may derive from its ability to inhibit the glutamate-activated NMDA receptor, as glutamate plays a pivotal role in stress reactivity and formation of traumatic memories.[72,73] However, more research is needed to better elucidate these mechanisms and to determine the long-term effects of ketamine on depression and PTSD.

## Pharmacodynamics and Pharmacokinetics

Ketamine exists as a racemic mixture of R(−) and S(+) stereoisomers. The S(+) stereoisomer is approximately 3 to 4 times more potent than its R(−) cousin consequent to its greater affinity for the PCP binding site on the NMDA receptor.[49] The S(+) stereoisomer has a shorter duration of action and possesses greater neuroprotective and analgesic properties than its R(−) counterpart, which might potentially make it a more ideal analgesic,[49,74] but preclinical and clinical analgesic studies comparing the 2 enantiomers have thus far yielded conflicting results.[75–77] Regarding the incidence of psychomimetic effects and abuse potential, studies comparing the different enantiomers have also produced mixed results.[78,79] For depression, 2 animal studies demonstrated more sustained antidepressant effects for the R(−) stereoisomer, but there are no clinical studies to guide treatment.[78,80]

Ketamine exhibits a unique combination of hypnotic, analgesic, and amnestic effects, which makes it ideal for treating post-traumatic and procedure-related pain. The hypnotic effects are likely secondary to inhibition HCN1 nonspecific cation channels that mediate "sag" currents, which help regulate and stabilize membrane potential.[81] The mechanisms behind the amnestic effects of ketamine are multifactorial in nature and probably the result of interactions at an assortment of receptors that include NMDA, serotonin, and nicotinic cholinergic.[82,83]

There is growing evidence for ketamine as a treatment for refractory seizures as well as for its use during electroconvulsive therapy. The anticonvulsant effects may be attributable not only to its effects on the NMDA receptor, but also to agonistic effects at the sigma and GABA-A and GABA-B receptors.[84,85] In electroconvulsive therapy, the propensity to induce seizures may be mitigated by the anticonvulsive effects of general anesthesia. Perhaps because of its interactions with the nicotinic receptor, the ability of ketamine to elevate the seizure threshold is less than that for other induction agents.[86] In animal studies, ketamine has been shown to decrease seizure threshold when given sequentially after aminophylline[87] and paradoxically to decrease enflurane-induced seizure activity.[88] In humans, ketamine has been shown to enhance epileptic discharges, which may explain the rare occurrence of seizures.[89,90]

Ketamine is a versatile drug that can be administered via many routes including IV, intramuscular, insufflation/intranasal, inhalational (smoked), oral (elixir or compounded pills), topical (minimal systemic absorption), and rectal (Table 1). It is both water and lipid soluble, which allows for extensive rapid distribution throughout the body and rapid crossing of the blood-brain barrier. Its predominant route of metabolism is via hepatic microsomal enzymes, most notably cytochrome P450, with approximately 12% remaining protein bound in plasma.[49] Although genetic polymorphisms of P450 isoforms (2B6, 2C9) may affect metabolism and clearance,[92,93] 1 study found that a genetic variant associated with decreased CYP2B6 expression and metabolism (CYP2B6*6) did not alter pharmacokinetics following single, low-dose (0.4 mg/kg) oral administration.[92] Thus, the effects of these polymorphisms in studies evaluating higher, IV dosages remains unknown.

Ketamine's half-life in plasma is approximately 2.3 ± 0.5 hours. The drug is rapidly metabolized to norketamine, hydroxynorketamine and dehydronorketamine, with norketamine possessing one-fifth to one-third of activity at the NMDA receptor as its parent compound, and 2R,6R hydroxyketamine, once considered to be an inactive metabolite, being an active inhibitor at the AMPA glutamate and α7 subtype of the nicotinic cholinergic receptor, which may contribute to antidepressant effects.[94–96] The excretion of unchanged ketamine (4%) and its metabolites is via the urine.

In low doses, ketamine causes analgesia and sedation, whereas in high doses, it produces general anesthesia. The clinical effects of ketamine result from both direct and indirect actions, with the latter predominating in most clinical contexts. Ketamine administration generally results in increases in heart rate, systolic and diastolic blood pressure, salivary and tracheobronchial secretions, and bronchodilation due to its stimulatory effects on the sympathetic nervous system. In clinically administered dosages, it has minimal effects on airway reflexes (ie, upper airway skeletal tone and responsiveness remain intact) and respiratory rate; paradoxically, some studies have shown an increased respiratory response to hypercapnea.[38,49,97] These effects make ketamine an ideal drug for trauma victims in the setting of hypovolemia, septic shock, or pulmonary disease and have led some experts to recommend and utilize ketamine as a potential first-line treatment for battlefield injuries.[98] The direct, dose-dependent negative inotropic effects on cardiac muscle are typically realized only in catecholamine depleted individuals (eg, long-term trauma or intensive care patients).[99]

The dissociative properties associated with ketamine are thought to result from the combination of reduced activation of the thalamocortical system and increased activity in the limbic system

**TABLE 1.** Pharmacokinetics of Ketamine for Different Routes of Administration[38,91]

| Route of Administration | Typical Dosing | Bioavailability, % | Time of Onset | Duration of Action After Dosing |
|---|---|---|---|---|
| Intravenous | 1–4.5 mg/kg for general anesthesia induction; 1–6 mg/kg per hour for anesthesia maintenance; 0.5–2 mg/kg for 1-d outpatient or 3- to 5-d inpatient awake ketamine infusions in chronic pain (higher dosages titrated to effect from lower doses); 0.2–0.75 mg/kg for procedural analgesia, can be repeated; 0.1 mg/kg for IV infusion test; 5- to 35-mg/h continuous infusion for acute traumatic or postoperative pain, 1–7 mg/demand dose mixed with opioids in patient-controlled analgesia | N/A | 30 s | 5–10 min for bolus doses |
| Intramuscular | 2–4 times IV dosing; 5–10 mg/ kg for surgical anesthesia; 0.4–2 mg/kg for procedural analgesia; bolus and treatment dosing 0.10–0.5 mg/kg for chronic pain | 75–95 | 2–5 min | 30–75 min |
| Intranasal | 0.2–1 mg/kg for chronic pain and sedation; 3–6 mg/kg for procedural analgesia and anesthetic premedication | 25–50 | 5–10 min | 45–120 min |
| Subcutaneous | 0.1–1.2 mg/kg per hour for chronic pain; bolus and treatment dosing 0.10–0.6 mg/kg | 75–95 | 10–30 min | 45–120 min |
| Oral | 0.3–1.25 mg/kg for chronic pain; up to 3 mg/kg for procedural analgesia and anesthetic premedication | 10–20 | 5–20 min | 2–4 h |
| Rectal | 5–10 mg/kg for anesthesia premedication and procedural analgesia | 25–30 | 5–15 min | 2–3 h |
| Topical | 1%–10% cream for chronic pain | <5 | <2 d | NA |

and hippocampus.[49] To a large extent, these effects may be reduced or eliminated with the concurrent use of benzodiazepines or α2 agonists, which act to reduce the psychomimetic effects by diminishing the cholinergic effects, which in turn mitigates the excessive stimulation of downstream corticolimbic neurons.[100,101]

The analgesic effects of ketamine are usually experienced when plasma concentrations approach 100 ng/mL. One advantage for using ketamine over opioid therapy for chronic pain is that long-term use is associated with less tolerance and tachyphylaxis.[102,103] This, in conjunction with the preliminary evidence touting its ability to prevent and reverse opioid tolerance and hyperalgesia, has led to its growing use as a rescue treatment in opioid-tolerant individuals (Table 1).[104–107]

## Evidence

### Preclinical Evidence and Challenges in Translation: Can Ketamine Reverse or Halt Central Sensitization?

The predominant therapeutic effect for ketamine is believed to involve its antagonistic effects at the NMDA receptor, which plays a major role in neuroplasticity and excitotoxicity. Hence, the NMDA receptor has been implicated in such diverse phenomena as memory and cognition, central sensitization and windup, and opioid tolerance and hyperalgesia.[18,108,109] Central sensitization may accompany any chronic pain condition but is most frequently linked to neuropathic pain.[110] Not surprisingly, although the preponderance of preclinical studies demonstrating an antinociceptive effect for ketamine have been conducted in neuropathic pain models, ketamine has also demonstrated analgesic effects in animal studies simulating inflammatory conditions.[111,112]

The simplest and most elegant explanation proposed for ketamine's chronic pain–relieving properties is that it "resets the CNS," in essence reversing the deleterious effects of central sensitization by virtue of its NMDA-receptor antagonistic effects.[113] However, the evidence for this hypothesis is inconsistent. Functional magnetic resonance imaging studies have shown that it is possible to reverse pathoanatomical changes associated with chronic pain with effective treatment,[114,115] but the effects of ketamine have not been extensively studied using functional imaging or instruments validated for measuring central sensitization.[116] Studies that have sought to measure quantitative sensory testing and conditioned pain modulation after ketamine administration have for the most part yielded negative findings.[48,117–123] Yet, an animal study showing that ketamine is more efficacious in chronic stages of CRPS, when central mechanisms predominate, than in acute stages, when peripheral mechanisms are more prominent, supports the reversal of central sensitization theory as the principal mode of analgesia.[124] Whereas most of ketamine's analgesic effects may be mediated via NMDA-receptor antagonism, it is likely that its effects on other systems including HCN1, cholinergic, aminergic, and opioid pathways also play a role.[125] Ketamine may exert its profound analgesic effects by not only affecting the sensory-discriminative system, but also modulating the affective-motivational component of pain.

As noted above, there is a preponderance of preclinical evidence supporting ketamine as an antidepressant and more mixed evidence supporting it as a treatment for PTSD.[59,69,126–128] The myriad physiological changes that mediate these benefits predominate in the CNS and are associated with enhanced neural activity in the prefrontal cortex and reduced activity in the amygdala and hippocampus.[129,130] Whereas animal models of pain use antinociception as a surrogate for analgesia, animal models of depression utilize tangible characteristics such as locomotor activity, aggression, preference for sucrose, and physiological responses (eg, electroencephalography to measure disturbances in circadian rhythm, laboratory tests to measure stress response, neuroimaging to measure CNS changes) to measure the subjective variable of mood.[131] For PTSD, the inherent challenges in translating a subjective condition to objective measures are equally challenging.[131] These factors may explain why most drugs shown to be beneficial in preclinical models of pain, depression, and PTSD fail in clinical trials.[18,131,132]

### Clinical Evidence for Use in Acute Pain Management

When used for chronic pain, many physicians will administer the highest dose tolerated in an effort to "reverse central

sensitization" or "unwind windup," attempting to pharmacologically counteract adverse effects, rather than tapering down the infusion. In contrast, in an acute pain setting, ketamine dosages are titrated to effect, carefully balancing analgesia with adverse effects, the latter of which may require a reduction in dosage.

Most studies evaluating ketamine in an acute pain setting have focused on the perioperative environment and a few other specific painful disease states, such as sickle cell pain crises. For patients outside the perioperative setting, evidence is limited to mostly case reports. The evidence suggests that most patients who benefit from ketamine in the acute pain setting fall into several categories. The first group of patients is those who are undergoing painful surgery, after which the expected postoperative pain rating is considered to be in the severe range.[133] Examples of surgical procedures in which the benefits seem to be the greatest include upper abdominal surgery and thoracic surgery; orthopedic limb, spine, intra-abdominal, and lower abdominal procedures also appear to be painful enough to warrant consideration of ketamine. Multiple reviews have demonstrated that ketamine reduces opioid consumption, pain levels, or both for a minimum of 24 hours after surgery and possibly 48 hours or more.[134–136] No (preincisional bolus only or very low dose) or only a very minor preventive effect on persistent postsurgical pain (number needed to treat >10) for ketamine is evident from existing studies, with 1 review suggesting that higher total dosages may be more likely to demonstrate a modest preventive effect (effect sizes −0.59 for dosages ≤0.5 mg/kg, −0.04 for dosages between 0.5 and 1 mg/kg, and −0.81 for dosages exceeding 1 mg/kg).[133]

Opioid-tolerant and opioid-dependent patients are frequently cited as groups that should receive ketamine, primarily because it makes conceptual sense given the role of the NMDA receptor in hyperalgesia and opioid tolerance.[55,137] Despite recommendations from several groups[138,139] for consideration of ketamine, the clinical evidence is limited to a few randomized controlled trials (RCTs). Loftus and colleagues[140] found ketamine reduced postoperative and long-term opioid use in opioid-dependent patients undergoing spine surgery, whereas another study reported that opioid-tolerant patients undergoing multiple different surgeries who received ketamine experienced improved average pain ratings postoperatively.[141] There are also less impressive[142] and negative studies[143,144] in this patient population. In studies examining the use of low-dose ketamine added to opioid patient-controlled analgesia for postsurgical pain, systematic reviews have found evidence for reduced pain scores and opioid consumption for up to 72 hours.[145,146]

Evidence for ketamine in acute painful exacerbations of chronic diseases such as sickle cell disease and nonoperative trauma (eg, rib fractures) is limited to mostly case reports and small case series.[147–151] In many of these conditions, limited numbers of patients and ethical considerations make prospective studies challenging. There is a clear need for well-designed, prospective studies in sickle cell disease and other painful disease states that acute pain physicians confront. The feasibility of performing such large-scale randomized studies, however, remains questionable.

## Clinical Evidence for Use in Chronic Pain

The efficacy of ketamine for chronic neuropathic pain and conditions with features of neuropathic pain has been investigated in double-blind RCTs.[44,117–119,123,152–169] Several of these trials found that ketamine, administered under ideal clinical conditions, was associated with significantly greater reductions in pain compared with the control condition. However, statistical measures of the treatment effect, or effect size, were not used in these studies. In the absence of measures of effect size, a comparison of pain scores between the ketamine and control groups could help guide decisions about the use of ketamine in clinical practice. For example, 4[117,123,160,162] of 7[117,123,155,160–162,164] double-blind RCTs reported that ketamine infusions were associated with significantly greater reductions in pain compared with placebo in patients with mixed chronic neuropathic pain diagnoses. The difference in pain reduction between the ketamine and control groups measured during the ketamine infusions ranged from 25% to 45% in 3 studies.[44,118,152] However, in the study by Kvarnström and colleagues,[118] the significant group difference measured during the 0.4-mg/kg infusion was no longer present 110 minutes following completion of the infusion. In the study by Max and colleagues,[152] in which ketamine provided (mean dose, 58 mg over 2 hours) superior pain relief to both alfentanil and placebo, the pain relief disappeared before the adverse effects resolved. In the study by Leung et al,[44] the authors attributed part of the analgesic benefit to peripheral mechanisms. In another study, patients in the ketamine group (0.24 mg/kg over 30 minutes) experienced a 10-point greater pain score reduction on a 0- to 100 mm visual analog scale (VAS) measured during the infusion compared with placebo.[153]

In 2 double-blind RCTs that involved patients with traumatic spinal cord injury pain, ketamine infusions (0.06-mg/kg bolus followed by 0.36 mg/kg per hour and 0.4 mg/kg over 40 minutes) were associated with a 35% to 40% reduction in pain measured during the infusion compared with placebo.[119,154] In a third RCT that involved patients with traumatic spinal cord injury pain, IV ketamine 80 mg infused over 5 hours was associated with a 22-point reduction in VAS pain scores compared with placebo at 2-week follow-up, but not afterward.[155] Among patients with phantom limb pain (PLP), greater than 90% pain reduction was observed 30 minutes following an IV ketamine infusion of 0.4 mg/kg over 1 hour compared with placebo in 1 RCT,[117] and in another trial, IV ketamine (0.1-mg/kg bolus followed by 0.42 mg/kg per hour) was associated with a 2-point reduction (10-cm VAS) in pain scores 48 hours following completion of the infusion compared with placebo.[156] In a single RCT that involved patients with postherpetic neuralgia (PHN), IV ketamine 0.15 mg/kg over 10 minutes was associated with a 50% reduction in pain measured 15 to 45 minutes following ketamine administration compared with placebo.[157]

For conditions with features of neuropathic pain, ketamine has been investigated in several RCTs, but the treatment effects are mixed. In patients with fibromyalgia, a condition often associated with central sensitization, the findings of 2 RCTs demonstrated a 20- to 25-point reduction in VAS pain scores 90 to 120 minutes following IV ketamine 0.3 mg/kg compared with placebo.[158,159] In 2 other RCTs that involved patients with fibromyalgia, ketamine (0.3 mg/kg over 30 minutes and 0.5 mg/kg for 3 hours) was associated with a 0.5- to 0.9-point reduction in pain scores (10-cm VAS) at 90 to 180 minutes following IV ketamine compared with placebo.[21,160] However, in the study by Noppers and colleagues[160] that enrolled 24 patients with fibromyalgia who received a ketamine infusion of 0.5 mg/kg for 3 hours, no differences were found in pain scores or quality of life during the 8-week follow-up period. In patients with CRPS, 1 RCT reported a 1.2-point (0- to 10-point numerical rating scale) difference in pain scores between the ketamine (0.43 mg/kg per hour continuously over 4.2 days) and placebo infusion groups at 11-week follow-up, but no group difference was observed at 12-week follow-up.[161] This study was limited to patients with CRPS type I, which does not meet the most recent International Association for the Study of Pain definition of neuropathic pain because of the absence of an identifiable nerve injury.[32] A second RCT that

TABLE 2. Randomized Placebo-Controlled Trials Evaluating Intravenous Ketamine for Chronic Pain With a Minimum of 48 Hours of Follow-Up

| First Author, Year | Patients | Ketamine Regimen | Follow-Up | Results | Comments |
|---|---|---|---|---|---|
| Amr,[155] 2010 | 40 patients with neuropathic pain after spinal cord injury | 80 mg over 5 h per day × 1 wk | 4 wk | Ketamine better than placebo for 2 wk | All patients also received gabapentin |
| Eichenberger,[117] 2008 | 20 patients with PLP | 0.4 mg/kg over 1 h with 48 h minimum interval between infusions | 48 h | Ketamine better than placebo and calcitonin. No difference between ketamine alone and combination for worst pain reduction, but combination superior for mean pain reduction. Mixed results for QST | Crossover study comparing ketamine to calcitonin to combination of both to placebo |
| Schwartzman,[123] 2009 | 19 patients with CRPS types 1 and 2 | Up to 100 mg over 4 h for 10 consecutive weekdays | 9–12 wk | Ketamine better than placebo for pain, but no improvement in QST and no correlation between response and serum levels | Study halted at midpoint because of lack of improvement in ketamine group |
| Sigtermans,[161] 2009 | 60 patients with CRPS type 1 | 0.43 mg/kg per hour continuously over 4.2 d | 12 wk | Ketamine better than placebo, but results were not statistically significant beyond 11 wk | Blinding ineffective |
| Noppers,[160] 2011 | 24 patients with fibromyalgia | 0.5 mg/kg over 30 min | 8 wk | Ketamine better than placebo only up to 3 h | Blinding ineffective |
| Mitchell,[162] 2002 | 35 patients with ischemic limb pain | 0.6 mg/kg over 4 h | 2–9 d (mean, 5 d) | Ketamine better than placebo | All patients also received opioids |
| Salas,[164] 2012 | 20 patients with cancer pain | 0.5 mg/kg per day increased to 1 mg/kg per day × 2 d for persistent pain | 48 h | No difference between treatment groups | All patients received morphine |

QST indicates quantitative sensory testing.

included individuals with both CRPS types I and II reported a 14-point difference on the short-form McGill Pain Questionnaire between the ketamine (up to 100 mg over 4 hours for 10 consecutive weekdays) and placebo infusion groups at 9- to 12-week follow-up (Table 2).[123]

In individuals with nociceptive pain, the results have been mixed. Among patients with ischemic pain attributed to severe peripheral vascular disease, 1 RCT reported a 19% difference in pain relief between the ketamine infusion of 0.6 mg/kg over 4 hours and a placebo infusion at 5-day follow-up,[162] but a second RCT reported no significant differences in pain scores between ketamine (0.15–0.45 mg/kg over 5 minutes) and morphine 10 mg when measured at the time of each drug's peak effect following completion of the infusions.[163] In a small, double-blind study evaluating an IV ketamine infusion (0.5 mg/kg per day increased to 1 mg/kg per day for 2 days) for persistent pain as an add-on treatment to morphine for cancer pain, no difference between treatment groups was found during the 48-hour follow-up period.[164]

The use of ketamine in headache disorders has surged over the past few years in light of several studies demonstrating benefit.[165–167] In a single RCT that involved patients with migraine headache, a bolus of subcutaneous ketamine 80 μg/kg was associated with an approximately 50% reduction in acute migrainous pain compared with placebo and an approximate 75% reduction in chronic migrainous pain at 7- to 10-day follow-up when administered in thrice-a-day dosing for 3 weeks.[168] However, a second RCT that investigated the effects of intranasal ketamine 25 mg compared with intranasal midazolam 2 mg found that ketamine reduced the severity but not the duration of migrainous aura, with no significant group differences in pain scores observed.[169] In a retrospective study that involved 49 patients diagnosed with 7 different chronic pain conditions with neuropathic pain features, a 5.9-point (10-cm VAS) reduction in pain scores was observed following a ketamine infusion (median dose, 0.9 mg/kg over 30–45 minutes; median number of infusions, 4), with 38% of patients reporting greater than 3 weeks of relief (Table 3).[37]

When interpreting controlled trials evaluating ketamine, one must consider that because of ketamine's psychomimetic effects, blinding can be difficult. In the study by Noppers and colleagues,[160] 75% of participants correctly guessed which group they were allocated to, and in the study by Sigtermans and colleagues,[161] 28 of 30 patients who received ketamine correctly guessed their treatment group. Systematic reviews and clinical studies have found that the absence of blinding exaggerates the effect size by approximately 35% and that unclear blinding increases the treatment effect by 13% to 25%.[170–172]

## Adverse Effects and Pathophysiology

### Cardiovascular and Pulmonary Effects

The challenge in describing the physiologic effects of ketamine used at subanesthetic doses are that: (1) many of the studies that reported these effects focused on anesthetic doses, which are typically 1.5 to 2 mg/kg or higher given as a bolus; and (2) there is no standard definition of what dose is considered "subanesthetic." Practitioners are left to make assumptions about the severity and frequency of these effects at lower doses based on limited evidence. Nevertheless, early work by Gooding and colleagues[173] in 1977 suggests that ketamine has greater effects on the pulmonary vasculature than the systemic vasculature. Furthermore, they note no significant changes in cardiac output, stroke volume, systemic vascular resistance, and other cardiovascular parameters. However, in critically ill patients, there appears to be a negative inotropic effect as demonstrated in a 1980 study.[174] Reviews have noted that ketamine has both a negative inotropic effect and

**TABLE 3.** Clinical Outcomes for Ketamine Therapy in Headaches

| First Author, Year | Study Design and Patients | Treatments | Results | Comments |
|---|---|---|---|---|
| Granata,[165] 2016 | Observational study in 29 patients with cluster headache | Low-dose IV ketamine (0.5 mg/kg over 1 h) every 2 wk up to 4 times | Cluster attacks were completely aborted in 100 % of patients with episodic headaches and in 54% of patients with chronic cluster headaches for a period of 3–18 mo | 13 had chronic cluster, and 16 had the episodic form |
| Moisset,[166] 2017 | Case report in 2 patients with cluster headache | Single IV ketamine infusion (0.5 mg/kg over 2 h) combined with magnesium sulfate (3000 mg over 30 min) | Complete relief in 1 patient and 50% for the other patient, for 6 wk in both cases | Both had chronic cluster headache |
| Pomeroy,[167] 2017 | Retrospective study in 77 patients with migraine or NDPH | IV subanesthetic ketamine infusion (0.1–1 mg/kg per hour); mean length of infusion, 4.8 d | 71.4% of patients were classified as acute responders; sustained response did not achieve statistical significance | Patients had chronic migraine or NDPH; acute responders defined as those with at least 2-point improvement in headache pain at discharge |
| Afridi,[169] 2013 | Randomized, double-blind, placebo-controlled, parallel study in 30 patients with migraine | 25 mg intranasal ketamine with 2 mg intranasal midazolam as an active control; each subject recorded data from 3 episodes of migraine | Ketamine reduced the severity but not duration of aura, whereas midazolam had no effect | Patients had migraine with prolonged aura. 18 subjects completed the study |
| Nicolodi,[168] 1995 | Randomized, double-blind crossover in 34 patients with migraine headache (17 each received acute and chronic therapy) | Acute therapy: SC ketamine hydrochloride (80 μg/kg) or SC saline (control); chronic therapy: SC ketamine (80 μg/kg) TID for 3 wk | Marked relief of pain both as an acute treatment and as a prophylactic therapy | Migraine headaches not diagnosed using the International Classification of Headache Disorders criteria; mild adverse effects in the majority of patients in both ketamine and placebo groups |

NDPH indicates new daily persistent headaches; SC, subcutaneous; TID, 3 times daily.

simultaneous indirect sympathetic nervous system stimulation, which is due to systemic release of catecholamines, vagal nerve inhibition, inhibition of norepinephrine reuptake at peripheral nerves, and other mechanisms.[175–177] Parameters such as heart rate, blood pressure, cardiac output, and myocardial oxygen consumption increase even with subanesthetic doses.[175,176] In the pulmonary system, ketamine causes bronchodilation that appears to be due to circulating catecholamines.[176,177] Pharyngeal and laryngeal reflexes are mostly preserved, as is respiratory function, and there are increased secretions.[176,177] The speed of injection may play a role in maintenance of respiratory function,[176] implying that subanesthetic infusions for analgesia may carry a lower risk of respiratory depression than when ketamine is administered as a bolus dose for use as an anesthetic, although no direct evidence exists to support this.

## Spinal Cord Effects

Several studies in animals suggest that ketamine may cause pathological changes when given intrathecally.[178–180] However, several other studies report that no histopathologic changes are observed when the preservative is omitted.[181,182] High-quality data are lacking in humans, but it seems prudent to avoid intrathecal ketamine given the lack of evidence showing clear benefit, except in rare circumstances. Currently, the use of intrathecal ketamine is listed as a sixth-line adjuvant to be used in conjunction with other neuraxial analgesics in individuals with refractory cancer or other terminal chronic pain conditions.[183]

### Psychomimetic Adverse Effects

Reviews and meta-analyses of perioperative ketamine have come to different conclusions regarding ketamine's adverse psychomimetic effects including hallucinations, visual disturbances, unpleasant dreams, and dysphoria, when it is used in subanesthetic doses.[133–135,175–177] Based on 37 RCTs that studied perioperative ketamine, Bell and colleagues[134] concluded that the incidence of psychomimetic adverse effects was similar in ketamine and placebo groups. After evaluating 10 studies examining intraoperative ketamine and 15 assessing postoperative infusions, a review also concluded that psychomimetic adverse effects were not increased by ketamine, with the exception of 1 study that reported a higher incidence of hallucinations.[135] These findings are in contrast to those of Laskowski and colleagues,[133] who reported that in 70 studies analyzing IV ketamine for postoperative analgesia, "neuropsychiatric effects" were increased in the ketamine treatment groups compared with placebo. A retrospective study analyzing 321 patients who received subanesthetic ketamine infusions for various acute pain indications reported an incidence of 16% for CNS excitation symptoms.[184] Although there was no control group, 35 of the 37 patients whose infusions were stopped because of CNS symptoms had resolution of symptoms upon cessation, suggesting that ketamine was responsible. Based on the totality of evidence, it appears that subanesthetic ketamine administered only intraoperatively is unlikely to cause major psychomimetic adverse effects; however, postoperative infusions are associated with limited and reversible psychomimetic adverse effects.

The issue of dosing as it relates to the occurrence of psychomimetic adverse effects is not clearly established in the literature. One review addressed this and found that safety is not correlated to the dose given when it comes to subanesthetic ketamine.[135] Another noted that, "psychedelic adverse effects occur in a dose-dependent fashion" but did not provide a reference for the claim.[175] Although CNS effects do seem to be dose-dependent when ketamine is used in anesthetic doses,[177] the evidence is not as clear for subanesthetic regimens, beyond a yet-to-be determined threshold. In a retrospective study by Schwenk and colleagues,[184] discontinuation of ketamine infusions secondary to adverse effects was unrelated to the maximum infusion rate, which further questions the notion that adverse effects at low doses are dose related.

### Hepatic, Genitourinary, and Gastrointestinal Effects

There are few studies that directly address the issues of hepatotoxicity and cystitis with subanesthetic ketamine use. Data must be extrapolated from animal studies and studies in ketamine abusers. Animal studies have demonstrated the potential of ketamine to cause hepatotoxicity as well as cystitis.[185] In humans, the incidence of hepatotoxicity and cystitis may be increased with higher doses and repeated exposure, although liver enzyme levels return to normal after discontinuation of the drug.[186] One study found that illicit ketamine had a greater propensity to induce urological pathology than legal ketamine, which the authors attributed to adulterants enhancing the inflammatory response.[187] Wong and colleagues[188] assessed a group of 297 chronic ketamine abusers with liver biopsy and magnetic resonance cholangiopancreatography and found the prevalence of liver injury to be 9.8%, all cases of which involved cholestatic pathology. Another study by Noppers and colleagues[189] reported that 3 patients being treated with ketamine for CRPS developed hepatotoxicity during their second exposure to the drug. All 3 had elevated liver enzymes that took several months to return to reference range.[189]

Ketamine-induced cystitis has been documented primarily in abusers of ketamine.[190] It typically presents as painful hematuria, dysuria, frequency, and postmicturition pain.[191] The entity was first described in 2007 in a case series of 9 patients who were ketamine abusers.[192] Treatment begins with cessation of ketamine use[191] and may also consist of mucosal protective agents such as hyaluronic acid or anticholinergic drugs.[191,193] More severe disease may require surgical intervention.[191] Almost all of the available literature on this topic involves ketamine abusers, with a single case report documenting a pediatric patient who developed cystitis while taking ketamine chronically for pain.[194] Therefore, the risk of developing cystitis with brief ketamine infusions or short-term therapy at subanesthetic doses is largely unknown but may be increased with repeated or frequent exposures.[190]

Nausea and vomiting appear to decrease in patients receiving ketamine in the perioperative period.[133,134] It is not clear whether this effect is due to ketamine itself or its opioid-sparing properties. It has been suggested that ketamine may have a higher propensity to cause nausea than other sedative hypnotics,[176] and several retrospective analyses reported rates of 2.8% to 6.5% for nausea and vomiting.[167,184] However, the overall findings from available meta-analyses demonstrate either no difference between ketamine and placebo groups in nausea and vomiting[136] or a reduction in nausea and vomiting (Table 4).[133,134,146]

### Monitoring

Ketamine is associated with adverse psychomimetic, cardiovascular, and gastrointestinal effects resulting from its action on a variety of substrate receptors including NMDA, acetylcholine, opioid, monoamine, and histamine. Monitoring methods for these possible adverse events have not been directly examined in clinical studies. In the available literature (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/AAP/A249),[21,44,117–119,123,152–163,197–199] the most common parameter reported is blood pressure measurement followed by monitoring of electrocardiogram (ECG), level of sedation/consciousness, and pulse oximetry. The use of capnography has not been reported in the literature, and psychomimetic adverse events have been collected as self-report measures.

**TABLE 4.** Adverse Effects and Pathophysiology Associated With Subanesthetic Ketamine

| Key Studies | Adverse Effects | Comments |
|---|---|---|
| Laskowski,[133] 2011; Bell,[134] 2005; Jouguelet-Lacoste,[135] 2015; Elia,[136] 2005; Drayna,[195] 2012 | • Psychomimetic (dysphoria, hallucinations, nightmares, and vivid dreams) | • Unlikely to occur with intraoperative use alone; may occur if used postoperatively<br>• If they occur, discontinuation of infusion often improves symptoms; benzodiazepines or α2 agonists may be effective |
| | • Blurry vision or diplopia | • Reported incidence 6.2%<br>• Dose-response relationship unclear at subanesthetic doses<br>• Incidence of intraocular pressure, a possible cause of visual symptoms, not known with subanesthetic dosages |
| Laskowski,[133] 2011; Bell,[134] 2005; Elia,[136] 2005 | • Nausea and/or vomiting | • PONV no worse with ketamine than placebo and may be decreased |
| Wai,[185] 2012; Bell,[186] 2012; Wong,[188] 2014; Noppers,[189] 2011 | • Hepatic toxicity | • Occurs mostly in ketamine abusers<br>• Reported upper incidence 9.8%<br>• Typically presents with elevated liver enzymes<br>• Mechanism may be cholestatic<br>• Resolves after ketamine cessation in most patients |
| Schwartzman,[123] 2009; Goldberg,[196] 2005; | • Headache | • Although reported at >10% in some studies, most report similar incidence to placebo<br>• At higher doses, serious causes such as elevated intracranial pressure should be considered<br>• Considered a treatment for headaches |
| Morgan,[190] 2011; Jhang,[191] 2015; Shahani,[192] 2007; Chen,[193] 2011 | • Cystitis | • Occurs mostly in ketamine abusers<br>• Typically presents with painful hematuria, dysuria, increased frequency, and pain postmicturition<br>• Mechanism may involve direct toxic effect, bladder barrier dysfunction, neurogenic inflammation, immunoglobulin E–mediated inflammation, overexpression of carcinogenic genes, abnormal apoptosis, and nitric oxide synthase–mediated inflammation<br>• First-line treatment is ketamine cessation; hyaluronic acid or anticholinergic agents may be helpful |
| Gomes,[178] 2011; Walker,[179] 2010; Vranken,[180] 2006; Rojas,[181] 2012; Errando,[182] 1999 | • Spinal cord injury | • Reported only with intrathecal use<br>• Weak evidence exists in animal studies; unknown effects in humans<br>• Toxicity may be more likely if preservative used but may still occur with preservative-free formulation |

PONV indicates postoperative nausea and vomiting.

Similar to other procedural interventions that are performed using sedation or monitored anesthetic care, the monitoring used during administration of ketamine should depend on the likelihood of deleterious signs (eg, elevated blood pressure and heart rate, ECG changes, loss of consciousness, psychotomimetic), symptoms (eg, chest pain, airway obstruction, hallucinations), and the potential for adverse consequences. The monitoring practices for ketamine infusions in the literature vary considerably and are not always consistent with ASA recommendations for the delivery of medications for moderate and deep sedation.[200] These recommendations include basic safety measures such as ensuring nil-per-os status, the use of supplemental oxygen during deep sedation, and monitoring the patient's level of consciousness, ventilation, oxygenation, and hemodynamic status prior to sedation, after the infusion has begun, periodically throughout the infusion, and prior to discharge, whereby certain discharge criteria must be met. The frequency and extent of monitoring depend in part on the presence and severity of associated medical comorbidities. For example, in patients with relative contraindications to ketamine such as poorly controlled angina, an infusion may still be indicated in refractory cases if the perceived benefits outweigh the risks. In patients with a history of angina, the physician might consider utilizing more frequent blood pressure monitoring (or continuous monitoring with an arterial line) in an intensive care unit setting.

## Guidelines

### Guideline Question 1: Which Patients and Chronic Pain Conditions Should Be Considered for Ketamine Infusions?

Chronic neuropathic pain is the most widely investigated indication for IV ketamine. Specific diagnostic categories that have been studied in RCTs include neuropathic pain of mixed diagnoses, traumatic spinal cord injury, PHN, and PLP. Conditions with features of neuropathic pain have also been studied including CRPS, fibromyalgia, and chronic ischemic pain.

In 7 double-blind RCTs, 78 patients with mixed neuropathic pain diagnoses were administered IV ketamine.[44,118,152,153,197–199] In 4 studies, significant reductions in pain during the ketamine infusion were observed compared with placebo.[44,118,152,153] However, in 3 studies, no significant differences in pain were observed between the ketamine and placebo groups.[197–199] The dose of the ketamine infusions ranged from 0.006 to 0.75 mg/kg per hour,[118,152,153,197–199] and the duration of the infusions ranged from 5 minutes to 2 hours.[44,118,152,153,197–199] The variations in dose and duration of infusion limited the identification of a definitive dose-response relationship between ketamine and pain scores. In the study by Leung and colleagues,[44] the dose of the ketamine infusion was not specified, but rather the authors titrated

the infusion rate to achieve 3 target serum concentrations (50, 100, and 150 ng/mL). In this study, the pain scores decreased in a stepwise manner as the targeted plasma level increased, consistent with a dose-response relationship.[44] In the study by Backonja and colleagues,[197] the duration of pain relief persisted for 2 to 3 hours following the infusion; otherwise, the duration of pain relief was not assessed beyond completion of the infusion in the remaining 6 studies.[44,118,152,153,198,199]

In 3 double-blind RCTs, the effects of IV ketamine were studied in 69 patients with traumatic spinal cord injury pain.[119,154,155] Significant reductions in pain scores during the ketamine infusion were observed in all 3 studies compared with placebo.[119,154,155] In 2 of these studies, the duration of pain relief was not assessed beyond the duration of the infusion.[119,154] In the study by Amr,[155] which added gabapentin to both treatment arms, a significant difference in pain scores was observed between the ketamine and placebo groups through 2 weeks following the infusions, but not afterward. There was considerable variation in the dose and duration of the ketamine infusions, which ranged from 6 μg/kg/min (0.42 mg/kg per hour) to 0.4 mg/kg for 17 minutes to 5 hours for 7 consecutive days.[119,154,155] Notably, less than 1 year after Amr's double-blind study evaluating IV ketamine for spinal cord injury neuropathic pain, Amr[201] performed a similar study comparing a single bolus of epidural ketamine (0.2 mg/kg) plus gabapentin to epidural saline on 40 patients with the same condition. The results were more auspicious in that short-term benefit was observed through 30 days, although not at longer follow-up periods.[201] However, the analgesic mechanisms behind a single neuraxial bolus and high-dose IV administration given over several days may be different, which makes generalizability difficult.

In 2 double-blind RCTs, the effects of IV ketamine were assessed in 21 patients with PLP,[117,156] with significant reductions in pain scores during the infusion observed in both studies compared with placebo. In the study by Nikolajsen and colleagues,[156] significant reductions in pain scores compared with placebo were observed up to 35 minutes following completion of the ketamine regimen, which consisted of a 0.1-mg/kg bolus administered over 5 minutes followed by an infusion of 7 μg/kg per minute (0.5 mg/kg per hour) for not more than 45 minutes.[156] In the other study, no significant differences in pain scores between placebo and ketamine (0.4-mg/kg infusion over 1 hour) or calcitonin as stand-alone treatments were found at 48-hour follow-up, although ketamine and calcitonin in combination was associated with significant improvements in average and worst pain.[117]

In a single double-blind RCT, the effects of IV ketamine (0.15 mg/kg administered over 10 minutes) were investigated in 8 patients with PHN.[157] Between 15 and 45 minutes following the ketamine infusion, significant reductions in pain scores were observed compared with placebo.

The clinical outcomes of several studies are available for conditions often associated with features of neuropathic pain including fibromyalgia, ischemic pain, migraine headache, low-back pain, and cancer. In 4 double-blind RCTs, the effects of IV ketamine infusions ranging from 0.3 to 0.5 mg/kg for 10 to 30 minutes were compared with placebo in 97 patients with fibromyalgia. In all 4 trials, significant improvements in pain were found during and immediately following the infusions.[21,158–160] Sustained improvements in pain compared with placebo were observed for up to 120 minutes in the 1997 study by Sorensen and colleagues.[159] However, in the study by Noppers and colleagues,[160] there were no significant differences in pain reduction between the ketamine and placebo groups at 2.5 hours, 1 week, or 8 weeks following the infusion.

The effects of IV ketamine on ischemic pain was assessed in 2 double-blind RCTs that involved 26 patients with severe peripheral vascular disease.[162,163] In the study by Mitchell and Fallon,[162] significant differences in pain relief between the ketamine (0.6 mg/kg administered over 4 hours) and placebo groups were reported 24 hours and 5 days following the infusions. In the study by Persson and colleagues,[163] 3 IV doses of ketamine (0.15, 0.3, 0.45 mg/kg) were compared with 10 mg of IV morphine, with both drugs infused over 5 minutes. No significant group differences in the analgesic effects of ketamine and morphine were observed when assessed at the time of the peak effects of each drug (5 minutes for ketamine and 20 minutes for morphine).[163]

In a double-blind study evaluating the effect of an add-on, low-dose IV ketamine infusion (up to 1 mg/kg per day or 0.025 mg/kg per hour) to morphine in 20 patients with cancer-related pain, which often has a neuropathic component, no benefit was observed in the treatment group during the 48-hour follow-up period.[164]

The effects of ketamine on migraine headache and chronic low-back pain have not been widely studied. In a single double-blind RCT that involved 17 patients with migraine headache, significant improvements in pain were observed compared with placebo for acute pain (<1 hour) and for at least 15 days in 12 subjects following administration of subcutaneous ketamine (80 μg 3 times daily for 3 weeks.).[168] However, a retrospective study failed to demonstrate prolonged benefit for migraine and new daily persistent headache following a multiday IV ketamine infusion.[167] For chronic low-back pain, the evidence supporting IV ketamine is purely anecdotal and derived from a retrospective study that included 7 patients.[37]

The effects of ketamine on CRPS were investigated in 2 double-blind RCTs involving 79 patients.[123,161] In the study by Sigtermans and colleagues,[161] significant improvements in pain were observed with S(+) ketamine (mean ketamine infusion dose, 22 [SD, 2.0]mg/h; mean duration, 4.2 days) compared with placebo at weeks 1 through 11 following the ketamine infusion. However, at the week 12 follow-up, the difference in pain scores between groups was no longer statistically significant.[161] In the study by Schwartzman and colleagues,[123] a significant difference in the short-form McGill Pain Questionnaire scores was observed between the ketamine (0.35 mg/kg per hour over 4 hours daily for 10 days) and placebo groups at 4 time points following the infusions (weeks 1–2, weeks 3 to 4, weeks 5–8, and weeks 9–12). However, the pretreatment McGill Pain Questionnaire total score in the ketamine group was lower compared with the placebo group, and among the 7 other parameters of pain assessed, few significant differences were observed between groups and none after 8 weeks. This trial failed to enroll the planned number of individuals, in part because the authors determined that higher dosages were necessary.[123]

In summary, for spinal cord injury pain, there is weak evidence supporting ketamine infusions (0.42 mg/kg per hour to 0.4 mg/kg ranging from 17 minutes to 5 hours for 7 consecutive days) for short-term improvements in pain (grade C recommendation, low level of certainty). For CRPS, there is moderate evidence supporting ketamine infusions (22 mg/h for 4 days or 0.35 mg/kg per hour over 4 hours daily for 10 days) to provide improvements in pain for up to 12 weeks (grade B recommendation, low to moderate level of certainty). For mixed neuropathic pain, PLP, PHN, fibromyalgia, cancer pain, ischemic pain, migraine headache, and low-back pain, there was weak or no evidence supporting ketamine infusions for immediate improvements in pain (grade D, low level of certainty). Excluding CRPS, there was no evidence supporting ketamine infusions for intermediate or long-term improvements in pain.

## Guideline Question 2: What Are the Contraindications for Ketamine Infusions?

When contraindications for ketamine are listed in textbooks and sources such as the Prescribers' Digital Reference, ketamine is classified as a Drug Enforcement Administration Schedule III, nonbarbiturate, sedative hypnotic.[202] It is FDA-approved for induction of general anesthesia, and as an anesthetic agent, it is given in higher dosages than for use in acute and chronic pain. In the subanesthetic doses used for acute or chronic pain, the IV ketamine boluses and infusion dosages are generally well tolerated.[203,204] In the majority of patients, ketamine is associated with minimal physiological effects on the neurologic, cardiovascular, respiratory, gastrointestinal, and ophthalmic systems.[205] Ketamine is metabolized by the liver and excreted by the kidney, but in the vast majority of cases, prolonged effects on hepatic or renal function have not been noted with subanesthetic doses.[189,206,207] Thus, the contraindications for anesthetic doses of ketamine may be relative contraindications or precautions when using subanesthetic doses, although definitive evidence is often lacking. In other words, patients with certain preexisting morbidities involving these systems are likely at a greater risk of complications when used at subanesthetic doses. Consequently, there are metabolic contraindications to the use of IV ketamine for chronic pain based on "best practices" noted in the literature.[205] Because ketamine is used as an elective treatment for a non–life-threatening condition (ie, pain), it is prudent to heed these relative contraindications and precautions, even though the likelihood of complications is low. Similarly, although there is evidence to indicate that some adverse effects are dose-dependent when ketamine is used in an anesthetic context, the evidence is less clear-cut for subanesthetic regimens beyond an unknown threshold dose. This is illustrated by a study from Schwenk and colleagues[184] in which discontinuation of ketamine related to adverse effects in a perioperative setting was unrelated to the infusion rate.

Medical contraindications and precautions regarding use of ketamine are listed in Table 5. In most instances, the evidence base for these recommendations is not robust enough to distinguish between absolute and relative contraindications except for elevated intracranial and intraocular pressure, brain tumor, and traumatic brain injury, which appear to be weak relative contraindications.[195,208,209] For example, there appears to be little to no risk of developing increased intracranial pressure when IV ketamine is used as an anesthetic induction agent prior to intubation in an operating room or intensive care unit setting in patients with brain tumors or traumatic brain injuries.[208,209] The same applies to concerns regarding elevated intraocular pressure when ketamine is used for sedation.[195] For cardiovascular events such as precipitation of angina, both anesthetic dosages and subanesthetic dosages used to treat chronic pain have been implicated.[210,211]

The American Psychiatric Association (APA) recently published consensus guidelines regarding the use of IV ketamine for treatment-resistant depression.[5] These guidelines as well as other reports[203,205,212] suggest few psychiatric contraindications. Large case series and systematic reviews indicate that there is an approximately 3.5% to 7.4% incidence of psychomimetic or dysphoric effects with IV ketamine.[134,136,203,205] The majority of these effects involve transient hallucinations or dissociative, out-of-body sensations, none of which lead to self-injurious behavior, extreme agitation, or extended psychosis. It is unclear from these studies if there is a dose-response relationship between ketamine and the incidence or intensity of psychiatric adverse effects, although adverse effects for most medications that act in the CNS are dose related. It is noteworthy that the treatment of choice to prevent or abort ketamine-induced hallucinations or dissociative effects is low-dose benzodiazepines (such as IV lorazepam or midazolam) or α2 agonists (clonidine), and not antipsychotics. As such, individuals with a history of serious psychomimetic effects and relative contraindications to rescue medications such as benzodiazepines (eg, use of some human immunodeficiency virus retroviral drugs, poorly controlled myasthenia gravis, history of adverse reaction) may not be good candidates for ketamine treatment. A history of psychosis as a contraindication is based on reports that the administration of subanesthetic IV ketamine to schizophrenics has caused reactivation of hallucinations and/or delusions.[213] It is also possible that patients with delirium can experience an exacerbation of symptoms with ketamine infusion.

Considering the growing recognition of its abuse potential,[214–217] a history of alcohol or other substance abuse is mentioned in several Web sites, drug monographs, and case reports as a relative contraindication to ketamine use. Unlike for acute pain in which there is a widely accepted mandate for urgent treatment, infusions are generally given on a 1-time basis, and the therapeutic alternatives (ie, high-dose opioids in an opioid-dependent individual) are often less appealing than ketamine; for chronic

**TABLE 5.** Contraindications to and Precautions for Use of Subanesthetic Doses of Ketamine for Chronic Pain

| Category | Contraindication/Precaution |
|---|---|
| Cardiovascular | • Unstable angina |
| | • Poorly controlled hypertension |
| | • High-risk coronary vascular disease |
| Neurological and ophthalmic | • Elevated intracranial pressure, including secondary traumatic brain injury or tumor |
| | • Elevated intraocular pressure, acute globe injury, or glaucoma |
| Endocrinological (due to possible potentiation of sympathomimetic effects) | • Hyperthyroidism |
| | • Pheochromocytoma |
| Metabolic | • Severe liver disease |
| Gastrointestinal | • Full stomach aspiration risk |
| Pregnancy | • Lack of data on safety |
| Psychiatric | • Intoxication with alcohol or other substances |
| | • Active substance abuse |
| | • Delirium |
| | • Psychosis |
| | • Refusal or inability to consent |

pain treatment, the use of a drug with abuse potential in a high-risk population may carry significant risks that outweigh the benefits. Risk stratification using instruments validated for opioid use such as Revised Screener and Opioid Assessment for Patients with Pain and Opioid Risk Tool may provide some information regarding abuse potential, although the instruments have not been validated for ketamine abuse, and unlike chronic opioid therapy, ketamine infusions are not typically accompanied by outpatient prescriptions.[218] In general, because repeated use (ie, serial infusions) for chronic pain often involves higher dosages given more frequently than when ketamine is administered for acute pain, the possible cumulative risks (drug-induced cystitis) and effects (hepatic dysfunction) of chronic administration should be taken into consideration when embarking on a scheduled multiday infusion regimen.

In summary, ketamine should not be used in patients with poorly controlled cardiovascular disease and should be avoided in individuals with certain poorly controlled psychoses (grade B evidence, moderate level of certainty). For hepatic dysfunction, it should be avoided in individuals with severe impairment but may be administered judiciously with proper monitoring in people with moderate disease (grade C evidence, low level of certainty). In patients with elevated intracranial and intraocular pressure, there is grade C evidence that ketamine should not be used or used only in lower dosages with extreme caution (low level of certainty). Serial ketamine infusions should not be undertaken in patients with an active substance abuse problem and should be used along with universal precautions to monitor for abuse (grade C evidence, low level of certainty).

### Guideline Question 3: Is There Any Evidence for a Therapeutic Dose Cutoff Threshold, a Dose-Response Relationship, Longer (ie, Continuous Versus Boluses), More Frequent (repeat) Infusions, or Higher Dosages to Be More Effective for Chronic Pain?

Adjuvants used to treat chronic pain are always associated with a therapeutic dose range, which may vary from patient to patient. Dosing below the therapeutic range is unlikely to result in significant benefit.[219] For depression, systematic reviews have concluded that repeat infusions have a larger effect size than single infusions and that a ketamine dosage of 0.5 mg/kg over 40 minutes was more effective than very low dosages, although the small numbers of patients involved and significant heterogeneity in study design limited the conclusions.[220,221] However, a recent consensus statement on ketamine use for depression found that alternative lower dosage schemes could be appropriate in different contexts.[5] In 1 case series, 3 patients received a total of 74 infusions over a 12-month period.[222]

Similar heterogeneity in treatment conditions and study design limits the conclusions one can draw for chronic pain, although the trends seem to suggest that higher dosages afford longer benefit. One small, randomized study that compared a single low-dose bolus of 0.4 mg/kg IV ketamine, calcitonin, ketamine plus calcitonin, and placebo for PLP found benefit that persisted through 48-hour follow-up.[117] Among RCTs for refractory pain that evaluated patients for longer time periods, the study by Noppers and colleagues,[160] which used a single, low-dose bolus (0.5 mg/kg) for fibromyalgia, reported benefits lasting only 3 hours, whereas a study on ketamine for spinal cord injury, which used an intermediate dose (80 mg/d for 1 week), reported benefits lasting 2 weeks.[155] For ischemic limb pain, the study by Mitchell and Fallon,[162] which administered a low-dose infusion of 0.6 mg/kg over 4 hours, described benefits that persisted for 5 days. However, in the only RCT evaluating IV ketamine for cancer-related pain, a low-dose, 24-hour infusion of 1 mg/kg found no benefit in individuals who were receiving concomitant opioid therapy.[164] In RCTs evaluating higher dosages administered as either serial outpatient infusions[123] or an inpatient infusion[161] for CRPS, significant improvement compared with placebo persisted for over 2 months.

In other studies, a small, retrospective analysis that administered IV ketamine titrated to a pain score of 3 or less out of 10 for at least 8 hours in 6 patients with refractory migraine headaches found no evidence of a dose-response relationship.[223] In a randomized study performed in patients with neuropathic pain, Huge and colleagues[224] reported a 38% reduction in pain score with 0.4 mg/kg of intranasal S(−) ketamine versus a 31% reduction with fewer adverse effects when 0.2 mg/kg was administered. Although this difference was not statistically significant, the study was underpowered (n = 16) to detect a dose-response relationship.

In 2 RCTs that examined the relationship between serum blood levels and postinfusion pain scores, no correlation was noted,[118,123] although a third RCT that compared 3 doses of ketamine to morphine did find a dose-response relationship.[163] An experimental study evaluating quantitative sensory testing in 12 subjects with neuropathic pain also found a dose-response relationship, with higher plasma levels resulting in greater reductions in cold pain and brush-evoked pain.[44] Multiday anesthetic-dose infusions of ketamine in dosages up to 7 mg/kg per hour have been successfully reported to alleviate severe, refractory CRPS and other chronic pain conditions, but require intensive care unit monitoring and intubation or other precautions to protect against aspiration.[225] The rationale for high-dose infusions is that subanesthetic dosages were anecdotally found to be less effective for advanced CRPS; however, no randomized studies have compared low- and high-dose infusions. A recent review by Maher and colleagues[36] concluded that higher total infused dosages of ketamine and longer infusions were associated with longer durations of pain relief. In an analysis accompanying a review by Noppers and colleagues,[226] the authors concluded that infusions less than 2 hours in duration were unlikely to provide benefit lasting more than 48 hours. They found that infusions longer than 10 hours, which resulted in higher dosages, were associated with an almost 95% probability of a patient attaining greater than 50% pain relief for more than 48 hours, whereas infusions over 30 hours increased that probability to almost 99%.[226] Although the authors did not specify whether the infusions should be continuous or cumulative hours, one might reasonably use the latter interpretation provided the serial infusions are performed before the analgesic benefit dissipates.

Overall, we conclude that there is moderate evidence to support higher dosages of ketamine over longer time periods, and more frequent administration, for chronic pain. Similar to the strategy used for opioids and other analgesic drugs with significant adverse effect profiles, it is reasonable to start dosing with a single, outpatient infusion at a minimum dose of 80 mg lasting more than 2 hours and reassess before initiating further treatments, similar to what is widely recommended for epidural steroid injections (grade C recommendation, low level of certainty) (Fig. 1).

### Guideline Question 4: Is There Any Role for Oral Ketamine or Another NMDA Receptor Antagonist as a Follow-Up Treatment in Lieu of Repeat Infusions?

The resources required for IV ketamine treatment have led to many attempts at utilizing oral ketamine and other NMDA-receptor antagonists, which are often used because of the lack of a readily available oral formulation for ketamine and concern for adverse effects, including those associated with compounding.

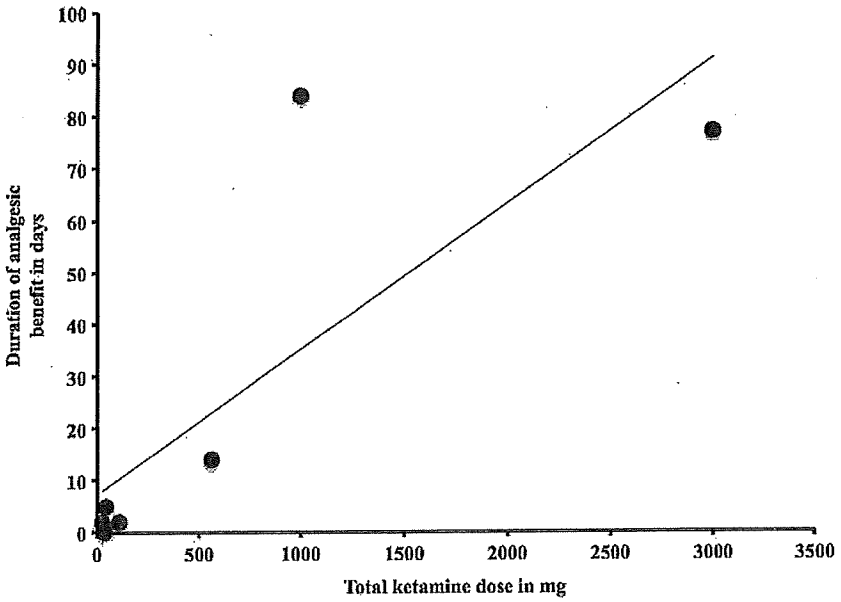


**FIGURE 1.** Graphical depiction of the relationship between ketamine dose and duration of analgesic benefit in randomized placebo-controlled trials that evaluated IV ketamine for chronic pain with a minimum of 48 hours' follow-up.[117,123,155,160–162,164] A trend line is been plotted to indicate the nature of this relationship.

Oral ketamine has been evaluated in several placebo-controlled trials,[227–230] with studies generally demonstrating no significant benefit, although 1 well-designed study found a significant opioid-sparing effect.[229] However, oral ketamine has poor bioavailability, and the relative dosages used in these studies were considerably less than in the studies evaluating IV administration. In 1 study that used oral ketamine (median dose, 150 mg/d) as a follow-up treatment after 10-day inpatient infusions, the authors reported that oral ketamine was effective (≥50% pain relief and/or improvement in quality of life) in 44% of patients, partially effective in 20%, and was associated with an opioid-sparing effect in the absence of pain reduction in 14% of 55 cases. Two-thirds of these patients obtained relief lasting longer than 6 months. Sixty percent of patients in this study had neuropathic pain, and those receiving opioids fared better than individuals not on opioid therapy.[231] In a small, placebo-controlled crossover trial performed in 8 patients with neuropathic pain who had responded to IV ketamine, oral ketamine syrup (0.5 mg/kg every 6 hours for 1 week) resulted in significantly better pain relief than saline, with 4 patients continuing treatment for longer than 9 months.[232]

Intranasal ketamine has a higher bioavailability than oral ketamine and has been studied in several randomized trials in individuals with chronic pain. These studies have demonstrated efficacy for breakthrough pain for a variety of chronic pain conditions in individuals with opioid tolerance (1–5 sprays of 10 mg ketamine),[52] neuropathic pain ((S)-ketamine 0.2 mg/kg compared with 0.4 mg/kg without a control group),[224] and the severity but not duration of aura in migraineurs (25 mg).[169] However, none of these studies demonstrated analgesia lasting more than a few hours, indicating the need for continued treatment. One issue that must be considered when starting a patient on oral or intranasal ketamine is the potential for accidents, as ketamine may cause hallucinations and impairments in judgment, visual and perceptual functions, and psychomotor ability. This is particularly relevant for motor vehicle collisions, such that if ketamine is considered as a treatment for incident or breakthrough pain, proper safety precautions must be exercised.[233]

Cohen and colleagues[234–236] performed a series of studies evaluating the use of a brief IV ketamine test (0.1 mg/kg) to predict subsequent treatment with oral dextromethorphan in patients with neuropathic pain, opioid tolerance, and fibromyalgia. When data for all 3 studies were pooled, the overall sensitivity, specificity, positive predictive value, and negative predictive value were 76%, 78%, 67%, and 85%, respectively.[237] One criticism of these studies is that expectation bias, which is an integral part of the placebo effect, may have enhanced the effect in infusion responders. In general, the use of nonketamine NMDA-receptor antagonists. such as dextromethorphan (conflicting), amantadine (conflicting), magnesium (positive findings in small studies), memantine (mostly negative), and carbamazepine, which may possess some NMDA antagonistic properties (positive), has yielded mixed results for neuropathic pain and possibly other chronic pain conditions characterized by central sensitization.[238,239]

Overall, we conclude that there is low-level evidence to support the use of oral ketamine (150 mg/d or 0.5 mg/kg every 6 hours) and other NMDA-receptor antagonists such as dextromethorphan (0.5–1 mg/kg every 8 hours) as follow-up therapy following IV infusions, and moderate evidence to support intranasal ketamine (1–5 sprays of ketamine 10 mg, 0.2–0.4 mg/kg (S)-ketamine, and single dose ketamine 25 mg every 6 hours as needed) as a treatment for breakthrough pain. From a clinical practice perspective, oral ketamine has significant abuse potential and a high street value. For these reasons, in patients with a history of abuse or who are at high risk of abuse, the risks of prescribing it chronically in a community-based setting should be weighed against the potential benefits, and proper surveillance, similar to what is done for patients on chronic opioid therapy, should be used. More research should also be conducted regarding the long-term effects of ketamine. Considering the costs and resources involved with IV infusions, it is reasonable to try a follow-up intranasal ketamine, oral ketamine, or oral dextromethorphan treatment regimen in lieu of serial treatments (grade B recommendation, low level of certainty for oral preparations, moderate level of certainty for intranasal ketamine).

### Guideline Question 5: What Tests Should Be Ordered Prior to an Infusion of Ketamine?

Although ketamine has direct negative inotropic effects that may be evidenced in individuals who are catecholamine depleted, in clinical practice the use of ketamine is generally associated with increased heart rate and blood pressure, owing to its sympathomimetic properties. In a randomized study evaluating the hemodynamic effects of propofol and ketamine in 16 individuals undergoing total hip replacement, the use of anesthetic ketamine dosages (1.5-mg/kg induction dose followed by 50 μg/kg per minute [3 mg/kg per hour]; mean dose, 157.5 mg/h) was associated with significant increases in mean arterial and pulmonary artery pressures, resulting in a 100% increase in myocardial oxygen consumption.[240] Of note, the maintenance dose of ketamine used in this study was similar to the high-end dosages used to treat chronic pain in some settings.[241]

The use of preinfusion testing to minimize risks is an important clinical consideration prior to IV ketamine administration for pain management. In a case report involving a patient with terminal disease with cancer-related pain and a history of angina, subendocardial myocardial infarction, and chronic obstructive pulmonary disease who received a subcutaneous ketamine infusion of 150 mg per day to supplement opioid analgesia for back pain related to spine metastases, angina was precipitated 15 days after the start of the infusion, requiring escalating doses of sublingual nitroglycerin.[211] This persisted even after his baseline antianginal medication was restarted and necessitated discontinuation of the infusion. However, in 21 double-blind RCTs that involved 395 patients with chronic neuropathic pain–related conditions,[21,44,117–119,123,152–163,197–199] 12-lead ECGs were obtained prior to the administration of IV ketamine in only 1 study.[153] This particular RCT included 20 patients with nerve injury pain who received a 0.1-mg/kg ketamine bolus over 10 minutes followed by an IV ketamine infusion 0.007 mg/kg per minute (0.4 mg/kg per hour) for 20 minutes. No adverse cardiovascular effects were reported.[153] In the remaining 20 RCTs, 9 studies used continuous ECG monitoring during the ketamine infusions.[21,44,117,123,155,156,158,159,163] No data were reported regarding changes in heart rate during the ketamine infusion in 5 studies,[21,123,156,158,159] and no significant changes in heart rate were reported in 2 studies.[44,117] In a randomized study conducted in 80 patients with spinal cord injury pain who received 80 mg of IV ketamine or placebo over 5 hours, a "15% increase" in heart rate was observed in 2 patients.[155] In another randomized, double-blind study involving 8 patients given ketamine dosages ranging from 0.15 to 0.45 mg/kg on 4 separate days to treat ischemic pain from arteriosclerosis obliterans, changes in heart rate were observed to stay "within the limits of ±10 beats/min in all patients."[163] Although ketamine has been anecdotally associated with cardiac arrhythmias,[242] no arrhythmias were reported in any of the 9 studies that used continuous ECG monitoring.[21,44,117,123,155,156,158,159,163] A literature review evaluating the use of ketamine for procedural sedation in more than 70,000 patients found the incidence of cardiovascular and other adverse events to be exceedingly low, reporting 1 case of hypoxic cardiac arrest secondary to respiratory depression in a debilitated adult.[243]

Ketamine undergoes extensive hepatic metabolism, and although short-term use of the drug has been infrequently associated with elevated liver function tests, clinically apparent liver damage has not been reported. In one of the earliest reports evaluating the effect of ketamine on liver function, Dundee and colleagues[206] found that 14 of 34 patients receiving 3 to 4 mg/kg of ketamine for anesthesia experienced significant elevations in liver function tests. Lower dosages used for chronic pain may also be associated with liver toxicity. In a randomized trial by Noppers et al,[189] 13 patients were randomized to a second exposure to ketamine 16 days following a 100-hour infusion (maximum infusion rate of 7.2 μg/kg per minute or 0.4 mg/kg per hour for a mean dose of 1813 mg), a second exposure 12 weeks after the initial exposure, or a first exposure of ketamine following treatment with midazolam. In the 6 patients who received their second treatment 16 days after the first, 1 patient developed severe hypertension, and 3 patients developed dramatic elevations (≥3 times baseline) in liver enzymes that returned to normal within 3 months; none of the patients in the other 2 groups experienced abnormal liver function tests.[189] Other studies have reported that approximately 10% of individuals receiving high-dose ketamine infusions will experience significant increases in liver enzymes.[225] In another RCT that included 60 patients with CRPS, patients received daily "liver function tests" during a continuous ketamine infusion that was on average 4.2 days in duration. The average ketamine dose was 22 mg/h, and no adverse hepatic effects were reported.[161]

In summary, there is insufficient evidence supporting preinfusion testing prior to the administration of IV ketamine for chronic neuropathic pain conditions in healthy individuals. In individuals at high risk of cardiovascular events or symptoms suggestive of cardiovascular disease, baseline ECG testing may be considered to exclude individuals with uncontrolled ischemic heart disease. In individuals with baseline liver dysfunction, at risk of liver toxicity (eg, alcohol abusers, people with chronic hepatitis), or who are expected to receive high doses of ketamine at frequent intervals, baseline and postinfusion liver function tests should be considered on a case-by-case basis (grade C evidence, low level of certainty).

### Guideline Question 6: What Training Is Prudent for Personnel Who Administer Boluses and Infusions and Oversee Dose Titration? Does This Recommendation Change With Dosage (That Is, Subanesthetic Versus Anesthetic Range) or Route of Administration?

The administration of ketamine as a bolus and/or infusion for the treatment of pain requires a knowledge and understanding of pain, familiarity with the drug's pharmacodynamic and pharmacokinetic effects, and the effects ketamine has on the symptoms and signs of pain (eg, allodynia, hyperalgesia). Ketamine is a dissociative anesthetic associated with significant neuropsychiatric, gastrointestinal, cardiovascular, and respiratory adverse effects that can vary depending on the dose and subject.[238,244] These neuropsychiatric adverse events include sedation, vivid dreams or nightmares, hallucinations, out-of-body experiences, headache, dizziness, fatigue, changes in mood, altered vision and hearing, light-headedness, paresthesias, changes in taste, dysarthria, euphoria, and inebriation. Hemodynamic adverse effects include tachycardia, arrhythmias, and hypertension, whereas possible respiratory events include hypoventilation or hyperventilation, oxygen desaturation, and hypoxia.[37,123,156,157,161,196,225,245] The majority of these adverse effects are transient and can be treated by lowering the rate of infusion or stopping it. Medications including benzodiazepines, α2 agonists, β-blockers, and antiemetics can be administered to counter these effects. Although none of the published studies have reported serious adverse events, it should be acknowledged that the number of participants in these studies was relatively small, and the risk of serious adverse events cannot be ruled out.

There are no published guidelines or recommendations outlining the specific training requirements for physicians involved in the administration of ketamine at dosages above those typically given for depression (>0.5 mg/kg), although its classification as an anesthetic agent has resulted in some institutions

mandating that boluses be given only by anesthesiologists or anesthetists. It has been suggested that credentialing in moderate (conscious) sedation should be a prerequisite for staff administering ketamine and the health care providers involved in caring for patients.[246] Staff and clinicians overseeing the care of patients receiving this medication should be trained in responding to cardiovascular and respiratory emergencies.[247] Health care providers involved in administration of ketamine should also have adequate training in titrating the dose of ketamine while ensuring the safety of the recipient and the availability of treatments to address adverse effects. Furthermore, it is also recommended that ketamine infusions should be performed in settings with appropriate monitoring and resuscitation facilities under the care of an appropriately trained physician.[248]

The APA guidelines for administration of ketamine to treat depression in dosages that are significantly lower (usually a single dose of 0.5 mg/kg administered over 40 minutes) than those used for chronic pain syndromes[247] recommend that hemodynamic (ECG, blood pressure) and respiratory monitoring (end-tidal carbon dioxide and oxygen saturation) be available during infusion.[5] The APA guidelines also recommend that an on-site clinician be available to evaluate and emergently treat potential behavioral risks including suicidal ideation, severe anxiety, and marked mental status changes before discharge home and that rapid follow-up evaluations of patients' psychiatric symptoms be provided as needed.[5]

This panel agrees with the APA recommendation that only a licensed physician who can administer a Drug Enforcement Administration Schedule III medication with Advanced Cardiac Life Support certification be in charge of administering ketamine, but because of the higher dosages used for chronic pain, we believe that person should also meet ASA requirements for the delivery of moderate sedation. For the person who actually administers subanesthetic IV bolus sedation, recommended credentials include a registered nursing degree with Advanced Cardiac Life Support certification, along with training in the administration of moderate sedation and specifically the pharmacology of ketamine. The training can be via courses given internally or by accredited organizations (eg, American Association of Moderate Sedation Nurses).

Although the APA consensus statement did not find any cases of clinically relevant respiratory depression at the low dosages given for depression, they did mention several instances of patients becoming unresponsive, putting them at risk of aspiration. Because the doses and/or duration of ketamine infusions used to treat pain are higher than those used to treat depression and the sedative midazolam is often given preemptively or as a rescue medication, it is appropriate to recommend that only those trained in the induction and maintenance of ketamine infusions, such as anesthesiologists, critical care–trained physicians, and pain physicians with appropriate credentials to include training in airway management, be responsible for decisions regarding administration of this medication in doses that may render a patient unresponsive. An appropriately trained health care provider[246] can monitor the patient receiving ketamine infusion in subanesthetic doses and change the infusion rate based on directions from the responsible physician who, for single-day infusions, should be immediately available.

Individuals respond with great variability to ketamine, so there is wide variation in hospital-based practices. Specific concerns regarding the monitoring of ketamine administration include airway protection, cardiovascular stimulation, the potential interaction of ketamine with concomitantly administered medications that may enhance certain effects (eg, midazolam), and the treatment of adverse effects.

Ketamine doses at levels that may result in serious adverse sequelae (bolus dose of ≥0.35 mg/kg and/or infusion of ≥1 mg/kg per hour) should be administered by clinicians experienced in ketamine administration in a unit that contains trained nurses available for monitoring and individuals trained in airway management and Advanced Cardiac Life Support (eg, anesthesiologist, nurse anesthetist, emergency department physician) who are immediately available to address any potential emergencies.[225] For some individuals (ie, elderly individuals and those with significant comorbidities), lower thresholds should trigger the requirements for more intensive monitoring and safety measures. Higher cutoffs using subanesthetic dosages may also be utilized in appropriately resourced environments in both inpatient and outpatient settings when patients have been "stabilized" or previously treated with higher dosages.[123,161] The basic monitoring requirements (hemodynamic and respiratory parameters, sedation levels using a validated scale) remain the same irrespective of the route of administration or dose in individuals receiving ketamine in a nonchronic treatment regimen. Availability of personnel and equipment for resuscitation at all times is also mandatory irrespective of the level of infusion (grade A recommendation, low level of certainty).

## Guideline Question 7: What Preemptive Medications Should Be Available for Administration as Rescue Medications to Treat Possible Adverse Events Related to Ketamine Infusions?

Ketamine is associated with myriad adverse effects including psychomimetic, cardiovascular, and gastrointestinal effects, resulting from its action on a variety of receptors, which include NMDA, acetylcholine, opioid, ion channels, monoamine, and histamine. For the treatment of CRPS, an open-label study found anesthetic doses (up to 117 μg/kg/min or 7 mg/kg per hour) resulted in 90% of patients experiencing moderate to severe psychomimetic effects including anxiety, dysphoria, and nightmares despite premedication and maintenance infusions of midazolam and clonidine.[225] These adverse effects were dose-dependent and persisted following infusion discontinuation. One pilot study using a subanesthetic infusion of S(+)-ketamine (up to 5 μg/kg per minute or 0.3 mg/kg per hour) produced mild psychomimetic effects including euphoria and disorientation[122]; however, a double-blind RCT using a modestly higher but still subanesthetic dosage (up to 7.2 μg/kg per minute or 0.4 mg/kg per hour) reported 93%, 63%, and 47% rates of mild psychomimetic effects, nausea, and emesis, respectively.[161] These last 2 studies also did not administer premedication to mitigate adverse effects, and neither specifically addressed the differential effects of the R and S enantiomers, as some studies suggest that the more potent S(+)-ketamine contains more psychedelic effects.[249] A double-blind RCT using subanesthetic doses of racemic ketamine (up to 5.2 μg/kg per minute or 0.3 mg/kg per hour), in combination with midazolam and clonidine premedication, reported no psychomimetic adverse effects.[123]

The literature evaluating the benefit or harm of premedication prior to ketamine use is primarily limited to pediatric sedation and general anesthesia for surgical procedures; therefore, it suffers from the bias of pediatric physiology or concomitant procedures and medications, which limit the conclusions that can be drawn for chronic pain. In a single RCT, midazolam and dexmedetomidine were found to reduce psychomimetic and cardiovascular adverse events when ketamine was used as a sole general anesthetic (2 mg/kg, once) in very brief surgical cases.[250] In populations receiving subanesthetic ketamine, the number-needed-to-harm, with "harm" defined as ketamine-induced

psychomimetic adverse effects, has been calculated. A meta-analysis of sedated and awake pediatric and adult patients estimated the number-needed-to-harm for hallucinations to be 21 when ketamine is used without coadministration of a benzodiazepine; when patients are given a benzodiazepine prior to ketamine administration, the number increases to 35, suggesting premedication may lessen but not eliminate psychomimetic events.[136]

Further indirect evidence of the benefits afforded by preemptive treatment with mitigating medications in adults includes double-blind RCTs evaluating premedicants in patients receiving subanesthetic dosages of IV ketamine (<70 mg/h) for sedation. In 1 study, lorazepam was found to decrease the emotional distress caused by ketamine but not the incidence of psychosis,[251] whereas another study reported that midazolam reduced agitation.[252]

Ketamine overdose is associated with loss of consciousness, respiratory depression, tachycardia, hypertension, and severe psychomimetic events including positive and negative signs of schizophrenia. No RCT directly addresses the use of rescue medications, and the recommendations for management of severe toxicity include supportive care addressing untoward signs and symptoms.[253] Treatment recommendations include the use of a benzodiazepine such as midazolam or diazepam to prevent or attenuate psychomimetic symptoms, mitigate sympathomimetic symptoms, and reduce the incidence of nausea; the butyrophenone haloperidol for its antiemetic properties, sedative effects, and reduction of psychomimetic symptoms and emergence reactions; and clonidine for its ability to reduce sympathomimetic effects and decrease the incidence of psychomimetic reactions. Dystonia is not commonly experienced but can be treated with the antihistamine, diphenhydramine. Seizures, although rare, should be treated with benzodiazepines followed by barbiturates or propofol if persistent.

Overall, we conclude there is limited direct evidence supporting the preemptive use of benzodiazepines and α2 agonists and no evidence to support antidepressant, antihistamine, or anticholinergic premedicants prior to the initiation of subanesthetic ketamine for chronic pain treatment (grade C recommendation, low level of certainty).

### Guideline Question 8: What Constitutes a Positive Treatment Response for Chronic Pain?

Guidelines have been published on what constitutes a clinically meaningful benefit for an individual for specific metrics, which can differ from what constitutes a significant improvement in a clinical trial.[254] Farrar and colleagues[255] analyzed data on more than 2500 patients from 10 clinical trials for a variety of different chronic pain conditions and found that a 2-point or 30% decrease in pain score corresponded to a patient rating of "much improved." Because pain scales are not linear,[256] a 30% decrease in pain would appear to be a reasonable benchmark. For acute pain, a systematic review found a 17-mm (interquartile range, 14–23 mm, on a 0- to 100-mm VAS) decrease to be the median "minimal clinically important difference" in terms of absolute pain reduction, with 23% (interquartile range, 18%–36%) being the median relative diminution.[257] The 23% reduction is similar to what Bicket et al[258] found to constitute the threshold for patient satisfaction when they analyzed the results of 3 RCTs evaluating epidural steroid injections for subacute and chronic radiculopathy. Besides pain, other factors that should be considered when identifying treatment responders include function, psychological and emotional well-being, sleep, and satisfaction.[259] Pain is subjective, and pain scores should never be considered in isolation. For example, a 1-point decrease in pain that is accompanied by cessation of analgesic use and return-to-work would be considered by most to constitute a better outcome than a 2-point decrease in pain in the context of a significant increase in opioid consumption and corresponding decrease in activity. The IMMPACT guidelines provide recommendations on the core outcome domains for chronic pain clinical trials, which can be adapted for individual use (ie, Oswestry Disability Index for a patient with back pain, Western Ontario and McMaster Universities Osteoarthritis Index for a patient with osteoarthritis, Beck Depression Inventory for a patient with a mood disorder, a sleep scale for a patient with a sleep disorder).[259]

Studies evaluating ketamine for chronic pain have generally enrolled patients refractory to conventional treatments, who may be less likely to respond to any intervention; this reflects clinical practice. In the RCTs that have designated specific pain reduction cutoffs for what constitutes a responder, 50% or greater pain relief is the most common,[117–119,160] with only the study by Salas and colleagues[164] noting the proportion of individuals who experienced 30% or greater benefit. In the placebo-controlled studies that evaluated intermediate- and long-term follow-up periods, none specified a time frame threshold for what was considered a positive response.[123,155,160,161]

The duration of a clinical trial and by extension the duration of relief required to designate a response as positive correlate with the cost and risks of the treatment. When balancing these factors, one must consider not only the perceived and objective benefits (eg, return to work, medication reduction), but also the need for repeat or additional treatments and the potential for long-term complications. In general, the required benefit for surgery exceeds that of nonsurgical procedural interventions, which in turn is greater than that for medications and alternative treatments. Along this spectrum, an IV ketamine infusion in an outpatient setting most closely resembles nonsurgical pain management procedures in terms of risks, costs, and the need for repeat treatments.

In conclusion, given the refractory nature of patients who receive ketamine infusions, we recommend that a positive outcome be considered as 30% pain relief or greater in conjunction with patient satisfaction and/or more objective indicators of meaningful benefit, such as a 12.8% improvement in Oswestry Disability Index score in a patient with back pain or a 20% or greater reduction in opioid use.[260,261] In terms of duration of benefit, patient expectations and satisfaction should be considered, but based on the cumulative risks and costs of treatment, greater than 3 weeks following a single outpatient infusion and greater than 6 weeks following an inpatient or series of infusions are a reasonable designation. Similar to multiple guidelines for epidural steroid injections,[262] a consecutive "series" of infusions should not be administered by rote, but rather tailored to patient response. Considering the risks of long-term ketamine treatment, limiting these to no more than 6 to 12 treatments per year is reasonable, although deviations may be made in exceptional circumstances (grade C recommendation, low to moderate level of certainty).

## Future Research

The use of ketamine has skyrocketed for chronic pain and depression, but many questions remain unanswered. The most prominent among these revolve around durability of benefit and implications of repeated administrations (ie, the development of pharmacodynamic, metabolic, and behavioral tolerance leading to tachyphylaxis and loss of analgesic benefit), standardization of treatment (ie, optimum dosages and infusion parameters), and acute and chronic adverse effects, including remote neuropsychiatric effects. Given the poor translational reproducibility and validity of preclinical chronic pain research to humans, only robust clinical trials with long-term follow-up will provide answers to these questions.

Identifying individuals likely to respond to treatment or those predisposed to significant adverse effects based on phenotypes and possibly genotypes can shift the risk-benefit ratio toward greater benefit. In an era characterized by an increased emphasis on precision medicine and efforts to contain spiraling health care costs, refining selection criteria can reduce risks and costs and improve treatment outcomes. Because back pain, neck pain, and other musculoskeletal disorders, along with depression, comprise the 4 leading causes of disability in the United States,[15] determining the effectiveness of ketamine in these predominantly nonneuropathic and mixed conditions[263,264] is of paramount importance. Although there is stronger evidence in preclinical and clinical studies evaluating ketamine for neuropathic pain and CRPS, there is a growing body of evidence in animals for inflammatory pain and for humans in nonneuropathic spine pain.[27,28,37] A role for ketamine infusions in other common chronic pain syndromes such as fibromyalgia and headaches has also been suggested and been explored in prospective case series with mixed results.[37,160,167,265]

**TABLE 6.** Summary of ASRA/AAPM/ASA Recommendations for Ketamine Infusions for Chronic Pain

| Recommendation Category | Recommendation | Level of Evidence* |
|---|---|---|
| Indications | (1) For spinal cord injury pain, there is weak evidence to support short-term improvement | (1) Grade C, low certainty |
| | (2) In CRPS, there is moderate evidence to support improvement for up to 12 wk | (2) Grade B, low to moderate certainty |
| | (3) For other pain conditions such as mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain, there is weak or no evidence for immediate improvement | (3) Grade D, low certainty |
| Dosing range and dose response | (1) Bolus: up to 0.35 mg/kg | (1) Grade C, low certainty |
| | (2) Infusion: 0.5 to 2 mg/kg per hour, although dosages up to 7 mg/kg per hour have been successfully used in refractory cases in ICU settings | (2) Grade C, low certainty |
| | (3) There is evidence for a dose-response relationship, with higher dosages providing more benefit. Total dosages be at least 80 mg infused over a period of >2 h | (3) Grade C, low certainty |
| Relative contraindications | (1) Poorly controlled cardiovascular disease, pregnancy, active psychosis | (1) Grade B, low certainty |
| | (2) Severe hepatic disease (avoid), moderate hepatic disease (caution) | (2) Grade C, low certainty |
| | (3) Elevated intracranial pressure, elevated intraocular pressure | (3) Grade C, low certainty |
| | (4) Active substance abuse | (4) Grade C, low certainty |
| Role of oral NMDA receptor antagonist as follow-on treatment | (1) Oral ketamine or dextromethorphan, and intransal ketamine can be tried in lieu of serial infusions in responders | (1) Grade B, low certainty for oral preparations, moderate certainty for intranasal ketamine |
| Preinfusion tests | (1) No testing is necessary for healthy individuals | (1) Grade C, low certainty |
| | (2) In individuals with suspected or at high risk of cardiovascular disease, baseline ECG testing should be used to rule out poorly controlled ischemic heart disease. | (2) Grade C, low certainty |
| | (3) In individuals with baseline liver dysfunction or at risk of liver toxicity (eg, alcohol abusers, people with chronic hepatitis), and those who are expected to receive high doses of ketamine at frequent intervals, baseline and postinfusion liver function tests should be considered on a case-by-case basis | (3) Grade C, low certainty |
| Positive response | (1) A positive response should include objective measures of benefit in addition to satisfaction such as ≥30% decrease in pain score or comparable validated measures for different conditions (eg, Oswestry Disability Index for back pain) | (1) Grade C , low-to-moderate certainty |
| Personnel and monitoring | (1) Supervising clinician: a physician experienced with ketamine (anesthesiologist, critical care physician, pain physician) who is ACLS certified and trained in administering moderate sedation | (1) Grade A, low certainty |
| | (2) Administering clinician: registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation | (2) Grade A, low certainty |
| | (3) Setting: at dosages exceeding 1 mg/kg per hour, a monitored setting containing resuscitative equipment and immediate access to rescue medications and personnel who can treat emergencies should be used, although this dose may vary based on individual characteristics | (3) Grade A, low certainty |

*Evidence was evaluated according to the US Preventive Services Task Force grading of evidence, which defined levels of evidence based on magnitude and certainty of benefit.[5]

ACLS indicates Advanced Cardiac Life Support; ICU, intensive care unit.

One of the biggest questions surrounding ketamine is whether the drug can prevent the transition from acute to chronic pain by virtue of its NMDA antagonist and opioid-sparing properties. Given the high prevalence rates of surgery and acute pain, and the growing use of ketamine in the context of posttraumatic (including postsurgical) pain, designing large, multicenter studies should be given high priority.

Finally, in addition to preventing the chronification of acute pain, another top National Institutes of Health chronic pain research priority is the establishment of registries. Unlike placebo-controlled clinical trials, which gauge efficacy in small, well-selected populations, registries can provide a better measure of effectiveness in large populations treated under real-life conditions and may provide important information regarding who is likely to benefit from a specific treatment (ie, phenotyping or precision medicine). In the absence of large, randomized studies, the establishment of ketamine treatment-based registries can help guide treatment decisions.

## CONCLUSIONS

The growing body of literature, both peer reviewed and aimed at lay audiences, recommending ketamine for chronic pain and depression has led to a surge in its use, with the growth in utilization outpacing the development of standards governing practice. This unrestrained growth has led to a chorus of calls from patient advocacy groups, physicians, payers, regulatory bodies and pain medicine organizations for the development of guidelines. Similar to other consensus statements, the guidelines contained here do not represent "edicts" aimed at establishing definitive standard of care, but rather provide a structural framework that should be considered when devising institutional protocols and developing individualized care plans. We appreciate that medicine is an art as well as a science and that evidence-based medicine considers not only scientific literature, but also clinical judgment based on physician experience and patient values and preferences.[266] Therefore, what may be warranted in some scenarios may prove to be suboptimal in other circumstances, and reasonable individuals may come to different conclusions based on the same data. In the current guidelines, we were able to come to a full consensus without dissension on all questions, although several questions required multiple revisions before agreement could be reached (Appendix 2, Supplemental Digital Content 2, http://links.lww.com/AAP/A250).

The recommendations in response to the questions we have addressed are often based on small randomized trials, observational and retrospective studies, clinical experience, and evidence extrapolated from the use of ketamine in other contexts and thus may change as better evidence emerges. This may be more relevant for the sections concerned with indications and, to a lesser extent, contraindications, which continue to evolve with more information. For example, adverse effects such as ketamine-induced psychosis may result from either 1-time use or cumulative effects (eg, psychosis, urinary tract dysfunction, liver disease),[189,267,268] and as the serial use of ketamine for chronic conditions such as depression and pain continues to rise, and the prevalence of abuse increases commensurately, the indications, contraindications, and surveillance recommendations may change in concert.

Based on specific requests, we tried to provide recommended dosing ranges whenever possible. Although these recommendations are based on the existing literature, which is characterized by a lack of large, high-quality studies, one must recognize that the mechanisms of pain are strikingly similar for certain conditions (eg, deafferentation and cortical reorganization for PLP and spinal cord injury) and share considerable overlap even in widely disparate conditions (eg, central sensitization for fibromyalgia and neuropathic pain). Therefore, one could reasonably extrapolate ketamine dosing schemes for a condition that has been adequately investigated to another condition that has not been well researched, as is typically done for other analgesic medications. Differences not only in disease features but also patient characteristics, and practice settings and capabilities, further highlight the need for dosing flexibility. As is true for all aspects of medicine, the decisions as to when a treatment is indicated, what setting and parameters to use, how to monitor its effects, and how to minimize risks should be made on an individualized basis after sufficient discussion with the patient (Table 6).

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# Ketamine Infusion for Treatment Resistant Depression and Severe Suicidal Ideation

**National Protocol Guidance**
**October 2025**

**VA Pharmacy Benefits Management Services, National Formulary Committee, and Office of Mental Health**

**Purpose:** To provide general guidance on ensuring access to intravenous ketamine for the treatment of treatment resistant major depressive disorder (TRD) or severe suicidal ideation under a National VA protocol.

**Disclaimer:** To be consistent with the purpose of this general guidance and not to be overly proscriptive, this guidance allows facilities the flexibility to exercise modifications to the protocol as necessary to operationalize the use of ketamine for treating TRD or severe suicidal ideation. Clinical circumstances for the treatment of individual Veterans may necessitate provider decision making that is outside of this guidance.

## Background

Ketamine is a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist approved for general anesthesia. Ketamine has demonstrated a rapid response in people with TRD following a single infusion. A systematic review and meta-analysis assessed nine non-electroconvulsive therapy studies that compared ketamine to placebo or midazolam in patients with treatment-resistant depression (n=192). Compared to controls, patients who received ketamine had significantly greater improvement on global depression scores within 24 hours of administration. Suicidal ideation was reduced in the two studies in which it was assessed. Ketamine's efficacy was maintained in patients on or off antidepressants in all subgroups and sensitivity analyses. A small randomized, double blind trial found ketamine to be as effective as ECT with a more rapid onset of effect. Common side effects included dry mouth, tachycardia, increased blood pressure and the feeling of disassociation. Additional serious side effects include increased intracranial pressure, increased intraocular pressure, and hypersalivation which can lead to upper airway obstruction or laryngospasm. A 2017 meta-analysis reported ketamine rapidly reduced suicidal thoughts in depressed patients with suicidal ideation.

Despite these preliminary positive findings in a limited number of studies, many questions remain unanswered. Studies to date have given a single dose of ketamine leaving the number and frequency of doses needed to treat an episode of TRD undetermined. Ketamine has also not been adequately studied in people with co-occurring conditions. Thus, the identification of patients who would most benefit from ketamine and the best approach to dosing has not been established.

**Departments Affected:** Pharmacy, Nursing, Mental Health (Anesthesia on Call)

## Procedure:

- Patients can either be treated as outpatients or inpatients

## Patient Selection

### Inclusion Criteria

**One** of the following must be selected to meet criteria for use

- Remission not achieved from 2 antidepressant trials including a trial of an augmentation strategy in the current episode of depression^1 and 4 total adequate antidepressant trials in the patient's lifetime
- Patient is hospitalized with TRD with acute suicidal ideation/behavior

^1 One augmentation trial could be an adequate course of evidence-based psychotherapy (EBP)

### Additional Inclusion Criteria

The answers to **ALL** of the following must be fulfilled to meet criteria

- Patient in current episode of depression is experiencing moderate to severe depressive symptomatology (i.e., PHQ-9 $\geq$ 15 within the last 30 days)
- Antidepressant treatment trials are considered unsuccessful if the patient has not responded to at least 6 weeks of an antidepressant at half maximum dose or greater.
- A VA psychiatrist or a VA licensed Mental Health care provider (i.e., CPP, NP, PA) has evaluated the patient and determined and documented that the patient qualifies for ketamine treatment in the patient's medical record.
- The patient or their legal representative can provide signed informed consent.
- The patient agrees to stay and be monitored after ketamine administration and agrees not to drive or operate heavy machinery/equipment and not to make major financial or legal decisions for the remainder of the day in which ketamine is administered.
- The patient has an adult who can accompany him/her and assist with transportation, or another method of safe transport has been arranged and documented.
- For women of childbearing potential
    - Pregnancy should be excluded prior to receiving ketamine and the patient provided contraceptive counseling on potential risks vs. benefits of taking ketamine if the patient were to become pregnant.

### Exclusion Criteria

If the answer to ANY item below is met, the patient should NOT receive ketamine

- Current or history of schizophrenia, schizoaffective disorder, or bipolar disorder
- Dementia
- Current or recent (within the 30 days) delirium
- Current uncontrolled hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg)
- Severe cardiac decompensation (Class IV heart failure or unstable angina)
- Severe hepatic impairment (Child-Pugh class C)
- Uncontrolled seizures
- History of non-response to ketamine or esketamine
- Pregnant (via positive pregnancy test) or lack of birth control method in women of childbearing potential
- Patient is breastfeeding

- Current or previous abuse of ketamine or esketamine
- Clinical evidence for current substance misuse except tobacco
- Current moderate or severe substance use disorder (SUD)
- Allergy or previous serious adverse effects to ketamine or esketamine

## Issues for Consideration

- In January 2025 FDA approved esketamine for TRD in adults as monotherapy. However, the use of ketamine as the sole agent for antidepressant treatment is not advisable for most Veterans, especially as long-term treatment. However, starting an antidepressant to simply ensure that Veterans meet criteria for ketamine treatment is not advisable either. Using ketamine in a time-limited fashion to achieve response or remission while also developing a long-term plan for an individual Veteran may represent the best course of action.
- Patients prescribed a benzodiazepine, a non-benzodiazepine sedative hypnotic or a monoamine oxidase inhibitor are eligible to receive esketamine; however, it is advised that concurrent use while receiving esketamine may cause sedation or blood pressure changes.
- Carefully review prior to use of esketamine, patients who are less than 6 months in remission from substance use disorder. Review Prescription Drug Monitoring Program (PDMP).
- May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential.

## Screening and Referral

- Each facility will be responsible for developing and operationalizing a procedure to screen and refer potential candidates for treatment with ketamine.
- Screening should be completed no more than 60 days prior to acceptance and administration of the first dose of ketamine.
- Screening will include the following:
    - Signed informed consent
    - Psychiatric examination including assessment of inclusion/exclusion criteria
    - The PHQ-9 depression rating scale. The PHQ-9 is required at screening and prior to each treatment. Additional depression rating scales may be used.
    - Evaluation of cognitive status (e.g., Mini-Addenbrooke's Cognitive Examination (M-ACE))
    - Assessment of suicide risk.
        - Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at the intake or initial evaluation (and within 24hours of discharge or as clinically indicated any time during treatment.
        - In addition the Comprehensive Suicide Risk Evaluation (CSRE; New Evaluation version) should be completed if it is the first CSREever. Otherwise, the CSRE should be updated as clinically indicated.
    - Physical examination including vitals (blood pressure, heart rate)

        - Patients with a SBP >140 mm Hg or a DBP >90 mm Hg at screening should be considered at higher risk and treatment for hypertension should be considered prior to initiating treatment with ketamine. Patients with a diagnosis of hypertension are to be adequately treated prior to receiving a dose of ketamine. Stimulants may increase blood pressure and heart rate, exacerbating the hypertensive effects of ketamine, increasing the risk of cardiovascular complications. The use of ketamine in individuals receiving a stimulant should be considered on a case-by-case basis.
        - Patients with a history of cardiopulmonary or cerebrovascular disease, recent myocardial infarction, symptomatic ischemic heart disease, dyspnea marked by shortness of breath or wheezing, poor exercise capacity (<6 metabolic equivalent of tasks (METs); bicycling – light effort (10-12 mph) =6.0), or any disease that could be associated with increased risk of acute cardiac demand or blood pressure or respiratory depression should be considered on an individual case basis, considering risk/benefit ratios.
        - Patients with a baseline heart rate of <60 beat per minute (bradycardia) or >100 beats per minute (tachycardia) should be considered on a case-by-case basis for the relative risks of ketamine.
    - Relevant laboratory measures, and urine toxicology and pregnancy screens.
        - Other physical and laboratory screening procedures should be determined according to the patient's individual risk factors based on his/her demographics, medical history and review of systems and is the responsibility of the prescribing provider

- Whether obtaining medical clearance from the patient's primary care provider or consultation from a cardiologist, anesthesiologist, or other medical specialist should be based on the patient's risk factors and is the responsibility of the prescribing VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA).
- Concurrent use or abuse of psychoactive substances
    - Considering ketamine's known addictive potential, a history of substance abuse or dependence including ketamine or esketamine, extent of past and current alcohol use, smoking history, a history of medication misuse, a positive urine drug screen, and length of sobriety are important factors to consider.
    - Patients with a history of SUD are at risk for relapse or development of a new SUD when exposed to psychoactive substances. There are case reports of recent substance abuse associated with the risk of relapse with ketamine, one that resulted in death in a single motor vehicle accident. While the length of sobriety may be considered when making a decision, at a minimum, all patients in recovery from SUD should be warned of the risk of inducing a relapse to previous SUD or a new addiction to esketamine or ketamine with this treatment. Other

strategies for managing TRD should be prioritized over strategies involving potentially addictive substances, especially for those with a history of SUD. If ketamine treatment is chosen, close monitoring for signs of substance use including random, monitored urine drug testing is recommended.

- Concurrent use or abuse of CNS depressants
  - Due to the theoretical potential for benzodiazepines, nonbenzodiazepine, benzodiazepine receptor agonists hypnotics (e.g., zolpidem), and naltrexone to attenuate ketamine's antidepressant effects, patients taking these agents should allow adequate time for the last dose to washout prior to receiving esketamine.

**Location of Administration, Monitoring and Recovery**

- The facility is responsible for identifying a physical location for the infusion of ketamine and monitoring the patient during and after the infusion. The place for administration and recovery should be private and large enough to accommodate the patient and required personnel.
- The treatment setting should be able to provide immediate care if necessary. A crash cart should be readily accessible. The facility must have the means to monitor basic cardiovascular functions (including electrocardiogram and blood pressure) and respiratory function (oxygen saturation or end-tidal $CO_2$). Facilities without these capabilities should provide a process for emergency response arrangements in their local SOP.
- The facility must also be capable of administering oxygen, medication and/or restraints to manage potentially dangerous behavioral symptoms. Facilities without these capabilities should provide a response plan in their local SOP.
- The facility must have a plan to rapidly address any sustained alterations in cardiovascular function including advanced cardiac life support or transfer to a hospital capable of caring for acute cardiovascular events.
- Patients determined to be at high risk for complications based on pretreatment evaluation should be treated at a facility equipped and staffed to manage any cardiovascular or respiratory events that may occur.

**Ketamine Procurement, Dosing, and Day of Administration Monitoring**

- The facility is responsible for determining the procedure that ketamine is ordered, prepared, and transported to the place of administration.
- A VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) will order the ketamine intravenous infusion and pre-medication and/or concurrent medication to prevent or manage adverse effects (e.g., intravenous lorazepam for agitation) following the facility's policy for ordering schedule III-controlled substances.
- The VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) will ensure completion of the day of treatment PHQ-9 prior to each treatment. Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at program intake or initial evaluation and within 24hours of discharge from the program. The CSSRS should be completed as clinically indicated at any time during treatment.
- The ordering VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) and an ACLS certified physician or nurse will be present during the infusion. The VA psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) can leave once the infusion is completed and the patient considered stable based on vital signs and cognitive status. The VA

psychiatrist or VA licensed Mental Health-care provider (i.e., CPP, NP, PA) must return 120 minutes after the start of the infusion to clear the patient for discharge. An ACLS certified provider is to remain with the patient until discharge.

- Ketamine infusion timeline guide
  - T-2 days or sooner: Urine drug screen and pregnancy tests are collected.
  - **T-60**: Intravenous line started by a nurse or other qualified provider. Perform vital signs (sitting/standing blood pressure, sitting/standing pulse, respiratory rate, and oxygen saturation) test. Administer PHQ-9 as baseline measure.
  - **T**-5: Time out
  - **T-0**: Provided vitals are acceptable, pregnancy tests are negative, and urine drug screen is acceptable. Administer ketamine 0.5 mg/kg (range 0.5mg/kg – 1mg/kg) by intravenous infusion using an infusion pump over 40 minutes. For patients with a body mass index $\geq$30 kg/m$^2$ it is suggested that the dose be calculated using the patient's ideal body weight (Men = 50 kg + (2.3 kg x each inch >5 feet); Women = 45.5 kg + (2.3 kg x eachinch >5 feet)) rather than their actual body weight. The most common dose has been 0.5 mg/kg of body weight. Higher doses may be more likely to result in cardiovascular adverse effects and no dose ranging studies have been conducted.
  - **T-0 to +40:** Monitor for sedation, dissociation, and other possible adverse events.
  - **T+10, 20, 30 and 40**: Vital signs
  - **T+80**: Vital signs, and check for resolution of sedation, dissociation, and other possible adverse effects
  - **T+120**: Vital signs, and readiness for discharge assessment (consider Modified Aldrete or Brief Confusion Assessment Method (bCAM))
- Parameters for stopping infusion
  - Blood pressure should always remain <180 mm Hg systolic and < 110 mm Hg diastolic during the infusion. Stopping the infusion often results in a rapid decline in blood pressure.
    - Systolic blood pressure can also drop by >10 mm Hg during the infusion. Should such a drop occur and be accompanied by an increased heart rate or any evidence of distress, then the infusion should be stopped.
  - Heart rate should remain below the age adjusted maximum heart rates of 20 yrs <140 bpm, 30 yrs <133, 40 yrs <126, 50 yrs <119, and 60 yrs <112. For patients 65 years and older the maximum heart rate should be individualized based on exercise capacity and other risk factors.
  - The appearance of any of the following necessitates stopping the infusion: 1) pallor, cyanosis, or any symptoms of poor perfusion, 2) respiratory symptoms such as shortness of breath, wheezing, 3) the appearance of chest, jaw or arm pain suggesting cardiac involvement, or 4) the patient's desire to stop.

## Repeat Infusion Schedule

- Ketamine infusion should be repeated no less 2 days apart and not more frequently than twice a week for 4 weeks
- After 4 weeks the frequency of infusion should be once a week to once every 3 weeks with the goal of extending the interval between to as long as possible (usually monthly). This will need to be individualized based on the patient's response, tolerability, and preference/availability. The time frame for maintenance use in TRD is undefined but long-term maintenance treatment with ketamine may be a reality for some Veterans and is not against guidance. Veterans receiving maintenance treatment should receive regular clinical review and/or re-evaluation for the

continued need for treatment or adverse effects.

### Ketamine Treatment Failure/Discontinuation

- Discontinue if patient wishes to for any reason.
- Discontinue if the patient needs to have the infusion stopped more than once due to exceeding the blood pressure or heart rate thresholds.
- Patients without a response (after 4 weeks) should not move to maintenance treatment
    - An adequate response is defined as a 50% or greater decline in the PHQ-9 score from baseline
- Discontinue if pronounced or slow to correct cognitive impairment (e.g., M-ACE) or repeated dissociative symptoms.
- Discontinue when dosing cannot be spaced out to a minimum of 1 dose per week by the second month of treatment.

### Longitudinal Monitoring of Ketamine Patients

- A PHQ-9 should be completed prior to each dose of IV ketamine
- A PHQ-9 and cognitive evaluation (such as M-ACE) should be completed at the end of the induction phase, every 6 months of treatment, and at the end of treatment course.
- Suicide risk should be assessed and monitored using a combination of the Comprehensive Suicide Risk Evaluation (CSRE) and Columbia-Suicide Severity Rating Scale (C-SSRS) Screener.
    - Minimum requirements for risk identification are Columbia-Suicide Severity Rating Scale (C-SSRS) at the intake or initial evaluation and within 24hours of discharge or discontinuation from the program for any reason. The CSSRS should be completed as clinically indicated any time during treatment.
    - In addition the Comprehensive Suicide Risk Evaluation (CSRE; New Evaluation version) should be completed at the intake or initial evaluation if it is the first CSRE ever. Otherwise, the CSRE should be updated as clinically indicated.
    - A positive C-SSRS Screener should result in a CSRE

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Editorial

# Guidelines for ketamine use in clinical psychiatry practice

Luke A. Jelen, Rupert McShane and Allan H. Young

In this editorial, we emphasise the efficacy and challenges of using ketamine in treatment-resistant depression. We highlight the need for comprehensive evidence-based guidelines to manage the use of both licensed and off-licence ketamine formulations and discuss recent efforts by Beaglehole et al to develop ketamine guidelines in New Zealand. We finally advocate for national registries to monitor ketamine therapy, ensuring its responsible and effective use in the management of depression.

**Keywords**
Depressive disorders; antidepressants; ketamine; esketamine; guidelines.



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The efficacy of ketamine in the treatment of treatment-resistant depression (TRD) is well documented,[1,2] and ketamine-based therapies offer new therapeutic hope for those that do not experience beneficial outcomes from conventional antidepressants. Consequently, there has been growing interest in incorporating the use of ketamine into psychiatry in diverse settings across the globe. However, the transition of ketamine treatments from research and specialist settings to routine clinical practice poses significant challenges, including concerns over potential misuse, dissociative effects and uncertainty regarding longer-term risks.

Ketamine is a racemic mixture composed of equal amounts of (S)- and (R)-ketamine (esketamine and arketamine).[3] Although an esketamine nasal spray has been developed and licensed for use in TRD (in combination with a conventional antidepressant) in Europe and New Zealand, neither the National Institute for Health and Care Excellence nor Pharmac (respective government agencies that evaluate cost-effectiveness of new treatments) has approved its public use. For some, the licensing of esketamine for TRD remains a controversial decision, and this has been a topic of considerable debate.[4,5] In the UK, although there has been some limited National Health Service use of nasal esketamine, approved on a named-patient basis, its availability is primarily confined to select, often costly, private providers. Owing to the risks of sedation, dissociation and misuse, in certain countries intranasal esketamine is only available through a restricted distribution system under a risk evaluation and mitigation strategy that specifies standards for healthcare settings, pharmacies and healthcare professionals administering the drug.

Meanwhile, the use of racemic ketamine for depression is increasing across public and private sectors as a cost-efficient off-label approach. Intravenous (i.v.) administration of ketamine is recognised as the gold standard for off-label use, with the best supporting evidence for efficacy in TRD.[2] Other modes of administering ketamine including subcutaneous, intramuscular (i.m.), oral and sublingual are being explored but require further research to validate their relative safety and efficacy and to determine the optimal dosing regime in each case. Each administration route presents distinct advantages and challenges relating to bioavailability, effect duration, practicality and patient comfort. Importantly, none of these treatment modes for racemic ketamine has received regulatory approval for on-label use for any psychiatric indication. As a result, there are no formal surveillance data on safety and effectiveness.[6] Therefore, there is a critical need to establish international expert consensus opinion, alongside comprehensive and clear guidelines to manage off-label use, including dosage recommendations for different administration routes and requisite monitoring practices.

To date, the major evidence-based guidelines for treating depressive disorders have either not mentioned[7] or only briefly touched on ketamine, with no formal recommendation for its use in depression[8,9] aside from that limited to specialist academic treatment centres.[10] However, a key consensus paper from an international group of mood disorders experts provides a helpful synthesis with respect to the efficacy, safety and tolerability of ketamine and esketamine in TRD.[11] This review of the evidence supports the rapid-onset efficacy (within 1–2 days) of esketamine and ketamine in TRD, which is best established for intranasal esketamine and i.v. ketamine routes. Conversely, there is rather limited evidence supporting the efficacy of oral, subcutaneous or i.m. ketamine in TRD. Intranasal esketamine has proven effective, safe and tolerable for up to 1 year in TRD, although the long-term effects of i.v. ketamine remain insufficiently studied.[12] Both ketamine and esketamine give rise to safety concerns encompassing psychiatric (dissociation, psychotomimetic and increased suicidality), neurological/cognitive, genitourinary and hemodynamic effects that require monitoring. The Ketamine Side Effect Tool was been developed as one approach to systematically monitor and report ketamine-related side-effects.[13] Considering safety concerns, the consensus view is that these compounds should be administered in environments with multidisciplinary personnel, including experts in mood disorder assessment. To aid clinicians and healthcare providers, a detailed discussion of the risks and practical recommendations for the use of oral, sublingual and nasal ketamine has been recently outlined.[14]

We welcome the efforts by Beaglehole et al[15] to establish ketamine guidelines for use by adult specialist mental health services

in New Zealand. A particularly novel aspect is that they seek to address the need for long-term treatment in a way that is scalable in a public health service. The primary identification of TRD patients for potential ketamine treatment provides a reasonable pathway for identifying those in need of intervention. The authors highlight a paradox in the clinical adoption of off-label ketamine for treating depression: clinicians' hesitance to use it is perpetuated by a lack of first-hand experience. The underpinning published research, on its own, appears to have been insufficiently persuasive to overcome this hesitancy and risk aversion. To address this, the authors propose an approach beginning with i.m. administration to gauge patient response, followed by an oral regimen. It is reasonable to use parenteral administration as a test of responsiveness and then follow this with something more pragmatic, but, as described, the current evidence base is for i.v. not i.m.; i.m. may give a variable response that depends more on administration technique. Another challenge the authors highlight is establishing the requisite experience level for psychiatrists to prescribe ketamine. It is recommended that psychiatrists observe at least three i.m. administrations to become acquainted with the dissociative effects experienced by patients. The guidelines suggest a maximum treatment duration of 12 weeks. This duration is a balance between practicality – allowing sufficient time to evaluate clinical responses and reinforce benefits – and caution, as the authors were reluctant to endorse long-term treatment. However, this approach could introduce complications, especially as ketamine-responders may, like responders to esketamine nasal spray, be at a high risk of relapse following cessation of regular dosing. Finally, we agree with the authors about the necessity of diligent monitoring in ketamine therapy clinics, with particular emphasis on assessing mood and cognitive function, which are crucial indicators of a patient's response to ketamine treatment. However, although the guidelines promote oral administration as a strategy to enhance treatment accessibility, this approach potentially increases the risks associated with overuse and potential misuse. Therefore, it underscores the need for more stringent oversight across any healthcare facilities offering ketamine therapies.

To address safety concerns and monitor the effectiveness of ketamine treatments, we believe it is crucial to establish mandatory national registers encompassing all individuals receiving these treatments, whether licensed or unlicensed. Such registries would address risk mitigation, facilitate pharmacovigilance and enable tracking of patient outcomes across diagnoses, routes and doses. In every state of the USA and in the Australian states of Queensland, Victoria and South Australia, Prescription Drug Monitoring Program mandate that prescriptions of controlled substances to be taken at home are logged centrally and that prescribers check before prescribing. This should be extended to ketamine, including in-clinic administration. The growing use of oral ketamine, which increases potential risks of overuse and diversion, emphasises the need for closer surveillance. Indeed, the recent legalisation of telehealth consultations and postal supply of ketamine in the USA during COVID increased access but raised concerns regarding patient safety, given the lack of rigorous monitoring. Significant efforts are being made towards reformulating oral ketamine to manage its misuse potential,[16] and ketamine formulations will be entering phase 3 trials. Therefore, guidelines need to focus on regulating the use of compounded oral or sublingual liquids, lozenges or capsules. Finally, owing to the limited long-term real-world dosing data for ketamine, a national registry would also allow for tracking of outcomes across different routes and doses, which could help to optimise treatment. Therefore, these registers are vital for ensuring optimal cost-effectiveness, patient safety and treatment efficacy. Voluntary registries, such as those used to improve service delivery of electroconvulsive therapy,[17] offer an alternative to mandatory national registries. These registries could be expanded to include treatments such as ketamine and esketamine, providing a framework for data collection and a shared clinical registry, informing how care is being delivered.

As we work to broaden the availability of ketamine treatments to those with TRD, any framework that promotes its use in a manner that is safe, effective and equitable is a step in the right direction. Refining our guidelines and vigilant monitoring will be imperative as we further our understanding of both the benefits and the limitations associated with ketamine therapy.

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L.A.J.: writing – original draft; R.M.: writing – review and editing; A.H.Y.: writing – review and editing.

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# CONCUSSION RETURN TO PLAY FORM

KSHSAA

The use of this form is not required, but a written release from a physician (MD or DO) is required before any student returns to full sports participation following a concussion injury (K.S.A 72-7119).

**TO BE COMPLETED BY ATHLETIC TRAINER/SCHOOL MEDICAL PERSONNEL:**

Student Name: _____ School: _____

Date of Injury: _____

Referring Athletic Trainer/School Medical Personnel: _____ Phone: _____

Athletic Trainer/School Medical Personnel Notes for Healthcare Provider:

_____

_____

**GRADUATED RETURN TO PLAY PROGRESSION**

| Step | Complete | Activity |
|---|---|---|
| 1 | ☐ | Symptom-limited activity. Daily activity that does not exacerbate symptoms (e.g., walking) |
| 2 | ☐ | Light aerobic exercise such as stationary cycling or walking at a slow to medium pace. May progress to a moderate intensity and add light resistance training provided there is no more than a mild exacerbation* of symptoms. |
| **Date:** | | **Supervising Medical/School Personnel:** |
| 3 | ☐ | Individual sport-specific exercise away from team environment. E.g., running, agility work, individual training drills. There should be no risk of head impact. |
| **Date:** | | **Supervising Medical/School Personnel:** |
| **Physician (MD or DO) release before progressing to steps 4-6.**<br>**Steps 4-6 should only begin after the resolution of any symptoms, abnormalities in cognitive function, and any other clinical findings related to the current concussion, including with and after physical exertion. Academic modifications should NOT be needed when progressing to step 4 and beyond.** | | |
| 4 | ☐ | Non-contact training drills, progressing to high intensity drill work. Can begin integrating to team environment/non-contact practice. |
| **Date:** | | **Supervising Medical/School Personnel:** |
| 5 | ☐ | Full contact practice; normal training activities. |
| **Date:** | | **Supervising Medical/School Personnel:** |
| 6 | ☐ | Return to competition |

*Mild and brief exacerbation of symptoms (i.e., an increase of no more than 2 points on a 0-10 scale for less than an hour when compared with the baseline value reported prior to physical activity.

- Step 1: May begin within 24-48 hours of injury **and before symptoms are completely resolved.**, Progression through each subsequent step typically takes a minimum of 24 hours.
- Steps 1-3: If more than a mild exacerbation of symptoms occurs, the athlete should stop and attempt to exercise the next day.
- Steps 4-6: Athletes experiencing concussion-related symptoms should return to Step 3 to establish full resolution of symptoms with exertion before engaging in at-risk activities.

**TO BE COMPLETED BY PHYSICIAN/HEALTHCARE PROVIDER:**

Date of Evaluation: _____ School/Academic Modifications: ☐ None ☐ As indicated on Return to Learn form

Sports Participation:

☐ Cleared for full participation **AFTER** successful completion of graduated return to play protocol under guidance of athletic trainer/school medical personnel.

☐ Not cleared at this time.

☐ May participate in graduated return to play protocol under guidance of athletic trainer/school medical personnel. **Must return for additional physician visit to be cleared for sports participation.**

☐ No concussion diagnosed. Cause for signs/symptoms:

_____

_____

Additional Physician Instructions: _____

_____

Physician Name: _____ Signature: _____ MD/DO

Address: _____ Phone: _____

_____