

David M. Dickerson, MD

Dr. Dickerson is the director of the Acute Pain Service at the University of Chicago. After completing medical school and anesthesia residency at the University of Chicago, he went on to complete a pain fellowship at UCSF. He also chairs the University of Chicago's Center for Quality Pain Stewardship Program.

Dr. Dickerson has no relevant financial relationships to disclose.

Ketamine for pain management

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DISCLOSURE

I have no financial relationships with commercial support to disclose.

Disclosures

- No conflicts of interest to disclose

Learning Objectives

- Recognize the risks and benefits of ketamine as an analgesic with a focus on:
 - Relevant Pharmacology
 - Dose response
- Identify ketamine's potential role in:
 - Inpatient pain care
 - Outpatient pain care
 - Infusion
 - Oral

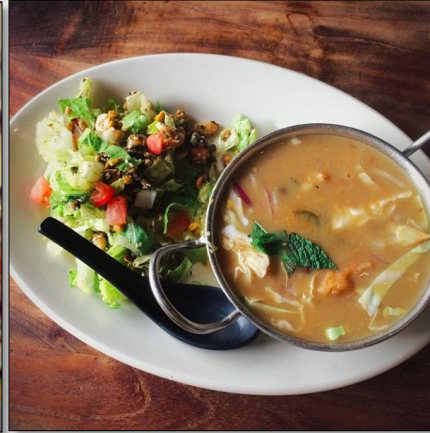


Outline: Ketamine and pain

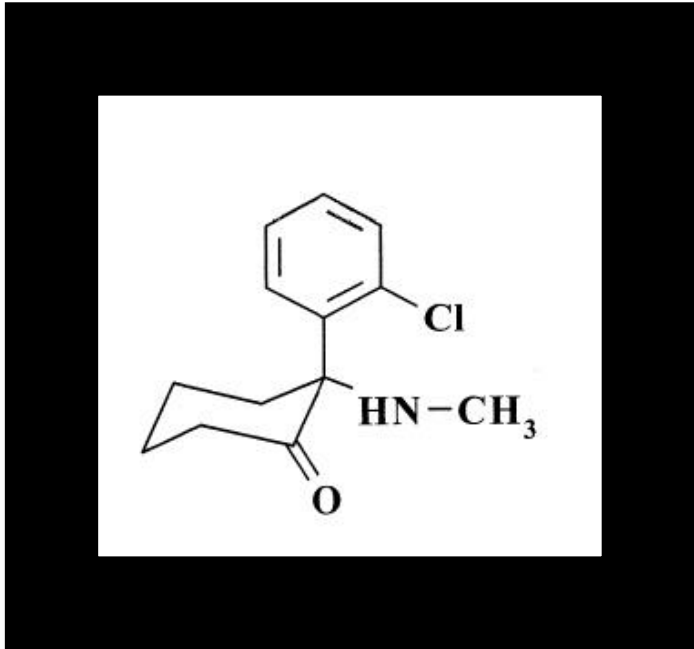
- Background: the monoanesthetic
- Mechanism of analgesia
- Pharmacokinetics
- Benefits of adjunctive ketamine
- Contraindications
- Inpatient pain care (acute and chronic)
- Outpatient pain care
 - Infusion
 - Oral



Recipes for success



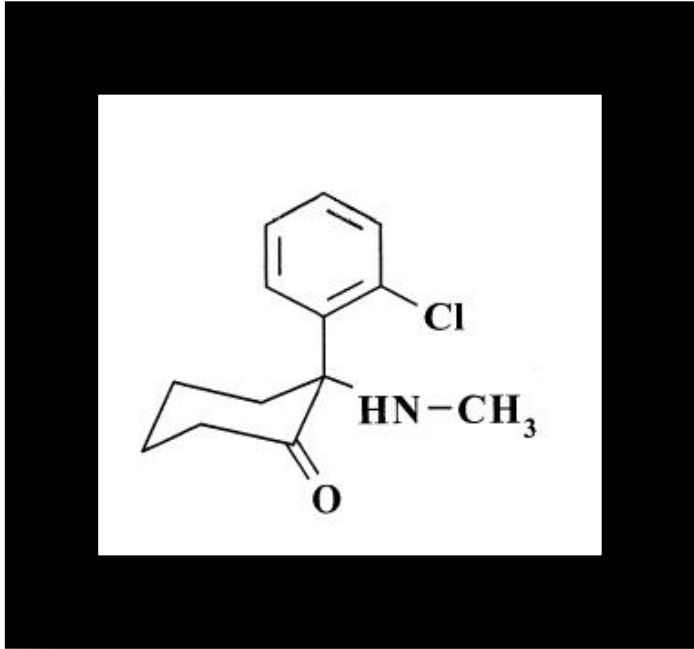
Adjunctive agents are like condiments ...



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Adjunctive agents are like condiments ...

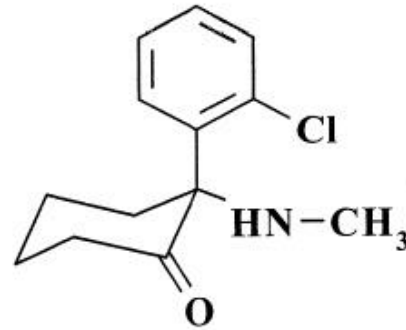


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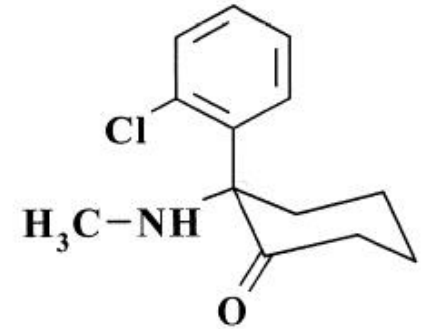


Background: Ketamine

- Developed in 1963
- Veterinary anesthetic
- PCP analog
- Schedule 1 narcotic
- Club drug
- ? Stigma → Knowledge gap



R (-) - ketamine



S (+) - ketamine

Background: Ketamine infusion

Br. J. Anaesth. (1979), 51, 1167

KETAMINE INFUSIONS: PHARMACOKINETICS AND CLINICAL EFFECTS

J. IDVALL, I. AHLGREN, K. F. ARONSEN AND P. STENBERG

~Infusions are safe and effective~ [two compartment model suggested, IBW dosing]

No post-op respiratory depression observed

Transient increased in arterial pressure, heart rate and cardiac output

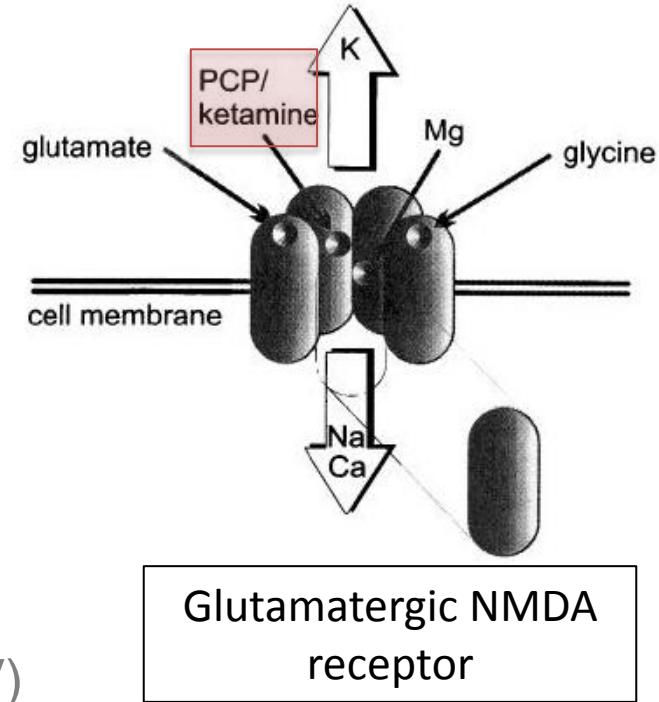
2 of 31 patients had unpleasant dreams postoperatively (2 of 31 had pleasant dreams)

3 of 31 patients had nausea (65% nitrous oxide given to all patients)



Mechanism of analgesia

- *Glutamatergic NMDA receptors*
 - Non-glutamatergic NMDA receptors
 - Opioid receptors
 - Influence on cholinergic and adrenergic signaling
 - GABA_A Signaling
 - Peripheral v. central debate
- C-fiber afferent and spinal modulation (RL V)
 - Recoupling of opioid receptor



Important pharmacology

- High plasma clearance of 17mL/kg/min
- Elimination half life of **153 minutes**
- Metabolized primarily to norketamine (30% relative potency) by hepatic microsomal enzymes (cytochrome p450[2B6])
- Norketamine: renally cleared
- Direct analgesic properties at 5-10 mcg/kg/min infusion
- Can be safely administered at low doses (2-4mcg/kg/min)



Adverse effects (anesthetic doses?)

- Increased oral secretions
- Increased pulmonary arterial pressure
- Psychotomimetic reactions (hallucinations, vivid dreams)
- Per the manufacturer: may be unsafe in the presence of uncontrolled arterial hypertension
- Caution has been suggested for CAD or right heart failure
- May increase CBF if preexisting increased vascular tone, appears dose dependent



Controversial Contraindications

- Paranoid or delusional patients (may exacerbate delirium)
- ICP (if doses > than 2mg/kg and non-controlled ventilation) (?)
- Renal Failure (?)
- Seizure disorder (?) (Modica et al, 1990)
 - Although myoclonic and seizure-like activity in normal patients– may possess anticonvulsant activity
 - Does not alter the seizure threshold in epileptic patients (Celesia et al, 1975)



Beneficial effects

- Bronchodilator
- Minimal respiratory depression with only mild hypercapnia
- At clinically effective doses, preservation of airway reflexes as compared to other IV anesthetics
- Mood elevator
- Improved analgesia
- Reduced opioid exposure



Table 3. Options for Components of Multimodal Therapy for Commonly Performed Surgeries

<i>TYPE OF SURGERY</i>	<i>SYSTEMIC PHARMACOLOGIC THERAPY</i>	<i>LOCAL, INTRA-ARTICULAR OR TOPICAL TECHNIQUES*</i>	<i>REGIONAL ANESTHETIC TECHNIQUES*</i>	<i>NEURAXIAL ANESTHETIC TECHNIQUES*</i>	<i>NONPHARMACOLOGIC THERAPIES†</i>
Thoracotomy	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ → i.v. ketamine¶		Paravertebral block	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Open laparotomy	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ → i.v. ketamine¶ i.v. lidocaine	Local anesthetic at incision i.v. lidocaine infusion	Transversus abdominis plane block	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Total hip replacement	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ → i.v. ketamine¶	Intra-articular local anesthetic and/or opioid	Site-specific regional anesthetic technique with local anesthetic	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Total knee replacement	Opioids‡ NSAIDs§ and/or acetaminophen Gabapentin or pregabalin§ → i.v. ketamine¶	Intra-articular local anesthetic and/or opioid	Site-specific regional anesthetic technique with local anesthetic	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Spinal fusion	Opioids‡ Acetaminophen† Gabapentin or pregabalin§ → i.v. ketamine¶	Local anesthetic at incision		Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
Cesarean section	Opioids‡ NSAIDs§ and/or acetaminophen	Local anesthetic at incision	Transversus abdominal plane block	Epidural with local anesthetic (with or without opioid), or intrathecal opioid	Cognitive modalities TENS
CABG	Opioids‡ Acetaminophen Gabapentin or pregabalin§ → i.v. ketamine¶				Cognitive modalities TENS

Recommendation 18

- The panel recommends that clinicians consider i.v. ketamine as a component of multimodal analgesia in adults (weak recommendation, moderate-quality evidence).

Table 5. Continued

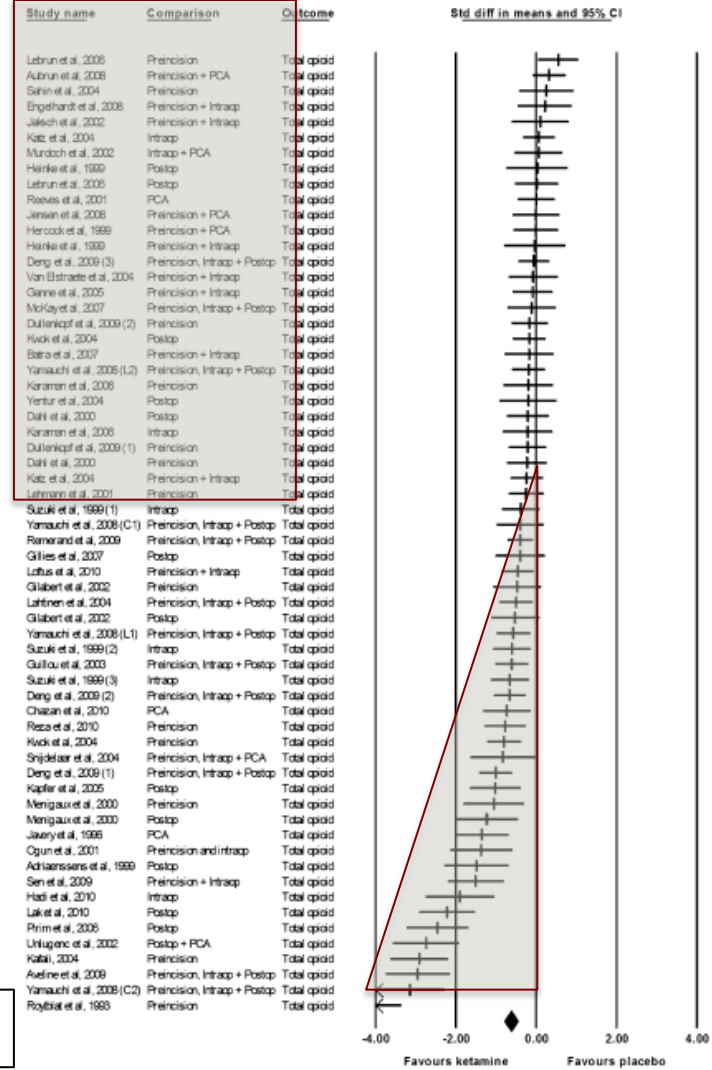
<i>INTERVENTION</i>	<i>SUGGESTED USE</i>	<i>COMMENTS</i>
Ketamine i.v.	Consider as a component of multimodal analgesia, in patients who undergo major surgery, opioid-sparing	Dosing varies widely, consider preoperative bolus of .5 mg/kg followed by an infusion at 10 μ g/kg/min intraoperatively, with or without a postoperative infusion at a lower dose Limited evidence for use in children

Perioperative ketamine

47 studies

Reduced pain, reduced time to first analgesic

Fig. 2 Forest plot of core meta-analysis (postoperative opioid consumption).



Can J Anesth/J Can Anesth (2011) 58:911–923
DOI 10.1007/s12630-011-9560-0

REPORTS OF ORIGINAL INVESTIGATIONS

A systematic review of intravenous ketamine for postoperative analgesia
Revue méthodique de l'utilisation de la kétamine intraveineuse pour l'analgésie postopératoire

Kevin Laskowski, MD · Alena Stirling, MD · William P. McKay, MD · Hyun J. Lim, MD

Received: 9 November 2010 / Accepted: 8 July 2011 / Published online: 20 July 2011
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Can J Anesth 2011;58:911-923.

Perioperative ketamine

Can J Anesth/J Can Anesth (2011) 58:911-923
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Greatest efficacy in: ortho, upper abd. thoracic

PONV reduced when effective reduction of opioids, NS as well however

Table 3 Side effects

Side effect		Ketamine	Placebo	P (corrected)
Neuropsychiatric	Overall	166 (7.35)	87 (4.95)	0.018
	When efficacious	60 (7.69)	20 (3.05)	<0.001
	When not	97 (8.24)	64 (7.3)	0.99
PONV	Overall	472 (25.64)	460 (30.4)	0.018
	When efficacious	124 (16.94)	155 (25.88)	<0.001
	When not	308 (34.34)	245 (33.61)	0.99
Sedation	Overall	17 (2.53)	25 (4.42)	0.99
	When efficacious	3 (1.23)	9 (4.15)	0.981
	When not	14 (5.12)	12 (5.8)	0.99

Values reported as counts (percentage)

Can J Anesth 2011;58:911-923.

Low dose infusion, postoperatively

39 studies

2482 patients, 1403 received ketamine

Pain Medicine

Pain Medicine 2015; 16: 383–403
Wiley Periodicals, Inc.



ACUTE & PERIOPERATIVE PAIN SECTION

Original Research Article

The Use of Intravenous Infusion or Single Dose of Low-Dose Ketamine for Postoperative Analgesia: A Review of the Current Literature

Opioid consumption reduced by 40%
Decreased pain scores
No major complications (up to 48h)
Optimal dose and regimen unknown
<1.2mg/kg/h = low dose?

Ketamine policy/protocol at UCM

1-5mcg/kg/min

University of Chicago Medicine | Department of Pharmacy Services
Guidelines & Pathways

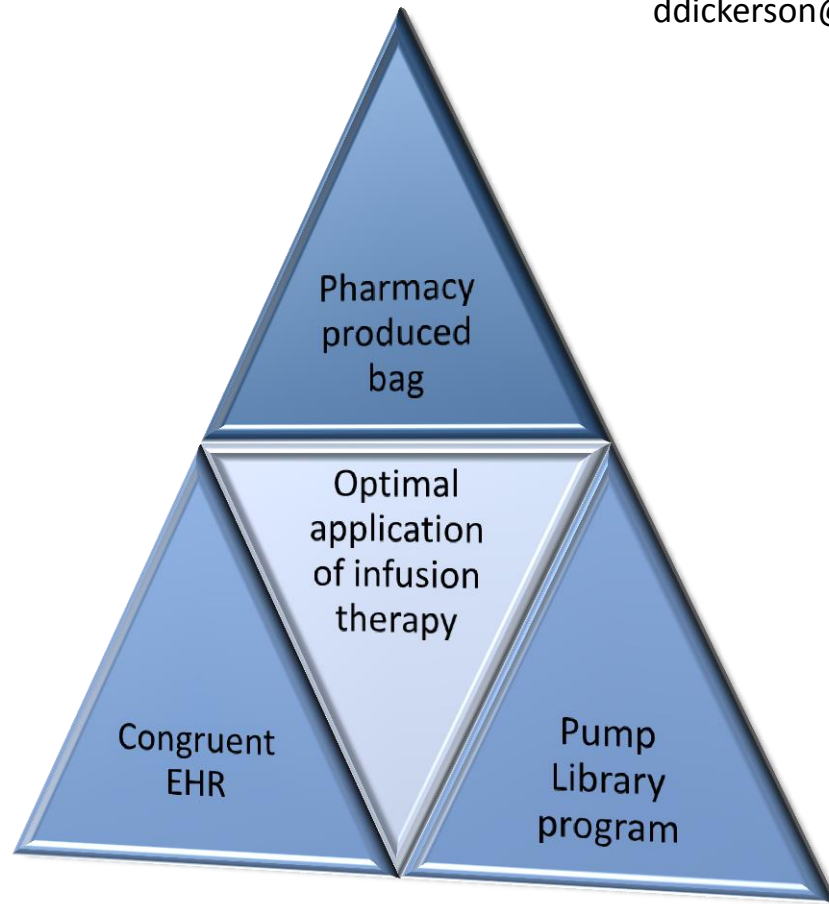
Low-Dose Ketamine Guideline

Scope:

The following protocol has been established in accordance to PC Policy 151 "Pain – Assessment, Documentation and Education" to reduce the likelihood of patient harm associated with low-dose ketamine for the management of treatment refractory pain. This protocol is designed to provide an evidence-based and standardized approach for the safe and effective use of low-dose ketamine for the management of acute and chronic pain. This protocol is applicable only to patients that have been deemed to have a limited response to conventional multimodal analgesia including opioid therapy as defined by the Acute Pain Service or Palliative Care consultation teams.



Effectively applying infusion therapy



Ketamine policy/protocol at UCM

1-5mcg/kg/min

Order Sets

▼ IP Low-Dose Ketamine Infusion Protocol (Adults) — **Required** Add Order

Process instructions: The intent of this order set is to reduce the likelihood of patient harm associated with IV ketamine for the management of treatment refractory pain.

- This protocol is applicable only to patients that have been deemed to have a limited response to conventional multimodal analgesia including opioid therapy as defined by the Acute Pain Service or Palliative Care consultation teams.

▼ Patient Care — **Required**

▼ Medical Consults — **Required**

Acute Pain Service or Palliative Care consultation is required to initiate therapy

Consult to Palliative Care
MD to Page 7255

Consult to Acute Pain Service
MD to page 3294

▶ Nursing Care 4 of 4 selected

Assess:

P ROUTINE, UNTIL SPECIFIED starting Today at 1038 Until Specified
Procedure: Blood Pressure, Pulse, Respiratory Rate, Pain Score and Sedation Level
Routine VS (blood pressure, pulse, RR), sedation and pain should be assessed Q2h x 2 followed by every 4 hours with initiation and any INCREASE.

Continuous Pulse Oximetry
ROUTINE, UNTIL SPECIFIED starting Today at 1038 Until Specified
Continue Assessment Throughout the Night: yes

Keep the Following at Bedside:
ROUTINE, UNTIL SPECIFIED starting Today at 1038 Until Specified
Item(s): Ambu Bag and Mask, Other

Notify Call: Ketamine
ROUTINE, UNTIL SPECIFIED starting Today at 1038 Until Specified
Name and Pager of Who to Contact: Pager # 3294 or Phone # 6-3294
Reason: Systolic Blood Pressure Greater than 160 mmHg, Respiratory rate is LESS than 10 breaths/min, Acute change in mental status (ie, blunted affect, emotional withdrawal, thought disorders, delirium), Difficult to arouse despite continuous stimulation



Ketamine policy/protocol at UCM

▼ **Respiratory Care**

☉ Oxygen Therapy

ROUTINE, UNTIL SPECIFIED starting Today at 1038 Until Specified
 Indications: Hypoxia
 Method: Nasal Cannula
 Liters: 2 L/min
 Titrate O2 to keep sat greater than: 92 %

▼ **Medications**

▼ **Ketamine Infusion and Supportive Medications**

ketamine 200 mg in sodium chloride 0.9% 100 mL
 Intravenous, CONTINUOUS

nalOXone (NARCAN) injection
 Intravenous Push, EVERY 5 MINUTES AS NEEDED

LORazepam (ATIVAN) syringe
 Intravenous Push, EVERY 6 HOURS AS NEEDED

prochlorperazine (COMPAZINE) injection
 Intravenous Push, EVERY 6 HOURS AS NEEDED

▼ **Laboratory**

▼ **Other Labs**

Basic Metabolic Panel
 ONCE

Urinalysis Chemistry Screen w/Microscopic and Culture Reflex
 ONCE

▼ **Order Set Details**

▼ **Review Details**

This order set was Review by Randall Knoebel, PharmD and Dr. David Dickerson. CPRC Review Completed on 11/5/14.

▼ **Ad-hoc Orders** [Add Order](#)

Click the Add Order button to add an order in this section



REGIONAL ANESTHESIA AND ACUTE PAIN

BRIEF TECHNICAL REPORT

TABLE 5. Adverse Drug Effects Occurring in 321 Patients During Low-Dose Postoperative Ketamine Infusion Administration on General Medical Floors

Adverse Event	Patients With ADE, n, % (95% Binomial CI)	Discontinued Ketamine Infusions in Patients With Specified ADE, Proportion, % (95% Binomial CI)
CNS excitation*	52, 16.2% (12.3%–20.7%)	18/52, 34.6% (22.0%–49.1%)
Sedation	30, 9.4% (6.4%–13.1%)	12/30, 40.0% (22.7%–59.4%)
Visual disturbances	10, 3.1% (1.5%–5.7%)	2/10, 20.0% (2.5%–55.6%)
Hemodynamic instability†	9, 2.8% (1.3%–5.3%)	2/9, 22.2% (2.8%–60.0%)
Nausea	9, 2.8% (1.3%–5.3%)	1/9, 11.1% (0.3%–48.3%)
Other	25, 7.8% (5.1%–11.3%)	2/25, 8.0% (1.0%–26.0%)
At least 1 ADE	102, 31.8% (26.7%–37.2%)	37/102, 36.3% (27.0%–46.4%)

*Delirium, agitation, dysphoria, hallucinations, and vivid dreams.

†Tachycardia, hypertension, and hypotension.

CNS indicates central nervous system.

5000 spine patients, 211 received ketamine

Schwenk et al., Reg Anesth Pain Med 2016; 41(4):482.

1. All patients will be monitored according to opioid monitoring guidelines, even if the patient is not receiving an opioid (may occur with intractable migraine headache patients). Minimal monitoring is q4hr: RR, BP, pain and sedation levels.
2. Initial bolus dosing is 10–15 mg IVP, MR \times 1. Dose must be administered by APMS physician.
3. Initiate infusion at 5 mg/h. Maximum dose is 1 mg/kg per hour. Dose titration may only be done by APMS physicians or nurses.
4. Assess patient's pain using 0–10 scale (0 = no pain, 10 = worst pain imaginable).
5. If patient using opioids appropriately and reports greater than 5 of 10 pain:
 - a. Bolus patient with ketamine 10 mg.
 - b. If no response in 10 minutes, may repeat bolus of ketamine 10 mg.
 - c. After bolus, increase rate of ketamine infusion by 5 mg/h (not to exceed 1 mg/kg per hour unless approved by APMS physician).
 - d. May be repeated as needed but no more frequently than every 60 minutes.

10-15mg bolus by apms physician then 5mg/h infusion
May repeat bolus in 10 min, and increase by 5mg/h
Max 1mg/kg/h

- a. Notify APMS physician for further instructions.
 - b. In headache patients, the Neurology Headache Physician will be notified if the patient has dose-limiting adverse effects or is reaching the upper limits of dosing and continues to have inadequate pain relief.
9. If patient experiences side effects, such as hallucinations, tremors, diplopia or confusion, from a ketamine bolus:
 - a. Verify that the patient is receiving a benzodiazepine. If the patient is not receiving a benzodiazepine, notify the APMS physician or attending neurologist for headache patients.
 - b. APMS nurse will remain with the patient and provide comfort and reassurance. Most adverse effects are self-limiting and will usually subside within 10–15 minutes after receiving a bolus dose. If adverse effects do not subside, notify APMS or Neurology attending physician.
 - c. APMS nurses may decrease infusion by 50% as per APMS physician order.

If an APMS physician wants a ketamine infusion discontinued, the APMS nurse may discontinue the order in Jeff Chart as a protocol user. The Neurology Headache Physician will discontinue ketamine infusions for headache patients.

Characteristic

Ketamine Infusions N=129

Number of Patients	115
Age (yr), mean (range)	44 (16-81)
Male Gender, n (%)	47 (36%)
Length of Hospitalization, days	16.5 (1-179)
APS Consult, n (%)	129 (100%)

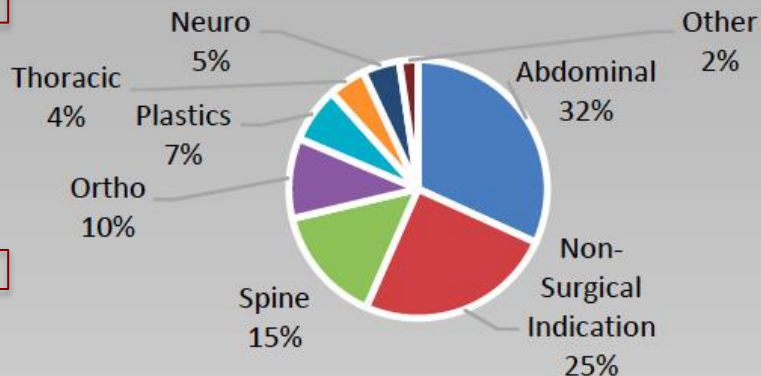
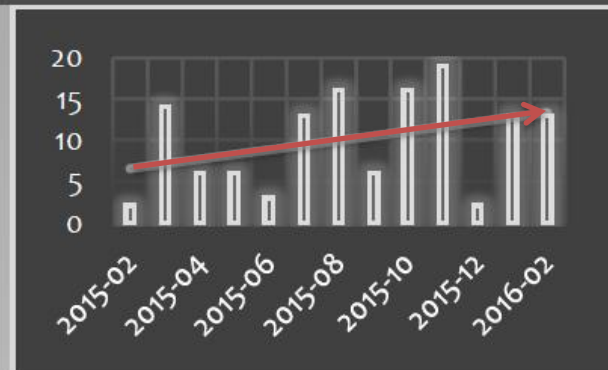
Indication

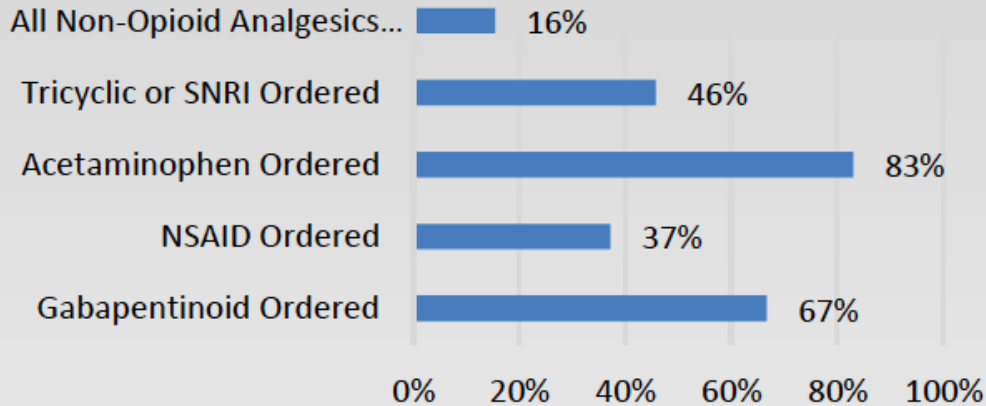
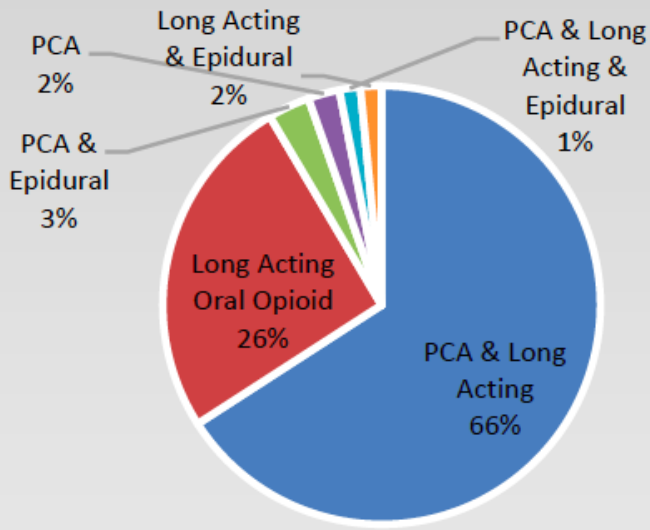
- Non-Surgical Pain 32 (25%)
- Surgical Pain 97 (75%)

Previous Ketamine Exposure, n (%) 33 (26%)

Ketamine Dosing Information

Initial Dosing Rate (mcg/kg/min)	2.67 (0.5-5)
Initial Dose > 3 mcg/kg/min	22 (17%)
Dose > 3 mcg/kg/min after 24 hours	28 (22%)
Dose down titrated from >3 mcg/kg/min after 24hr (n=22)	6 (27%)
Duration of Ketamine Infusion (h)	44 (0.5-128)
Started prior to closure time (n=97)	20 (21%)





Safety

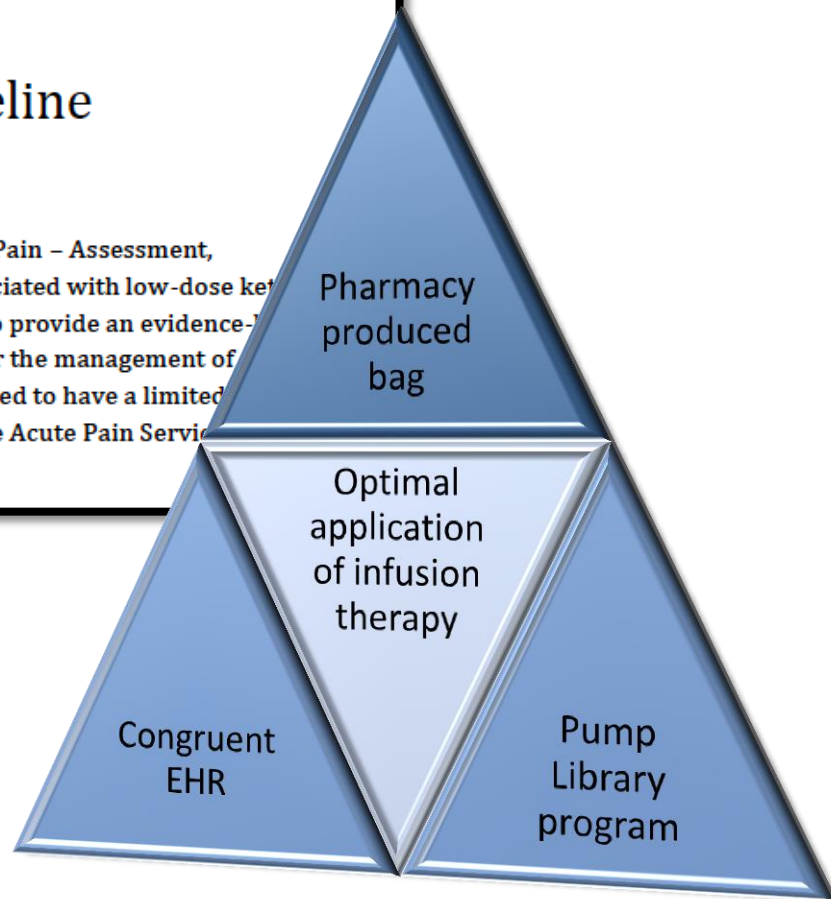
- Naloxone was administered 5 times for the 129 infusions (3.8%)
- No patients received ketamine at an infusion rate ≥ 3 mcg/kg/min
 - 3 of the 5 patients had methadone started within 48 hours of ketamine initiation
 - 3 of the 5 patients on current PCA had a lockout frequency of less than 10 minutes

Low-Dose Ketamine Guideline

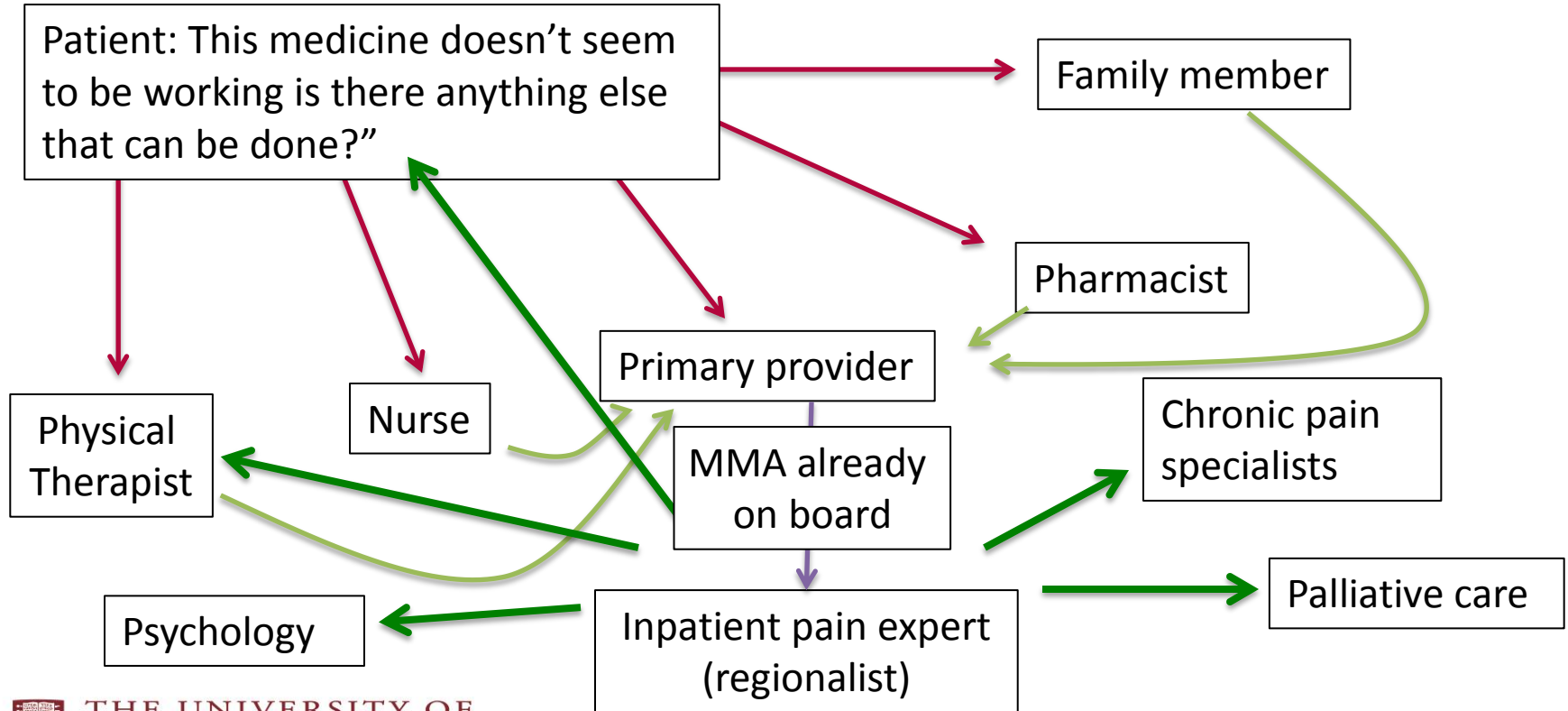
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1-5mcg/kg/min



Providing comprehensive rescue therapy



Outpatient infusion therapy

Pain Medicine



Pain Medicine 2012; 13: 263–269
Wiley Periodicals, Inc.

Efficacy of Outpatient Ketamine Infusions in Refractory Chronic Pain Syndromes: A 5-Year Retrospective Analysis

Patil, S et al., *Pain Medicine* 2012;13:263-269.

Outpatient infusion therapy

Table 2 Infusion data by patient subgroup

	Patient Subgroup		
	CRPS (N = 18)	Non-CRPS (N = 31)	Total (N = 49)
Infusion dose (mg/kg)			
Mean	1.0	0.9	0.9
SD	0.5	0.4	0.4
Infusion duration (minute)			
Median	43.8	34.7	38.3
Range	30–60	30–165	30–165
Days between infusion			
Median	30.8	34	33.7
Range	18–680	12–95	12–680
VAS before infusion			
Mean	8.5	7.0	7.6
SD	1.1	2.0	1.9
VAS after infusion			
Median	0.8	1.0	0.9
Range	0–6	0–9	0–9

CRPS = complex regional pain syndrome; SD = standard deviation; VAS = visual analog scale.

Patil and Anitescu

Table 3 Adverse events

	Patient Group: N (%) of Patients		
	CRPS (N = 18)	Non-CRPS (N = 31)	Total (N = 49)
Any event	9 (50.0%)	14 (45.2%)	23 (46.9)
Agitation	1 (5.7%)	1 (3.2%)	2 (4.1%)
Confused state	1 (5.7%)	2 (6.5%)	3 (6.1%)
Disorientation	0 (0.0%)	1 (3.2%)	1 (2.0%)
Dissociation	0 (0.0%)	1 (3.2%)	1 (2.0%)
Feeling cold	0 (0.0%)	1 (3.2%)	1 (2.0%)
Hallucination	1 (5.7%)	4 (13.2%)	5 (10.2%)
Hypertension	4 (22.2%)	2 (6.5%)	6 (12.2%)
Nausea	1 (5.7%)	1 (3.2%)	2 (4.1%)
Nystagmus	0 (0.0%)	1 (3.2%)	1 (2.0%)
Paresthesia	0 (0.0%)	1 (3.2%)	1 (2.0%)
Pharyngolaryngeal pain	0 (0.0%)	1 (3.2%)	1 (2.0%)
Restlessness	1 (5.7%)	0 (0.0%)	1 (2.0%)
Sedation	2 (11.1%)	2 (6.5%)	4 (8.0%)
Somnolence	0 (0.0%)	1 (3.2%)	1 (2.0%)
Tachycardia	1 (5.7%)	0 (0.0%)	1 (2.0%)
Vertigo	0 (0.0%)	1 (3.2%)	1 (2.0%)
Vomiting	2 (11.1%)	1 (3.2%)	3 (6.1%)

CRPS = complex regional pain syndrome.

One patient may have experienced more than one adverse event.

Challenges in outpatient ketamine infusion

- Billing, billing, billing, opportunity cost
- Facility fee
- Profee <60min infusion
 - CPT: 96365-66 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial up to 1 hour, 16-60 minutes (less than 16min = IVP)
 - 30 min
 - Variable recovery period (policy driven)
 - Benefit: additional option for refractory patients.

Outpatient oral ketamine



ELSEVIER

Contents lists available at [ScienceDirect](#)

European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

Review

Use of oral ketamine in chronic pain management: A review

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^cUtrecht Institute for Pharmaceutical Sciences, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, P.O. Box 80 082, 3508 TB Utrecht, The Netherlands

Blonk, MI et al., Eur J Pain 2010;14(5):466.

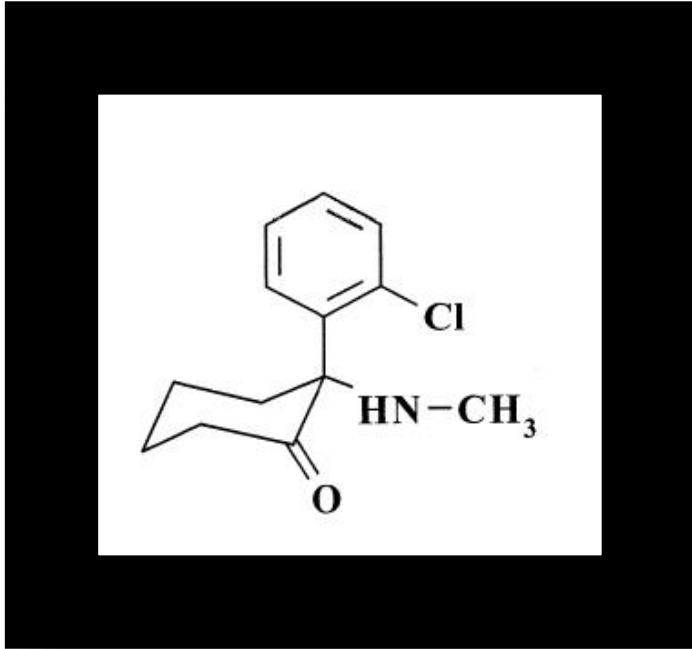
ORIGINAL ARTICLE

Efficacy and safety of oral ketamine for the relief of intractable**Table 1** Characteristics of patients and type of pain by ketamine treatment response.

	Effective 44% (n = 24)	Partially effective 20% (n = 11)	Opioid sparing only 14% (n = 8)	Failure 22% (n = 12)	Total (n = 55)
Patient characteristics					
Pain lowering on a numeric scale	67 ± 17%	30 ± 11%	6 ± 12%	4 ± 9%	40 ± 33%
Age (years)	47 ± 13	49 ± 11	46 ± 9	45 ± 13	46 ± 12
Sex ratio, M/F, n	13/11	2/9	0/8	3/9	17/34
Body mass index, kg/m ²	25 ± 4	26 ± 5	22 ± 3	26 ± 4	25 ± 4
Type of pain (n)					
Neuropathic	13	7	5	8	33 (60%)
Rheumatologic	6	3	2	2	13 (24%)
Fibromyalgia	2	0	1	2	5 (9%)
Miscellaneous	3	1	0	0	4 (7%)

Data are mean ± standard deviation unless indicated.

Conclusion: limit the cooks in the kitchen



=



Thank you!

Feel free to email me questions:
ddickerson@dacc.uchicago.edu



REFERENCES

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