THE UNIVERSITY OF CHICAGO MEDICINE

The Road from Theory to Practice: Ketamine Tales in Pain Management and Beyond

Magdalena Anitescu, MD, PhD

Professor of Anesthesia and Pain Medicine

Director, Pain Medicine Fellowship Program
Section Chief, Pain Management Services
Department of Anesthesia and Critical Care
University of Chicago Medical Center

Disclosure

- Medtronic Pain fellowship

Learning objectives

- Identify **mechanisms of action** of the drug ketamine
- Describe various **chronic pain-related clinical indication** of ketamine
- Describe emerging **indications** for the use of ketamine in clinical practice for **conditions NOT associated with chronic pain**

10+ years of outpatients ketamine infusions
Comments from colleagues, residents, friends

Why do it? Does it even work?

BOOORING! Why do we do this infusion?

This crazy attending made me use it…

All of them will be psychotic, look at their eyes…

We will never get them (patients) out of PACU

Ketamine, a versatile drug: tales of an infusion

- ***First Story*: Meet Ketamine, an old friend**
- ***Second Story:* Perioperative use of ketamine**
- ***Third story:* Ketamine and chronic pain**
- ***Fourth Story:* Psychiatry use of ketamine**
- ***Fifth Story*: Ketamine in Palliative care**
- ***Sixth Story*: Ketamine in our institution**
  - Pain clinic infusions
  - Intraoperative protocols
  - Inpatient ketamine protocols: oral and intravenous

FIRST STORY

Ketamine, old friend:

There can Not be Good without Evil

St. Augustine, 354-430

Ketamine

- Product CI-581 (1962), FDA approved as dissociative anesthetic (1970): clinical and military use
  - Analgesic in battlefields
  - Better that alternatives (phencyclidine)
- Routes of administration
  - Oral-low availability
  - Intravenous-most use
  - Other: subcutaneous, transdermal, rectal
  - New: inhalation (palliative, geriatric, battlefields)

Jonkman K et al, F1000 Research 2017, 1711(6): 1-9

Clinical Use of Ketamine

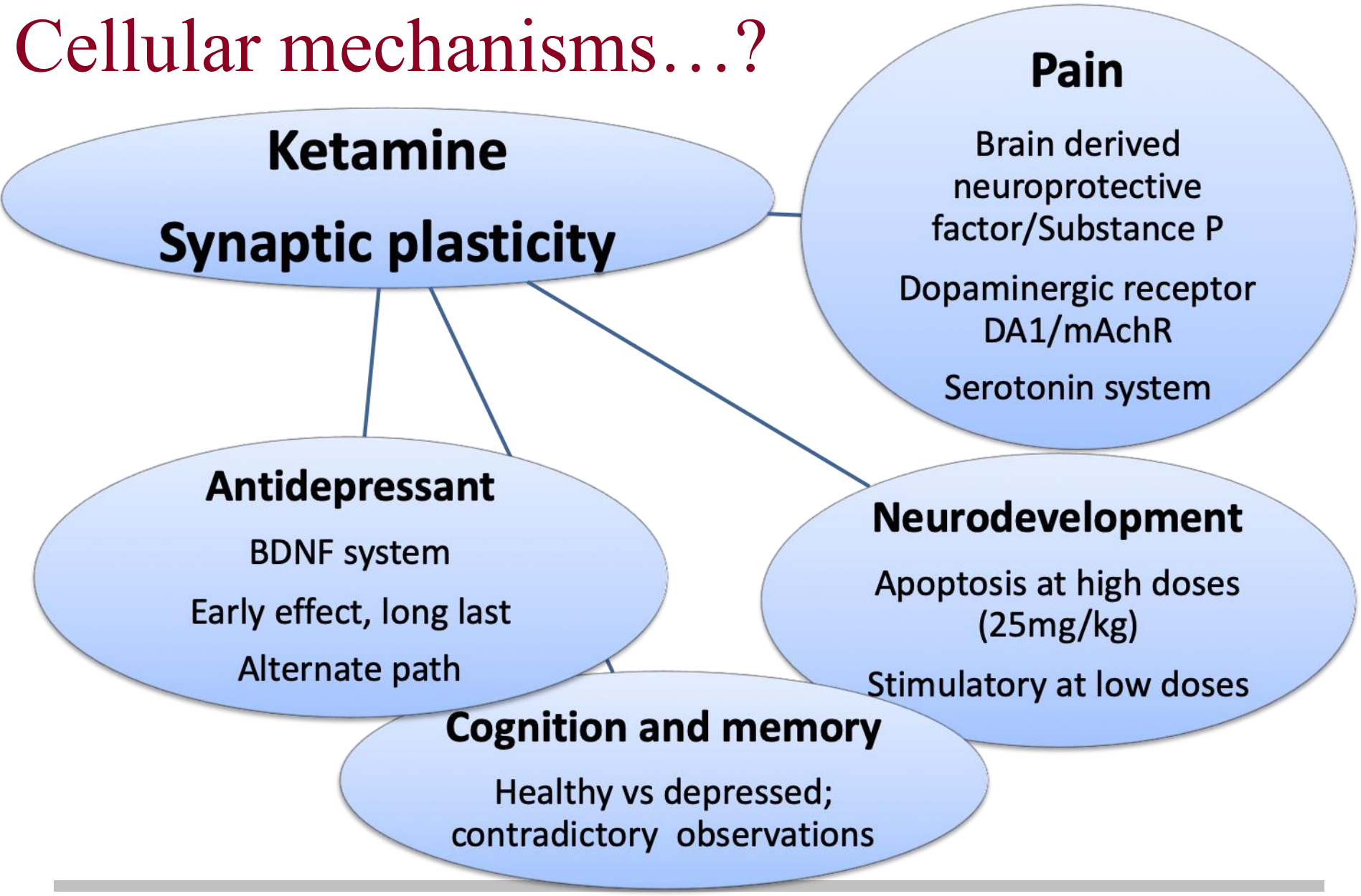
System Effects	
CVS	↑heart rate, ↑blood pressure ↑CVP, ↑CO, baroreceptor function is maintained and dysrhythmias are uncommon
RS	Bronchodilation, ↑ RR, relative preservation of airway reflexes
CNS	↑Cerebral blood flow/metabolic rate and intraocular pressure
AS	Nausea and vomiting, ↑salivation
GU	↑uterine tone
Other	Emergence delirium/dreams/ hallucinations

- Anesthetic (limited effect airway and respiration)
  - Out of hospital emergencies
  - Disaster situation/Battlefield
- In obstetric as analgesic
- In burns for dressing changes
- In pediatrics
- In sedation after premedication with midazolam
- Asthmatics, depressed

Known mechanism: NMDAr Blocker, but...

The "Impure" Drug: MANY other receptors

Cellular mechanisms…?

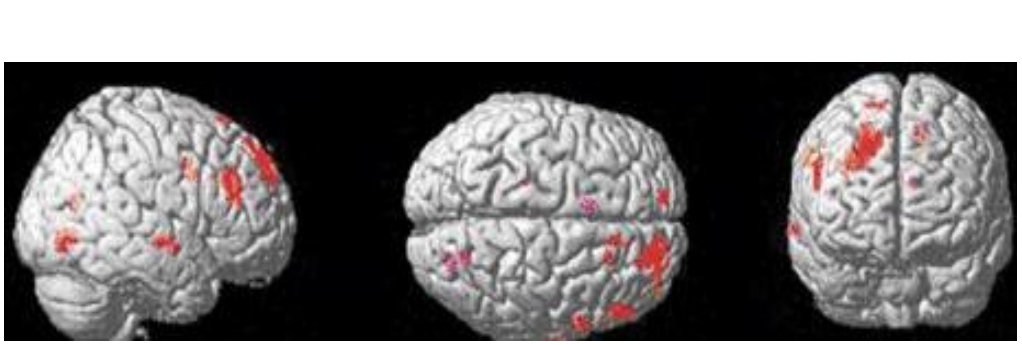


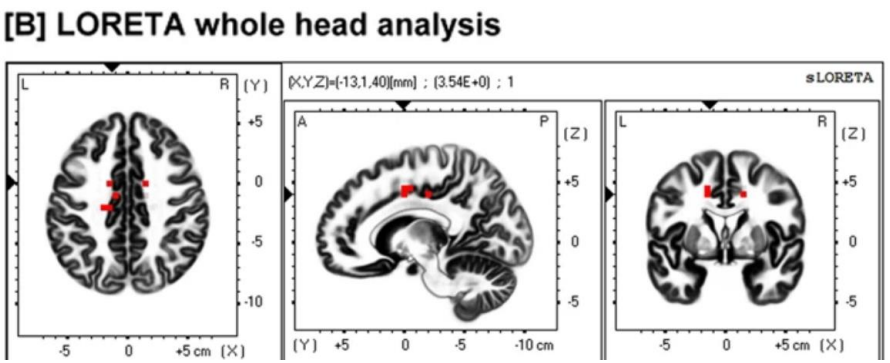
Not Harmless

- Persistent, dose-dependent, **behavioral/memory deficits** persisting in adulthood in rats/primates (20-75mg/kg)

- **Heavy ketamine users: severely impaired on short term memory.**

Schizotypal effects-dopaminergic hyperfunction





•Up-Regulation of **D1 receptor** activity in dorso-lateral prefrontal cortex-**MEMORY & JUDGEMENT**

•Imbalance **cortical and subcortical DA Systems-increase DA in limbic system** with positive symptoms

Huang L et al. Brain Research. 2012; 1476: 164-171; Narendran R, et al. Am J Psychiatry 2005, 162 (12), 2352-2359; Trujillo (2011). ILAR Journal/Nat Res Council,, 52(3), 366-378; S Curic et al, Neuropsychopharmacology, feb 2019

Illicit use:

*Special K * Vitamin K * Kit Kat * Cat Valium * Honey Oil * Special LA Coke * Kelly's Day * Super Acid * Blind Squid

Risk for abuse?

- In ED- ketamine alone abuse/diversion is low
  - "Put off" by **adverse effects** (nausea, anxiety, agitation)
    - Effective **only in intravenous formulation**
    - Mortality: low, related to **dangerous behavior**
- **Duration** of neurobehavioral alterations (depression/anxiety, cognitive deficits, schizoid ideation): **UNCLEAR**

First Story Moral:

You can not separate GOOD and EVIL

Learn your Good, Know your Evil!

SECOND STORY

Perioperative use of Ketamine:

What's dreamt in the OR's stays in the OR's!

Magda's advise to her patients…

Excellent evidence: In total knee arthroplasty

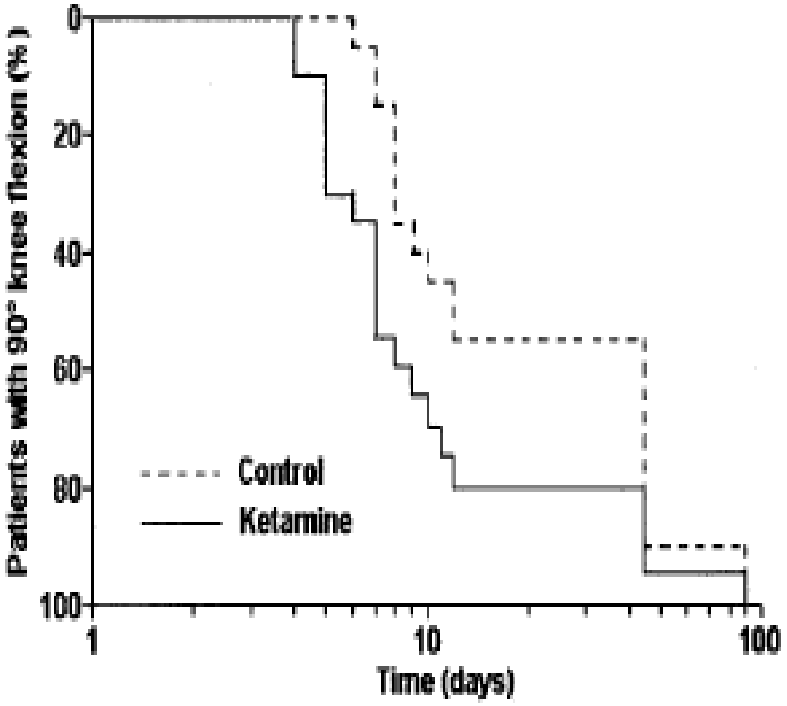


Table II: Cumulative morphine consumption and VAS pain scores during the first 24 hours postsurgery*.

	Placebo Group**	Ketamine Group**
Cumulative morphine consumption (mg)		
At 1 h	24.26 ± 4.77	14.70 ± 10.77
At 3 h	41.63 ± 10.79	23.96 ± 13.12
At 6 h	55.76 ± 12.56	28.73 ± 11.88
At 12 h	70.60 ± 10.44	35.30 ± 10.64
At 24 h	85.20 ± 8.01	47.00 ± 15.30
VAS score (cm)		
At 1 h	3.46 ± 0.86	2.83 ± 1.20
At 3 h	2.86 ± 0.81	1.60 ± 0.81
At 6 h	2.10 ± 0.80	0.90 ± 0.66
At 12 h	1.40 ± 0.77	0.26 ± 0.44
At 24 h	0.63 ± 0.61	0.20 ± 0.48

*Values are expressed as mean ± SD; **n = 30

- **35% reduced morphine consumption 0-48 hrs**
- **Time to 90° flexion reduced** (7 vs. 12days)

- Reduced VAS/opioid consumption up to 24 hrs

Adam F, et al,. Anesth Analg 2005; 100:475-480.
Cehgis P et al. J of the Col of Phys and Surg, 2014 24(5):299-303

Spine Surgery

Table 6. Ketamine Effect Stratified According to Preoperative Morphine Use

	Treatment			Placebo			
	N	Mean (mg)	SD	N	Mean (mg)	SD	*P* Value
≥0.556 mg/hr intravenously							
24-hr ME	17	168.8	94.4	22	302.5	216.8	0.014
48-hr ME	16	241.3	145.7	22	471.3	441.3	0.031
<0.556 mg/hr intravenously							
24-hr ME	34	129.3	73.8	27	119.9	59	0.58
48-hr ME	33	172.7	83.2	25	166.3	86.8	0.78

ME — morphine equivalent.

- **Morphine consumption was reduced** at 24hrs, 48 hrs and 6 weeks in the treatment group
- **Pain scores were reduced in PACU and at 6 weeks** in treatment group

TABLE 2. Pain-free Period and Rescue Analgesic Requirement

Parameters	Group C	Group D	Group K	*P*
Total pain-free period (min) (median and interquartile range) in 48 h; upper and lower limits of interquartile range	265.26/295; 760/0	580/1470; 2880/0	860/2628; 2880/60	0.002
Rescue morphine requirement at 12 h (mg)	3.75 ± 2.525	1.64 ± 2.167	0.14 ± 0.640	0.000
Rescue morphine requirement in first 24 h (mg)	15.64 ± 9.31	6.89 ± 5.886	2.45 ± 2.067	0.000
Rescue morphine requirement in first 48 h (mg)	21.09 ± 12.88	7.98 ± 7.724	2.59 ± 1.974	0.000

Data represented as mean ± SD.

- Control, Dexmedetomidine, Ketamine, prospective: **Reduced rescue morphine to POD#2**

Loftus RW, et al, Anesthesiology 2010; 113: 639-646
Garg N et al. J Neurosurg Anesthesiol. 2016; 28: 27-31.

Reviews and Consensus

- Effectiveness/tolerability of ketamine for acute postoperative pain in adults in randomized controlled studies (37-2240pt)
- Results:
  - 27/37 trials can not identify optimal dose
    - **Decrease rescue analgesic requirements**, pain intensity or both
    - **Reduce 24 hours PCA morphine use**/Reduce postoperative N/V
    - Minimal or inexistent adverse events

THE COCHRANE COLLABORATION®

REGIONAL ANESTHESIA AND ACUTE PAIN

SPECIAL ARTICLE

OPEN

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

Eric S. Schwenk, MD, Eugene R. Viscusi, MD,* Asokumar Buvanendran, MD,† Robert W. Hurley, MD, PhD,‡ Ajay D. Wasan, MD, MSc,§ Samer Narouze, MD, PhD,|| Anuj Bhatia, MD, MBBS,** Fred N. Davis, MD,†† William M. Hooten, MD,‡‡ and Steven P. Cohen, MD§§*

Summary of ASRA/AAPM recommendations

- **Patients and acute pain conditions considered for ketamine treatment**
- **Dose range; does the evidence support dosing in this range for acute pain-**
- **Evidence to support ketamine infusions as an adjuvant to opioids and other analgesic therapies for perioperative analgesia**
- **Contraindications to ketamine infusions in the setting of acute pain management and do they differ from chronic pain setting - Evidence to support non parenteral ketamine for acute pain management -,**
- **Evidence support for patient controlled IV ketamine analgesia for acute pain**

Recommendation Category	Recommendation	Level of Evidence*
Indications for use	(1) Perioperative use in surgery with moderate to severe postoperative pain (2) Perioperative use in patients with opioid tolerance (3) As analgesic adjunct in opioid-tolerant patients with sickle cell crisis (4) As analgesic adjunct in patients with OSA	(1) Grade B, moderate certainty (2) Grade B, low certainty (3) Grade C, low certainty (4) Grade C, low certainty
Dosing range	Bolus: up to 0.35 mg/kg Infusion: up to 1 mg/kg per hour	Grade C, moderate certainty
Relative contraindications	(1) Poorly controlled cardiovascular disease (2) Pregnancy, psychosis (3) Severe hepatic disease, ie, cirrhosis (avoid), moderate hepatic disease (caution) (4) Elevated intracranial pressure, elevated intraocular pressure	(1) Grade C, moderate certainty (2) Grade B, moderate (3) Grade C, low certainty (4) Grade C, low certainty
Personnel	Supervising clinician: a physician experienced with ketamine (anesthesiologist, critical care physician, pain physician, emergency medicine physician) who is ACLS certified and trained in administering moderate sedation Administering clinician: registered nurse or physician assistant who has completed formal training in safe administration of moderate sedation and is ACLS certified	Grade A, low certainty (see Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain from ASRA, AAPM, and ASA)[35]

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

Schwenk ES, Viscusi ER Buvanendrum A et al. RAPM 43(5):456-466

Second Story Moral:
What's dreamt in OR is an Opioid Free, Pain Free Dream

THIRD STORY

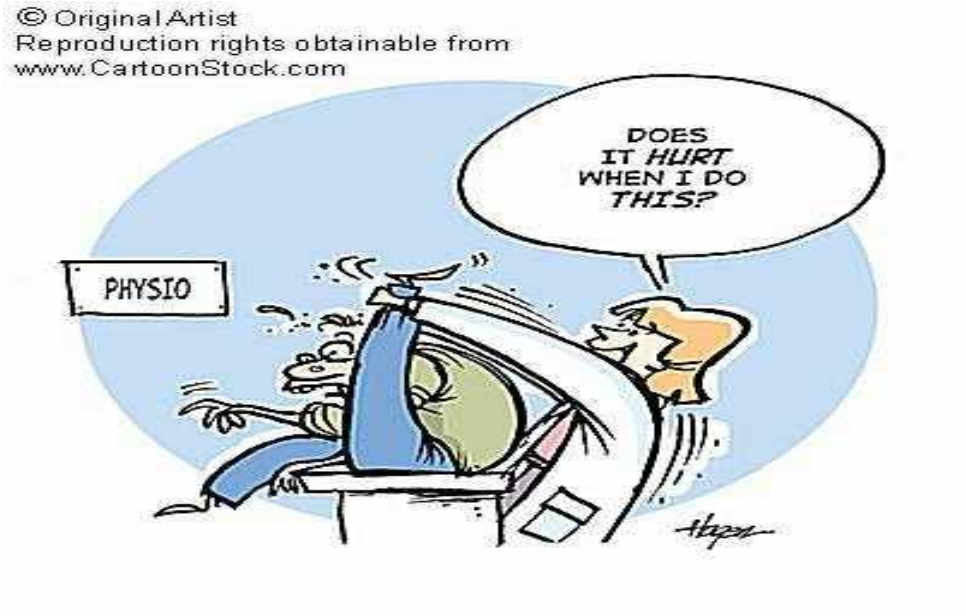
Ketamine and chronic pain:

The road to hell is paved with good intentions.

St. Bernard de Clairvaux, 1150:
"L'enfer est plein de bonne volontes et desirs".

Studies of ketamine for Chronic Pain?

- Complexity/Study design: **difficult randomization**
- Ethical issues/Safety profile: **patients guessed** the groups



Suggestive indications in “wind up” phenomenon

CRPS,

Neuropathies,

Post herpetic neuralgia,

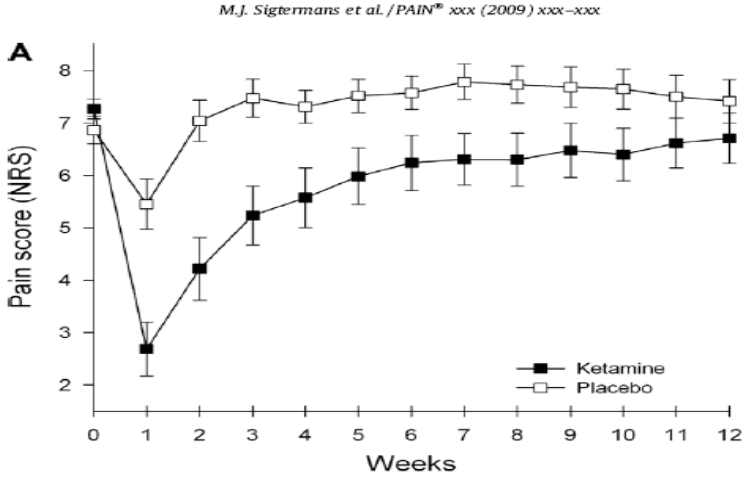
Fibromyalgia

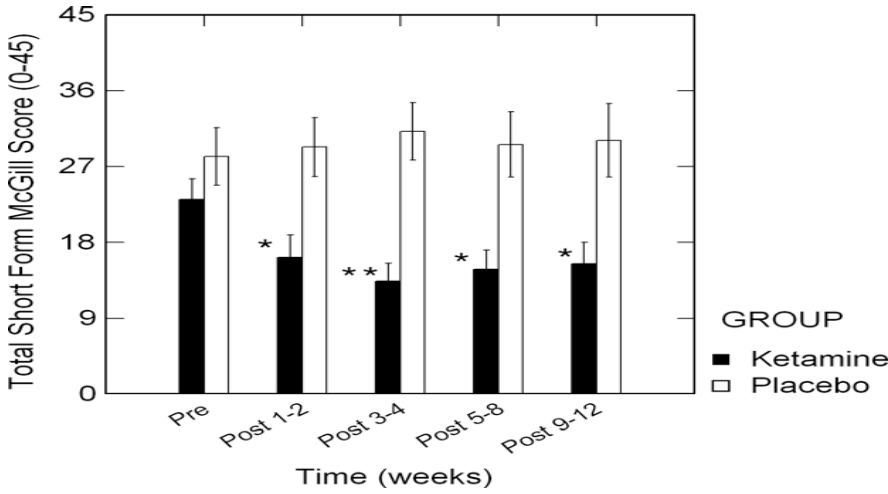
Migraines

Burns

Abdominal pain

Extended infusions with ketamine



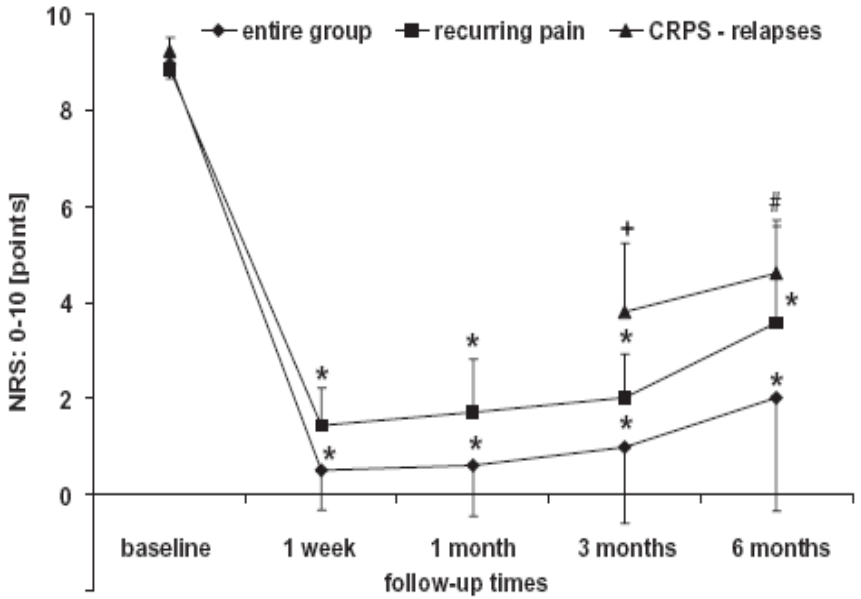


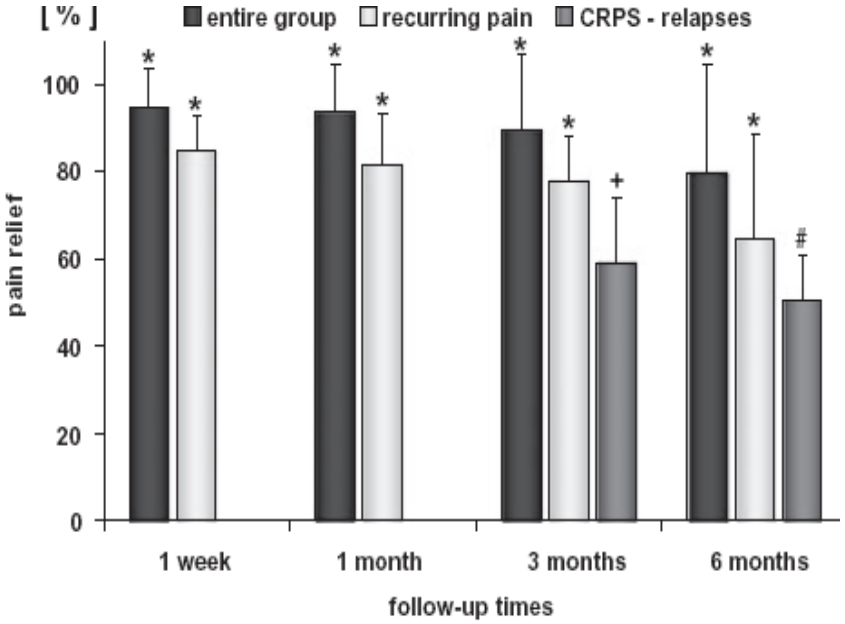
CRPS, 4.2 days infusion:Lowest pain score at end of week 1,
Effects **lost at 12th week** ;
no functional improvement
Side effects in treatment group (76% vs. 18%)-mild and short lived

10 days, 4 hours/day ketamine: **Maintaned decreased McGill scores,**
No Psychotic side effects only nausea, headache, No change in quality of life scores

Sigtermasn et al, Pain 2009, 145: 304-311
Schwartzman RJ, et al. Pain, 2009 147:107-115.

Ketamine coma





20 (17 intubated) **refractory CRPS, general anesthesia**: ketamine 1.5mg/kg bolus (midazolam, clonidine) + 3mg/kg/hr up to 7mg/kg/hr over 5 days

Side effects: Anxiety, dysphoria, nightmares, difficulty sleeping in majority of patients upon emergence, more severe in initial days

Psych s/e gone within 1st week following treatment

5 patients reported nightmares for a month

THE UNIVERSITY OF CHICAGO MEDICINE

Kiefer RT, et al, Efficacy of Ketamine in anesthetic dosage for the treatment of Refractory Complex Regional Pain Syndrome: An Open label Phase II study, Pain Medicine 2008.

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

Steven P. Cohen, MD,† Anuj Bhatia, MBBS, MD,‡ Asokumar Buvanendran, MD,§ Eric S. Schwenk, MD,// Ajay D. Wasan, MD, MSc,** Robert W. Hurley, MD, PhD,†† Eugene R. Viscusi, MD,// Samer Narouze, MD, PhD,‡‡ Fred N. Davis, MD,§§|||| Elspeth C. Ritchie, MD, MPH,***††† Timothy R. Lubenow, MD,§ and William M. Hooten, MD‡‡‡*

- Ketamine use sky-rocketed recently
- Small RCT, retrospective/observational studies, clinical experience
- Various doses (**generally longer infusions with higher doses**), various conditions treated
- As versatile of a drug, use of ketamine based on **physicians medical decision making** corroborating **patient and disease**/pain unique characteristics

Metanalysis on ketamine infusion for chronic pain

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight (%)
Sigtermans,[23] 2009	2.7	1.3	30	5.4	1.2	30	-2.70 (-3.33, -2.07)		25.48
Eichenberger,[26] 2008	2.5	1.7	10	3.6	1.6	10	-1.10 (2.55, 0.35)		9.78
Schwartzman,[24] 2009	6.3	2.7	9	7.6	1.9	10	-1.30 (-3.42, 0.82)		5.21
Noppers,[28] 2011	0.8	0.3	12	2.0	0.3	12	-1.60 (-3.57, 0.37)		5.93
Amr,[27] 2010	2.5	0.6	20	4.3	0.4	20	-1.80 (-2.13, -1.47)		35.13
Mitchell,[29] 2002	4.5	1.3	16	5.8	1.1	12	-1.31 (-2.21, -0.42)		18.47
Total (95% CI)			**97**			**94**	**-1.83 (-2.35, -1.31)**		**100.00**

Heterogeneity: Tau^2=0.17, Chi^2 =9.71, df=5 (P=0.084): I^2=48.5%
Test of Overall effect: Z =6.93, P<0.0001

-6 -4 -2 0 2
FAVORS KETAMINE FAVORS PLACEBO

A Nausea

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Sigtermans,[23] 2009	19	30	5	30	3.80 (1.63, 8.85)		69.63
Eichenberger,[26] 2008	4	10	0	10	9.00 (0.55, 147.95)		6.35
Schwartzman,[24] 2009	4	9	2	10	2.22 (0.53, 9.37)		24.03
Total (95% CI)		**49**		**50**	**3.52 (1.74, 7.14)**		**100.00**

Heterogeneity: Chi^2 = 0.88, d.f.=2 (P=0.643): I^2 = 0.00%
Test of Overall effect: Z = 3.50, p<0.00001

0.10 1 10 100
Decreased Risk Increased Risk
RELATIVE RISK, RR

B Psychotomimmetic effect

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Sigtermans,[23] 2009	29	30	5	30	5.80 (2.60, 12.95)		75.48
Eichenberger,[26] 2008	5	10	0	10	11.00 (0.69, 175.86)		6.33
Amr,[27] 2010	3	20	0	20	7.00 (0.39, 127.32)		5.78
Mitchell,[29] 2002	6	16	1	12	4.50 (0.62, 32.60)		12.41
Total (95% CI)		**76**		**72**	**5.92 (2.95, 11.89)**		**100.00**

Heterogeneity: Chi^2 = 0.28, d.f.=3 (P=0.963): I^2 = 0.00%
Test of Overall effect: Z = 5.00, p<0.00001

0.10 1 10 100
Decreased Risk Increased Risk
RELATIVE RISK, RR

C Headache

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Sigtermans,[23] 2009	11	30	10	30	1.10 (0.55, 2.20)		81.26
Schwartzman,[24] 2009	4	10	2	9	2.22 (0.53, 9.37)		18.74
Total (95% CI)		**40**		**39**	**1.26 (0.67, 2.34)**		**100.00**

Heterogeneity: Chi^2 = 0.75, d.f.=1 (P=0.387): I^2 = 0.00%
Test of Overall effect: Z = 0.71, p=0.475

0.10 1 10
Decreased Risk Increased Risk
RELATIVE RISK, RR

D Tiredness

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Schwartzman,[24] 2009	4	10	2	9	2.22 (0.53, 9.37)		72.21
Amr,[27] 2010	2	20	1	20	2.00 (0.20, 20.33)		27.79
Total (95% CI)		**30**		**29**	**2.16 (0.64, 7.33)**		**100.00**

Heterogeneity: Chi^2 = 0.01, d.f.=1 (P=0.939): I^2 = 0.00%
Test of Overall effect: Z = 1.23, p=0.218

0.10 1 10
Decreased Risk Increased Risk
RELATIVE RISK, RR

Third Story Moral:

We “trick” the BRAIN into analgesia

FOURTH STORY

Ketamine in Psychiatry:

The magic potion of power and positive emotions

"Not you Obelix, you know you fell jn the pot as a baby"
Psychoanalytics, pupil of Getafix, Village Druid

Incidental findings-paradigm shift

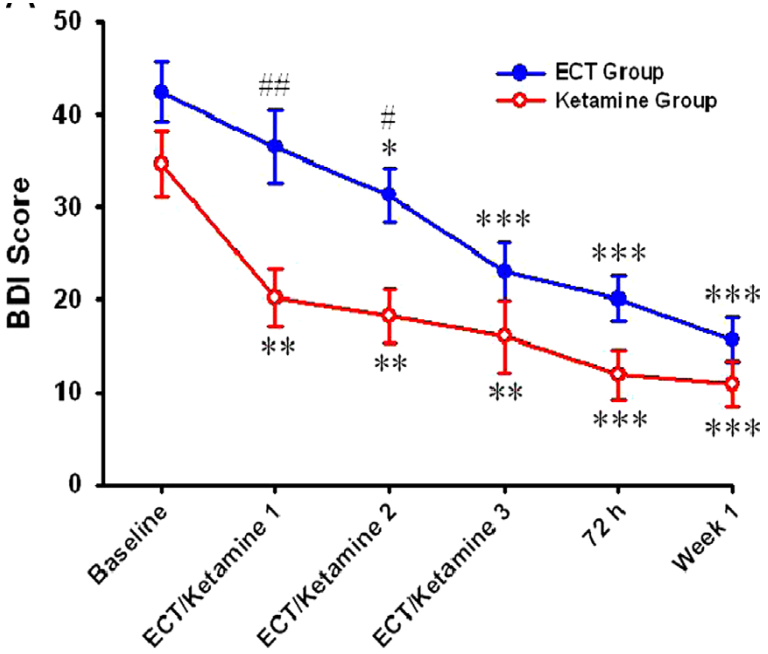
- Classic antidepressants (serotoninergic/NE system) response rate plateau at 60% need **days/weeks**
- ECT treatment-needs **days** to work
- Ketamine: **peak 4 hrs to work** and **stable at 3 days**
- Path: involving Brain Dependent Neuroprotective Factor via glutaminergic pathway (NMDAr)
- **Li and Mg (low in depression) co-administration enhance antidepressant effects**-

Ketamine: the Magical Wand to help patients emerge from deep depression within hours

Murrogh JW et al. Am J of Psychiatry 2013: 170:1134-42

Antidepressant

- Early studies *
  - Dose **0.5mg/kg in 45 minutes,** saline vs ketamine
  - **Rapid antidepressant effect of ketamine in hours**
- Later studies (unipolar and bipolar depression)**;
  - Response at 24 hrs-25-70% patients
  - Response at 72 hrs-14-50% patients
  - Suicidal ideation decreased at 40', kept 3 days-3 weeks

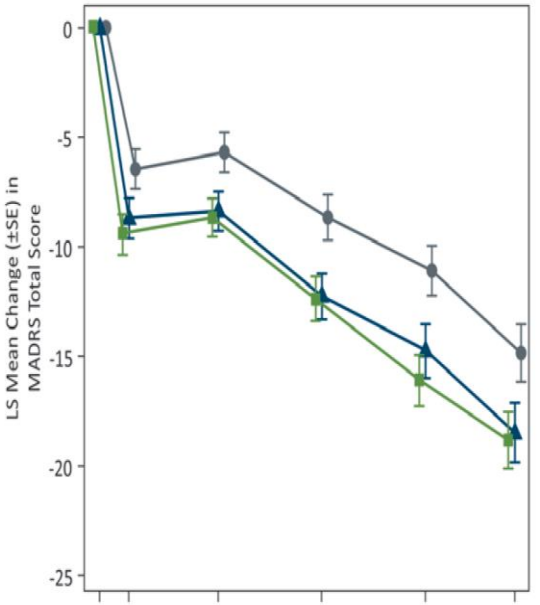


- 3 treatment done every 48 hours, Results
  - Similar patients, similar medication, refractory depression
  - **Ketamine with initial significant effects but similar with ECT in 1 week**

*Berman et al, Biol Psy.2000 Feb15; 47(4):351-4
*Zarate et al Arch Gen Psy, 2006 63 (8): 856-64 **Zarate CA, Biol Psy 2012 72(7): 537-47
Price RB, et al, Biological Psychiatry 2009, 66(5):522-526.Price et al: Depres Anxiety 2014 31 (4): 335-43
Ghasemi et al, Psychiatry Research 215 (2014) 355-361

Ketamine and antidepressant

- Intranasal formulation esketamine approved in spring 2019 for treatment resistant depression
- Phase 3 double blind multicentered; 346 patients randomized 1:1:1, twice weekly esketamine for 4 weeks
- Not statistically significance but clinically meaningful by depression scale



No. of Patients :	Baseline	Day 2 (24hrs)	Day 8	Day 15	Day 22	Day 28
Esketamine 56 mg/Oral Antidepressant	115	105	114	110	107	111
Esketamine 84 mg/Oral Antidepressant	114	104	107	99	96	98
Oral Antidepressant/Placebo	113	101	111	106	105	108
LS mean (SE) treatment difference vs. placebo:						
Esketamine 84 mg		-2.2 (1.29)	-2.7 (1.26)	-3.6 (1.48)	-3.7 (1.65)	-3.6 (1.86)
Esketamine 56 mg		-3.0 (1.29)	-3.0 (1.24)	-3.8 (1.45)	-5.0 (1.61)	-4.0 (1.81)

M Fedhin et al. Int J of neuropharmacology (2019) pp 1-15|

Obsessive compulsive disorders

- Initial studies*
  - Near constant obsession symptoms responds to ketamine
  - **Peak effect in 24 hours, lasts 7 days**
- Later studies*
  - Refractory OCD **effects immediate, lasting 24 hours**

Post-traumatic stress disorders

- 41 patients in randomized, double blind, crossover study
- Ketamine vs midazolam
- PTSD symptoms reduced in ketamine group at **24 hrs, lasting 7 days**

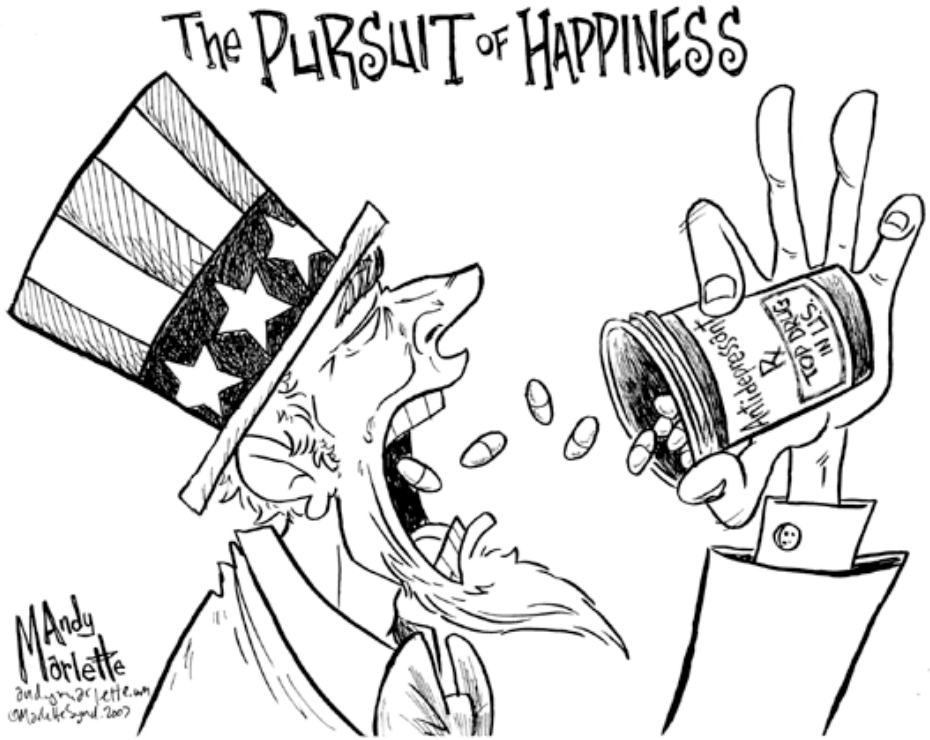
Addictions: alcohol, heroine, cocaine

- Small studies
- Promote abstinence for alcohol
- Promote abstinence for heroine dependence
- Reduces craving and self administration of cocaine

- Rodriguez CI et al, Neuropsychopharma 2013 38)12): 2475-8
- **Block MH, Biol Psy 2012 72(11): 964-703
- *Feder A et al, JAMA Psy, April 2016 on line
- Ezquerra-Romano II et al. Neuropharmacology (2018) ahead of print

Fourth Story Morale:

We make our patients HAPPIER



FIFTH STORY

Ketamine and end of life:

The Calm Agitation

Pediatric and adults in palliative service care

- Effective adjuvant in adult/pediatric refractory cancer pain
- Adults studies>peds studies
- Doses recommended in refractory cancer pain
  - Inpatients (iv): start 0.5mg/kg/hr
  - Outpatient (oral):
    - 0.2-0.5 mg/kg 2-3 times per day
    - Max dose 50 mg tid

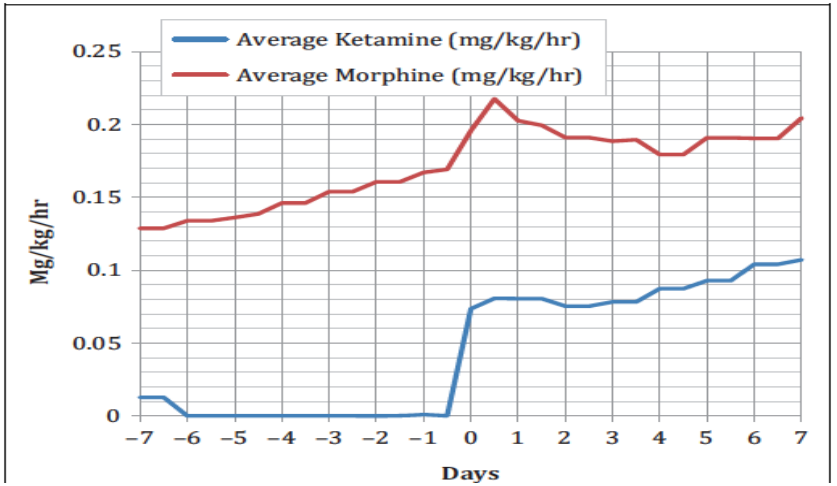
Adverse Event	Reported Occurrences N (%)
Somnolence [18,21,23,65,66]	88 (45)
Nausea/vomiting [17,18,21,23,66]	52 (33)
Constipation [17,18,21,66]	46 (31)
Insobriety [19,38]	31 (46)
Hallucinations [17–20,24,28,38]	24 (14)
Dizziness/vertigo [21,22,24,66]	21 (12)
Depersonalization/derealization [22–24,38]	20 (30)
Injection site problems [19,21,22,66]†	19 (11)
Drowsiness/fatigue [18,22,67]	17 (23)
Evoked nystagmus [24]	12 (100)
Anorexia [18,23,66]	12 (26)
Confusion [66] [21]	11 (10)
Elevated blood pressure [21,22]	8 (6)
Hypoxia [21,66]	7 (6)
Cardiac arrhythmia [21]	6 (6)
Dysuria/urinary retention [17,38]	6 (26)
Speech difficulty [22]	5 (42)
Pruritis [17]	3 (15)
Memory changes [24]	2 (17)
Dream changes [66]	2 (9)
Anxiety [66]	2 (9)
Leg weakness [38]	1 (33)
Agitation [67]	1 (6)
Spasms [66]	1 (5)
Diplopia [66]	1 (5)
Dysphagia [66]	1 (5)
Sterile abscess [22]	1 (2)

† Subcutaneous or epidural.

Bredlau AL, Pain Medicine 2013;14:1505-1517

Ketamine PCA in pediatric cancer

Initial continuous PCA dose, mg/kg/h	Initial demand dose, mg/kg	Initial lockout, minutes
0.078	0.08	10
0.072	0.04	15
0.035	0.05	20
0.020	0.03	60
0.014	0.03	15
0.071	0.07	60
0.308	0.38	10
0.094	0.10	15
0.076	0.08	15
0.045	0.09	15
0.202	0.50	30
0.016	0.03	20
0.050	0.05	15
0.033	0.03	10



- Allows D/C home to hospice in severe end of life neuropathic pain in children
- Limited adjustment after initial titration
- Co-administration of benzodiazepine
- Peds side effects milder than adults counterparts

However, ketamine works as adjuvant in palliative care.

No RCT but open label, observational, retrospective studies

Taylor M, Jakacki R, May C et al. Am J Hosp Palliat Care, DOI: 10.1177/1049909114543640, on line 15 July, 201
Jonkman K et al. 2017 Curr Opin. Supp and Pall Care, 11(2): 88-92

Ketamine infusions

- Retrospective review if 70 patients for reducing opioid use and pain score
- Positive response in 70% (52 patients)
- All subcutaneous infusion
  - Mean 200mg/day (50-400)
  - 10 days average
  - Increased 35mg/day

- Retrospective review if 44 patients for reducing opioid use and pain score after burst ketamine
- Positive response in 24 patients
- All intravenous infusion
  - 100mg/day for 48 hrs
  - Co-administer midazolam

Mercadante, Sebastiano, et al . "*Annals of palliative medicine* 7.2 (2018): 205-210
Cheung, Ka Wai Alice et al. *Annals of palliative medicine* (2019).

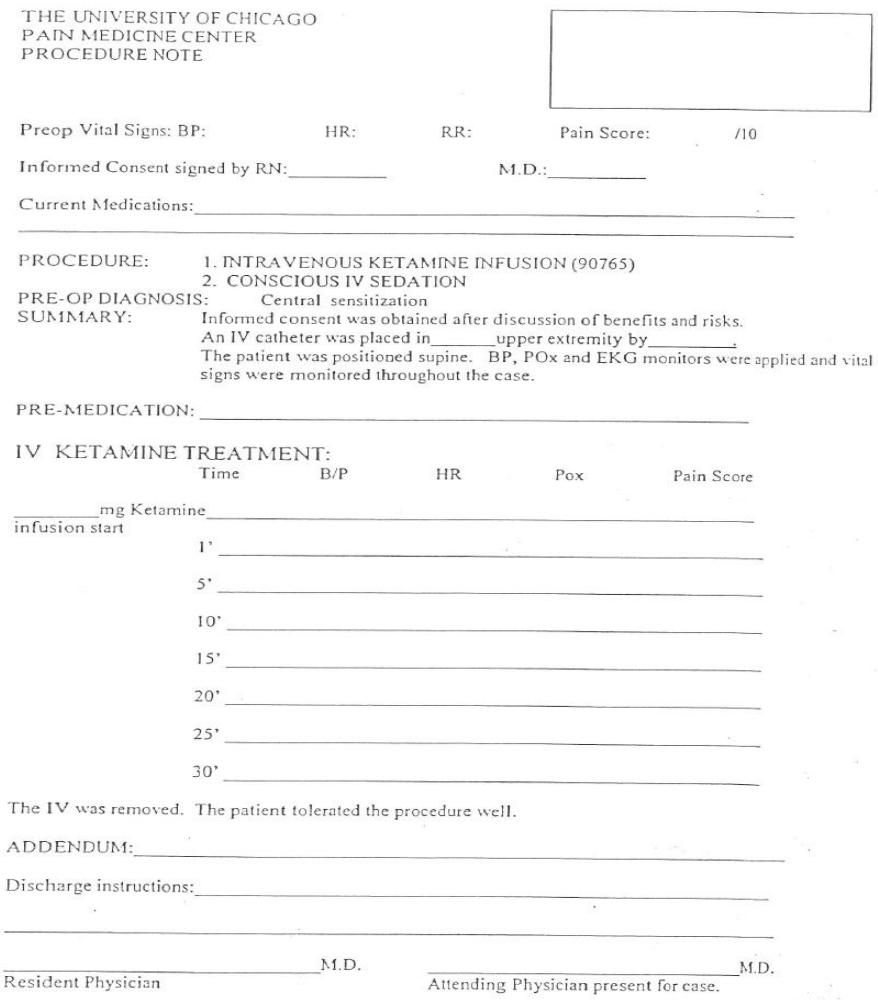
Fifth Story Moral:

We help our patients be calm, sleep and dream at END OF LIFE

SIXTH STORY

Our use of Ketamine

At our Pain Clinic-Outpatient



THE UNIVERSITY OF CHICAGO
PAIN MEDICINE CENTER
PROCEDURE NOTE

Preop Vital Signs: BP: HR: RR: Pain Score: /10

Informed Consent signed by RN:_____ M.D.:_____

Current Medications:_____

PROCEDURE: 1. INTRAVENOUS KETAMINE INFUSION (90765)
2. CONSCIOUS IV SEDATION

PRE-OP DIAGNOSIS: Central sensitization

SUMMARY: Informed consent was obtained after discussion of benefits and risks. An IV catheter was placed in_____upper extremity by_____. The patient was positioned supine. BP, POx and EKG monitors were applied and vital signs were monitored throughout the case.

PRE-MEDICATION: _____

IV KETAMINE TREATMENT:

	Time	B/P	HR	Pox	Pain Score
_____mg Ketamine infusion start					
1'					
5'					
10'					
15'					
20'					
25'					
30'					

The IV was removed. The patient tolerated the procedure well.

ADDENDUM:_____

Discharge instructions:_____

_____M.D. Resident Physician

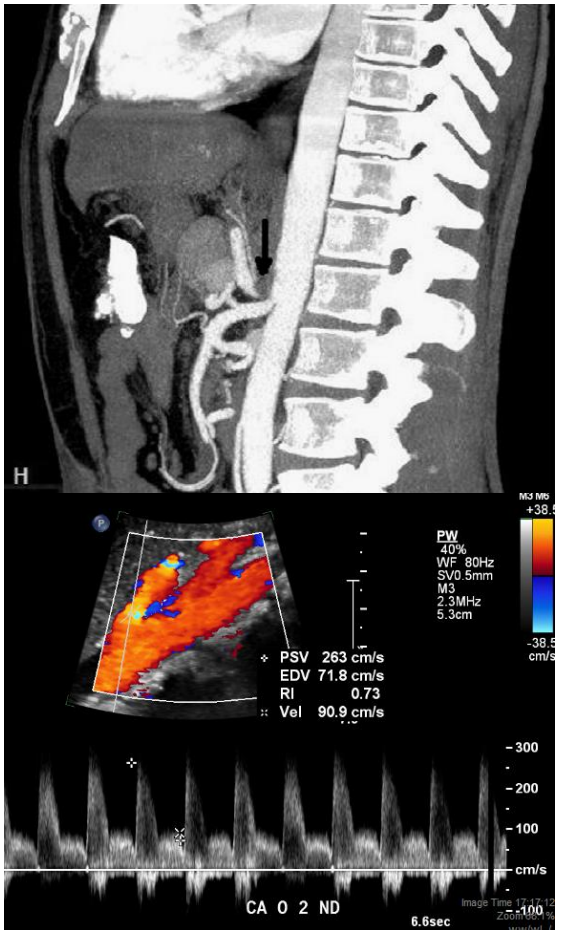
_____M.D. Attending Physician present for case.

- Protocol:
  - Start 0.3 mg/kg over 30 min
  - 1 month fu, double dose
  - Repeat if effective
- What we found:
  - Positive response to ketamine >3 weeks: 25-50% chance
  - Most common side effects: HTN, hallucinations
  - Conditions: chronic central sensitization

Patil S, Anitescu M,, Pain Medicine 2012, 13 (2):263-269.

Intraoperative advisory- MALS

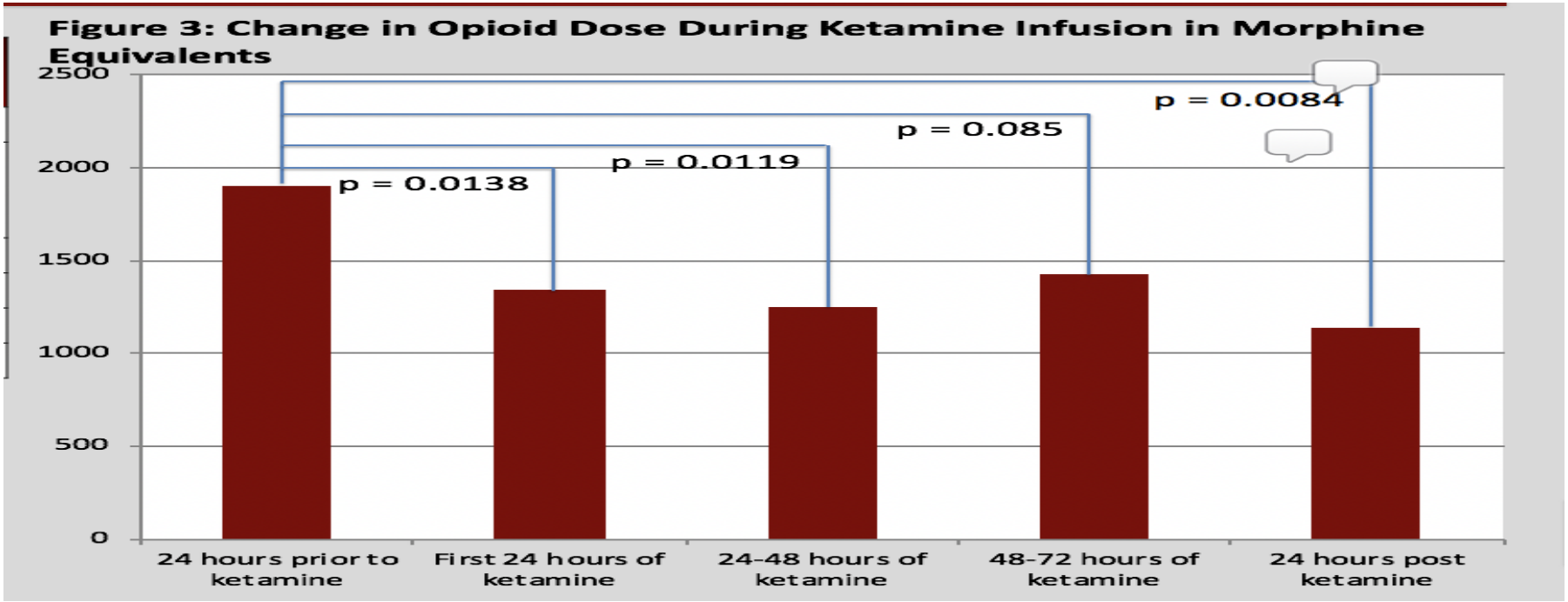
- Protocol
  - Epidural for all patients
  - Ketamine for all patients (0.5mg/kg bolus followed by 0.5mg/kg/hr till skin closure)
  - Postop Fentanyl PCA
  - Adjuncts: precedex, TIVA, etc



Abdominal pain, high celiac velocities, psych co-morbidites

Jimenez JC, et al, J Vasc Surg. 2012;56(3):869-873.
Jimenez JC, et al. J Vasc Surg, 2012;56(3):869-73.
Tulloch AW, et al.. J Vasc Surg, 2010;52:1283–1289.
Skelly C&Anitescu M. 2018 Nov 1; 68 (5): 1414-21

Sickle cell Vaso-occlusive crisis



- 12 unique patients with 24 admissions
- Vaso-occlusive crisis protocol: Tylenol, gabapentin, NSAIDS, methadone
- Ketamine initiated by acute pain service
- Decrease opioid consumption after initiation and at end of infusion time (48hrs)

Inpatient ketamine

- Oral ketamine
  - **Normal renal/hepatic function: 0.5 mg/kg** by mouth every 6 hours (2 mg/**kg**/day)..
  - **Renal /hepatic failure**: Not indicated
- Indications:
  - Cancer pain
- Intravenous low dose ketamine
  - **Doses 1-5 mcg/kg/min**, 24-48hrs
- Indications
  - Hyperalgesic states
  - Peri-operative analgesia
  - High opioid requirements
  - Sickle cell vaso-occlusive crisis
  - Cancer patients
  - Severe refractory neuropathic pain

So…we have a drug

- Whose exact mechanism of action is unknown
- Whose optimal analgesic dose is debatable
- Whose modes of administration vary from 30 minutes to 1 week
- Whose efficacy varies from 2 hours to 6 months
- Whose costs are high and not always reimbursable

SHALL WE USE IT?

And the answer is YES

- Ketamine-excellent intravenous analgesic
- An useful drug in the opioid abuse epidemic world
- Excellent adjuvant in perioperative period
- Modulation of pain with ketamine is part of a comprehensive multimodal analgesic regimen in various medical conditions
- Indications specific for presence of wind up phenomenon-can be used in MANY pain syndromes and beyond

Thank you!