THE SPECIAL K CHALLENGE: KETAMINE USE IN PALLIATIVE CARE

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DISCLOSURE

- We do not have any financial relationships with any commercial interests.
- Some case details were modified to preserve patient anonymity.

OBJECTIVES

- Clinical considerations for Ketamine Use
- NMDA Receptor
- Pharmacology Review
- Recreational Use of Ketamine
- Barriers to Ketamine
- Practical Use of Ketamine
- Next Frontiers for Ketamine

CASE #1

- 30 year old man with gastric adenocarcinoma, complicated by biliary obstruction from tumor extension.
- Started on chemotherapy, doing well.
- After 7 months, diagnosed with peritoneal carcinomatosis. Started on second line of chemo.

- Two months later, presents with nausea, vomiting "not related to chemo", assumed due to peritoneal carcinomatosis.
- Abdominal pain is worse, opioid regimen is increased.
- Over the next few of months, pain and nausea worsen; gastric outlet obstruction is diagnosed, two duodenal stents are placed endoscopically.
- Subsequently admitted and gets ex lap revealing large burden of disease and requiring placement of venting G-tube with feeding J-tube.

- Post-op is placed on fentanyl then hydromorphone PCA with titration over 3 days.
- Nausea accompanies the pain.
- KUB shows ileus, an NG tube is placed. Pain remains poorly controlled.
- POD 6, ketamine is started.

- "Considering degree of pain, importance of minimizing GI dysmotility, and avoiding oversedation, would recommend START ketamine drip at 1 mcg / kg /min, can titrate up after reassessment 1 hour after start, and increase to 2mcg/kg/min if not controlled. Can reassess q 2 hours, and increase by 1mcg/kg/min if pain not well controlled to a max of 4mcg/kg/min."

- Leaves AMA before ketamine started, but comes right back that same evening.
- Discussion of progression and goals with Palliative provider.
  - "Pt said (addressing his dad) "this is the end of the road." "
  - ""I don't care if you have to knock me out, just take the pain away." Said that only other thing that was important to him was "to say goodbye to [his] family.""

- Over next 2 days, ketamine gtt is titrated to 4mcg/kg/min. The patient remains on hydromorphone PCA.
- Another day, ketamine drip increased to 4.5 mcg / kg /min (from 4mcg/kg/min).
- Finally, ketamine drip gets titrated over two more days to 5.5 mcg/kg/min.

- Discharged to residential hospice facility.
- Pain and nausea continue.
- Ketamine briefly continued, but shortly after transfer and after discussion with patient, transitioned to palliative sedation with continuous benzodiazepine and opioid infusions.

CASE #1 QUESTIONS

- Could we have introduced ketamine earlier?
- What could have been potential triggers for consideration?
- Was the titration of ketamine appropriate, too fast, too slow?
- Could ketamine have been used in the setting of palliative sedation?

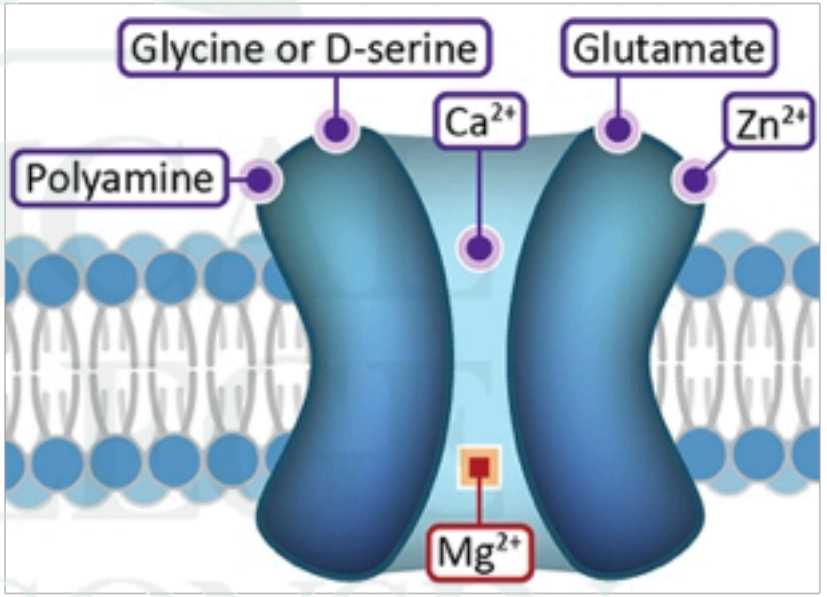
CLINICAL HISTORY OF KETAMINE

- First synthesized 1962
- First human use in 1965
- Clinical use in 1970

- Antagonistic action at PCP site of NMDA receptor -> Dissociative anesthesia
  - Adverse psychological effects
  - Does not depress CV/respiratory systems

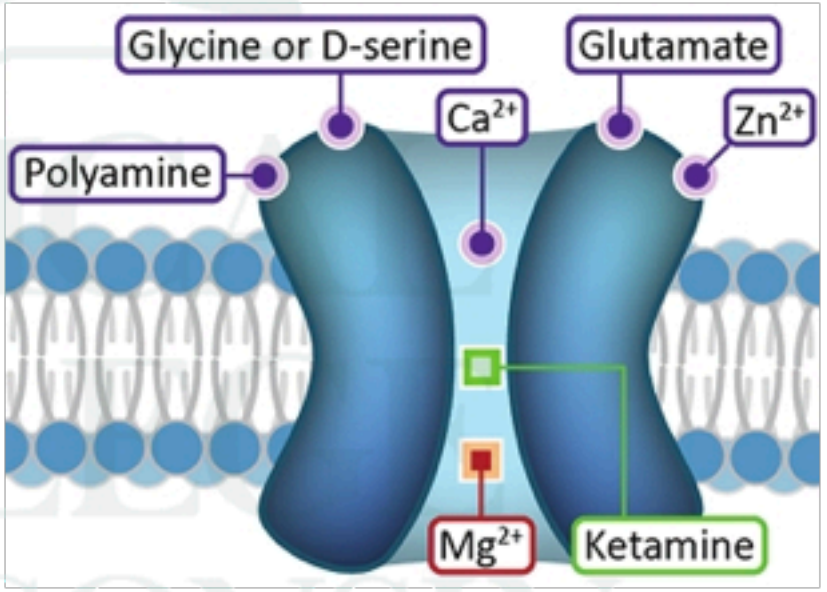
NMDA RECEPTOR

- Excitatory receptor-channel complex
- Expressed by unmyelinated (C-fiber) nociceptors in spinal cord
- Blocked by Mg2+ at resting/inactive state (voltage-dependent block)
- Prolonged firing of C-fiber nociceptors cause release of glutamate which acts on NMDAR



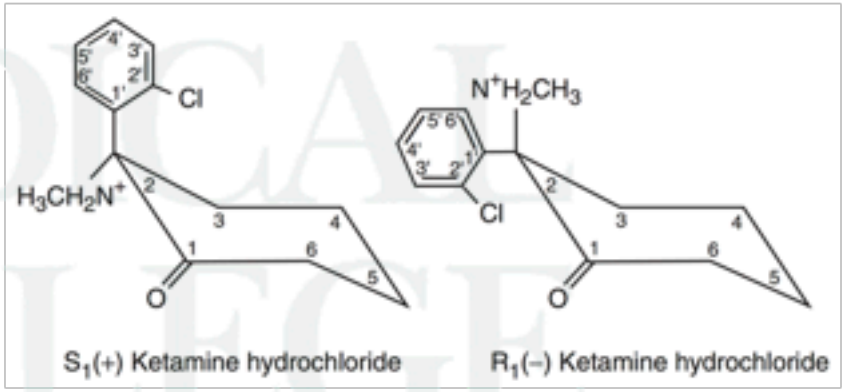
NMDA RECEPTOR

- Blocked by drugs that act at PCP site (e.g. ketamine, dextromethorphan, methadone)
- Ketamine binds to PCP site when NMDAR channel is open/ activated, and decreases frequency of channel opening



CHEMICAL PROPERTIES

- Racemic mixture of R(-) and S(+) ketamine
- S(+) isomer 3-4x more potent analgesic
  - Faster clearance and recovery
  - Fewer psychomimetic side effects



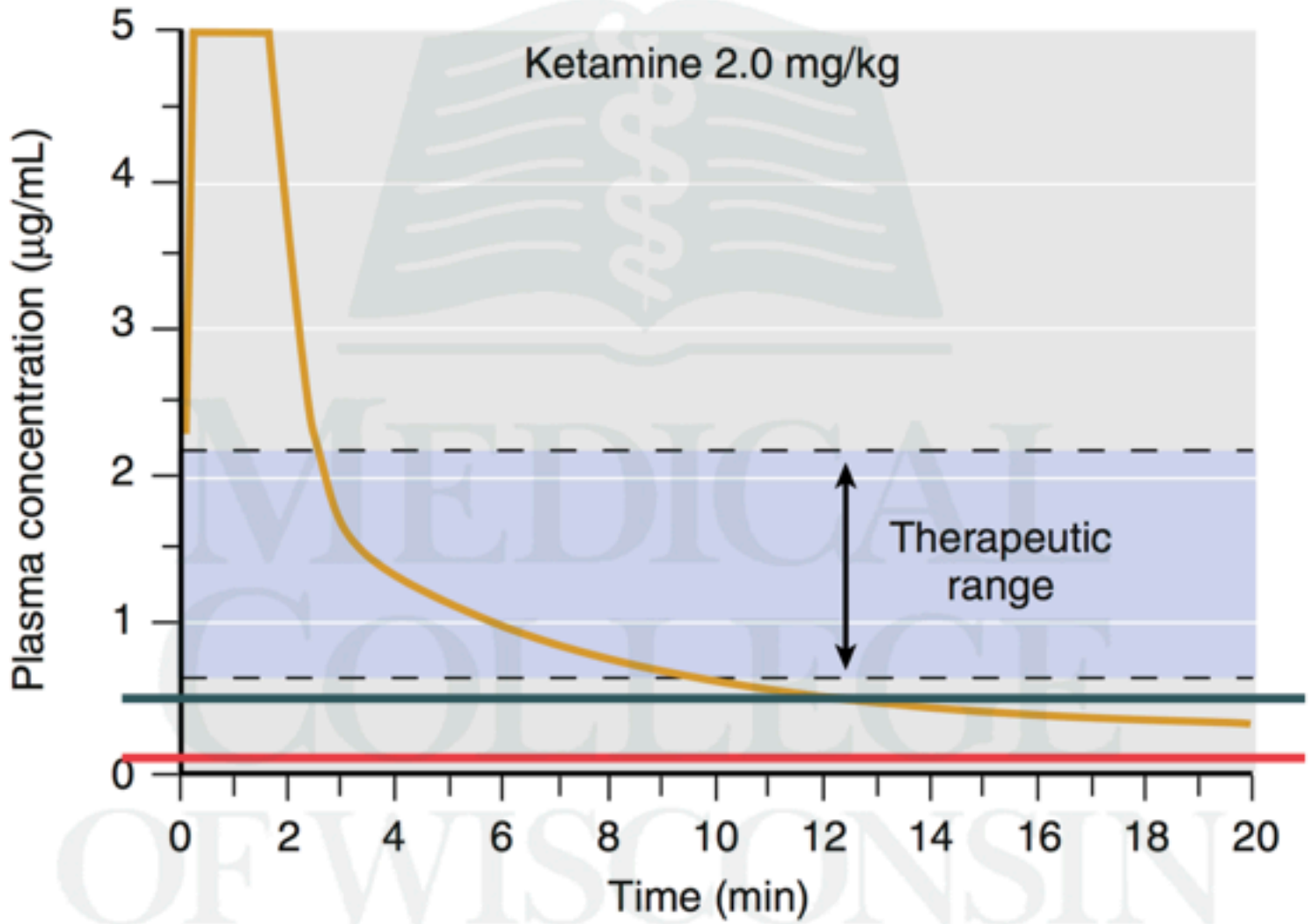
$S_1(+)$ Ketamine hydrochloride $R_1(-)$ Ketamine hydrochloride

PHARMACOLOGY

- Partially water soluble, high lipid solubility
- 12% protein bound
- 20-30% bioavailability after oral use
    - High first-pass metabolism — Hepatic microsomal enzymes
- 40-50% bioavailability after intranasal absorption
- Urine excretion

PHARMACOKINETICS

- Onset of action:
  - IV: 30 seconds (anesthetic effect)
  - PO: 30 minutes (analgesic effect)
- Plasma $T_{1/2}$:
  - Alpha: 10-15 minutes, Beta: 2.5 hours
- Duration:
  - IV: 5-10 minutes for anesthesia, 1-2 hours for recovery
  - PO: 4-6 hours, sometimes longer


Ketamine 2.0 mg/kg
Therapeutic range
Plasma concentration (µg/mL)
Time (min)
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16
18
20

CNS EFFECTS

- Dose-related unconsciousness
- Acts at: NMDA receptor, Opioid receptors, Monoaminergic receptors

- Cataleptic state
- Profound analgesia, Eyes open
- Corneal, cough, and swallow reflexes all may be present
- Amnesia less prominent

ANALGESIC EFFECTS

- Postoperative analgesia occurs after ketamine general anesthesia
- Lower plasma level required — Allows for sub-anesthetic doses

ADVERSE EFFECTS

- Side Effects:
    - Increases sympathetic nervous system activity
    - Impaired attention, memory, judgement
- Toxicity:
    - Neuropsychiatric, Urinary Tract, Hepatobiliary Tract
- Caution with CYP450 medications (PO *S*-Ketamine)

CONTRAINDICATIONS

- Absolute:
    - History of schizophrenia, regardless of control or medication
- Relative:
    - "Any situation in which an increase in blood pressure would constitute a hazard"
        - Glaucoma, Hypertension, Heart Failure, Ischemic Heart Disease, CVA, Acute Intermittent Porphyria, Hyperthyroidism
- Other reported/listed contraindications:
    - Epilepsy, Excessive secretions

INTRACRANIAL PRESSURE

- Traumatic Brain Injury
  - 101 adult and 55 pediatric patients
  - ICP did not increase in any of the studies during Ketamine administration
  - 3 studies reported significant decrease in ICP
  - No significant adverse events related to ketamine were recorded in any of the studies

INTRACRANIAL PRESSURE

- Nontraumatic neurological illness
  - 127 adult patients and 87 pediatric patients
  - ICP did not increase in any of the adult studies
  - No significant non-ICP-related adverse events from ketamine were recorded in any of the studies

RECREATIONAL USE OF KETAMINE

- Seen as early as 1971, increased in 1990's
- Began in United States, spread internationally with "rave" culture
- *Special K, Jet, Cat valium, Vitamin K, K-hole, Kit Kat, Liquid E*
- Causes "psychedelic" state of mind at lower doses, "out of body" experience at higher doses

RECREATIONAL USE OF KETAMINE

- Lifetime Incidence: 0.1% in US to 4% in UK
- Reports of abuse published in: Australia, Italy, UK, China, Southeast Asia, Eastern Europe
- Low risk of death due to wide therapeutic range
  - Traffic accidents, drowning, hypothermia cause harm to users
- In US: Adolescent to Adult users, 2012 prevalence 0.4% among college students, 0.8% among "young adults"

RECREATIONAL USE OF KETAMINE

- Most commonly intranasal use of insufflated powder
- Frequently adulterated with other substances, associated with poly-substance abuse
- Abuse dosing range from 100 to 200mg per dose, often multiple doses per day
- No described ketamine withdrawal syndrome

RECREATIONAL USE OF KETAMINE

- Neurobiological reinforcement:
  - Pleasant sensations from dissociative effects
  - Increased Dopamine activity
  - Analgesic effect (mu receptor agonism)
- Long-term effects:
  - Cognitive deficits
  - Lower Urinary Tract Symptoms (1/3rd of chronic users)
  - "K Cramps"

CASE #2

- 25 year old with recurrent fibrosarcoma s/p initial resection of gluteal tumor, now with metastases to lungs and paraspinal soft tissues.
- Seen by Palliative team for pain management, titrated to:
  - Methadone 10mg PO q 8 hours
  - Hydromorphone 8mg PO q 3 hours PRN
  - Gabapentin 300mg qAM and 400mg qPM

- On day of planned discharge, notices weakness of lower extremities. Imaging reveals impending cord compression.
- Started on dexamethasone and undergoes cervical and upper thoracic decompressive surgery with fusion.
- Post-op on:
  - Fentanyl 50-100mcg q 1 hour PRN (taking max dose and frequency)
  - Ketamine infusion at 3mcg/kg/min
  - Methadone 10mg PO q 8 hours
  - Acetaminophen 1g PO q 6 hours
  - Gabapentin 300mg TID
  - Lidocaine patch

- Pain is in neck and back, patient felt partially relieved with ketamine.
- Anesthesia/Pain team POD 1 recommends:
  - Switch fentanyl to hydromorphone PCA with 0.5mg q 15 mins PRN.
  - Increase ketamine to 4 mcg/kg/min, can uptitrate to 8 mcg/kg/min to effect.
    - Titrated to 6mcg/kg/min per RN same day

- Next day:
  - Anesthesia recommends increase of ketamine gtt to 8mcg/kg/min as well as increasing hydromorphone PCA dose to 0.6mg q 15 mins PRN.
    - Primary did not increase ketamine rate.
- Following day:
  - Ketamine downtitrated to 3 then tapered off over next few days by Anesthesia, while uptitrating gabapentin.
  - 6 days total on ketamine drip.

CASE #2 QUESTIONS

- What are barriers to ketamine use in your institution? Are there any limitations as to who can order ketamine?
- Why do you think the titration did not follow the recommendations in this case?

CASE #3

- 40 year old with recurrent metastatic angiosarcoma, presenting with recurrent spinal cord compression. Palliative consulted for pain management.
- Based on home regimen and uncontrolled pain, at admission placed on morphine PCA with basal rate 4mg/hr, breakthrough 3mg q 20 mins. Also started on dexamethasone.
- OR for thoracic laminectomy and tumor debulking.

- Post-op started by Anesthesia/Pain team on ketamine infusion 2 mcg/kg/min, morphine PCA continued.
- Two hours later (overnight), pain uncontrolled, on-call Anesthesia/Pain increases ketamine drip rate to 4 mcg/kg/min.
- Two more hours elapse, pain somewhat improved, on-call Anesthesia/Pain increases ketamine to 6 mcg/kg/min.
- During day, pain is improved, ketamine decreased to 2 mcg/kg/min.

- Following day, morphine PCA basal is downtitrated due to sleepiness to 2mg/hr (from 3mg/hr)
- Ketamine still at 2 mcg/kg/min.
- Following day, Anesthesia team recommends stopping ketamine and using primarily morphine PCA.
- Total time on ketamine infusion: 6 days.
- Continued management with morphine PCA and adjuvants, eventually converted to PO opioids.

CASE #3 QUESTIONS

- Was the titration of ketamine appropriate?
- How long do you keep someone on ketamine drip?

POSSIBLE TRIGGERS FOR CONSIDERATION OF KETAMINE

- Gastric outlet obstruction / Malignant obstruction?
- Peritoneal carcinomatosis
  - Limited evidence regarding exact etiology and treatment, but animal model study provides basis for decreased sensitivity to opioids (mu-receptor downregulation)

POSSIBLE TRIGGERS FOR CONSIDERATION OF KETAMINE

- Relative hemodynamic instability
- On ketamine for analgesia and/or pain uncontrolled by opioid, need for palliative sedation

POSSIBLE TRIGGERS FOR CONSIDERATION OF KETAMINE

- Conclusion: all need further study to provide true evidence-based recommendation.
- Of note, opioids have not always been studied carefully (i.e. RCTs) in similar settings.

PRACTICAL OBSTACLES

- Dosing considerations
  - Does your hospital have a protocol?
- Unfamiliarity with ketamine - in particular across providers
  - Provide detailed sign-out and include clear and detailed titration regimen and parameters in notes
- Even when recommend by specialists (Palliative or Anesthesia), recommendation sometimes not followed due to primary team's unfamiliarity with order / order set
  - Institutional policy: who enters the order for ketamine? If primary team, consider offering assistance when placing order.

PRACTICAL OBSTACLES

- Who's available to titrate off hours?
  - Even if parameters given for titration, different providers assuming care off hours may not have same level of comfort and/or not have received complete handoff.
- Miscommunications in dosing regimen due to units used
  - Ensure everybody including nursing on the same page, consider writing dosage regimen in full letters (i.e. micrograms / kg of ideal body weight / hour) - explain that doses we use for analgesia are orders of magnitude less than for sedation.

GETTING OFF KETAMINE

- No direct trial data.
- "The subcutaneous infusion may be stopped abruptly, or tailed off as the PO dose is titrated." (All Gwent Palliative Medicine Consultants Group)

	Indication	**Adult Dosing** (uses Ideal Body Weight unless actual weight < IBW)
IV push	- ED use for trauma/ emergent situation with cardiorespiratory concern with use of opioids	0.25-0.5 mg / kg IBW (to max cumulative 1mg/kg) IV push over 60 seconds Older adults: 0.1mg/kg
IV infusion	Analgesia (onset expected in 10-30 mins)	• Start 1mcg/kg/min unless tolerant to higher doses • Double rate every 15 mins • Max infusion rate 15mcg/ kg/min

	Indication	**Adult Dosing** (uses Ideal Body Weight unless actual weight < IBW)
Subcutaneous infusion	Analgesia Dose reduce opioid at start if possible by 30-50%	• Frail patient start dose: 25-30 mg / 24 hours • Fit patient: 50-100 mg / 24 hours • Max dose ~ 500mg / 24h • Increase rate: • 50-100% q 8 hours if uncontrolled pain • 50-100% daily otherwise

Source: All Gwent Palliative Medicine Consultants Group

PAYING ATTENTION TO UNITS

- 1 mcg/kg/min x IBW 75kg x 60 mins x 24
- 108,000 mcg / day = 108 mg / day

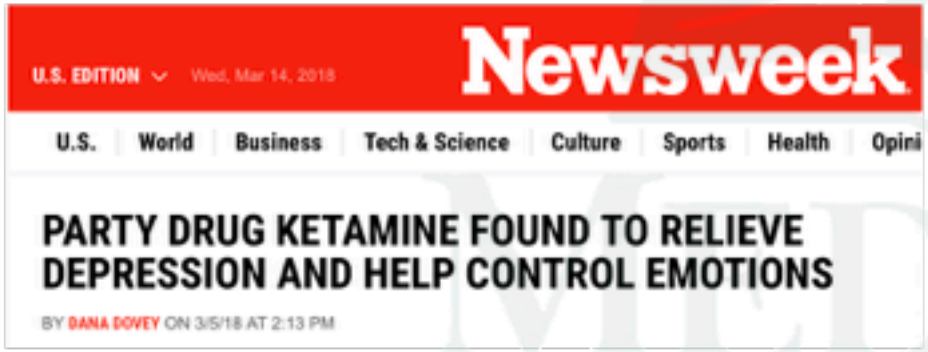
MONITORING WITH KETAMINE GTT

- Monitor pain scores, vitals, sedation (initial risk of oversedation more from opioids if concurrently administered). Suggest frequent checks during first hour, then q 4 hours.
- Dysphoria/hallucinations/nightmares more common earlier in treatment, tolerance does develop. Can be prevented/treated by concurrent benzodiazepine tx. (caution: diazepam may increase ketamine levels).

MONITORING WITH KETAMINE GTT

- Downtitrate if tachycardia or hypertension develops (common threshold is 20-30% increase from baseline).
- Urinary symptoms.
- Note that some experts recommend baseline urinalysis and liver function tests.

KETAMINE IN THE MEDIA



WHY KETAMINE FOR DEPRESSION?

- Current antidepressants:
    - Deficient hypothesis of depression
    - Prolonged onset of action
    - High remission rates
- Identifying intervention that directly address underlying physiology

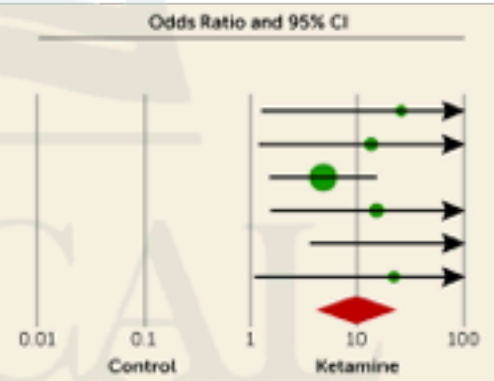
MECHANISM OF ACTION

- Other NMDA channel blocks do not replicate antidepressant effect
    - Ketamine exceeds physiologic capacity of NMDA receptor's magnesium-dependent voltage gating
    - Greater propensity to become trapped within channel
- Ketamine has activity at sigma receptors, actions within dopaminergic and serotonergic systems
- Ketamine-induced synaptogenesis
- Activation of glutamatergic AMPA receptors

THERAPEUTIC RESPONSE IN DEPRESSION

A

Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	26.053	1.359	499.339	2.164	0.030
Lapidus et al. (84)	13.600	1.238	149.455	2.134	0.033
Murrough et al. (87)	4.833	1.578	14.803	2.759	0.006
Sos et al. (91)	15.294	1.610	145.305	2.374	0.018
Zarate et al. (88)	79.545	3.762	1681.833	2.811	0.005
Zarate et al. (86)	22.176	1.133	434.158	2.042	0.041
	9.865	4.366	22.293	5.503	0.000



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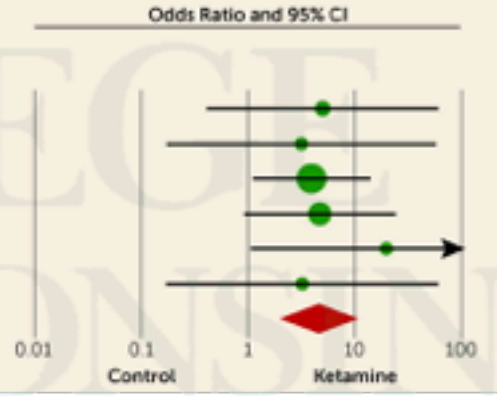
Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	5.000	0.426	58.636	1.281	0.200
Lapidus et al. (84)	3.171	0.179	56.222	0.787	0.431
Murrough et al. (87)	3.937	1.149	13.492	2.181	0.029
Sos et al. (91)	4.706	0.950	23.302	1.898	0.058
Zarate et al. (88)	19.783	1.060	369.109	1.999	0.046
Zarate et al. (86)	3.222	0.176	58.849	0.789	0.430
	4.610	2.076	10.236	3.754	0.000



CONSENSUS STATEMENT

- Patient Selection: Treatment of major depressive episodes without psychotic features; Avoid with history of substance use and psychotic disorders
- Clinician: Clinician with ACLS certification (due to CV risks) and familiarity with behavioral management (risk of emergency behavioral situation with psychotomimetic effects)
- Facility: Capable of ECG, BP, O_2 Saturation, ability to stabilize patient

CONSENSUS STATEMENT

- Dosing for MDD: 0.5 mg/kg per 40 minutes IV, dosed for ideal body weight
- Administration: Intra-procedural monitoring; Immediate post treatment evaluations, assessment, management
- Follow-up/Repeat Infusions: Limited data
- Long-term repeated infusions: Extremely limited data; Known/ suspected risks of cognitive impairment and cystitis

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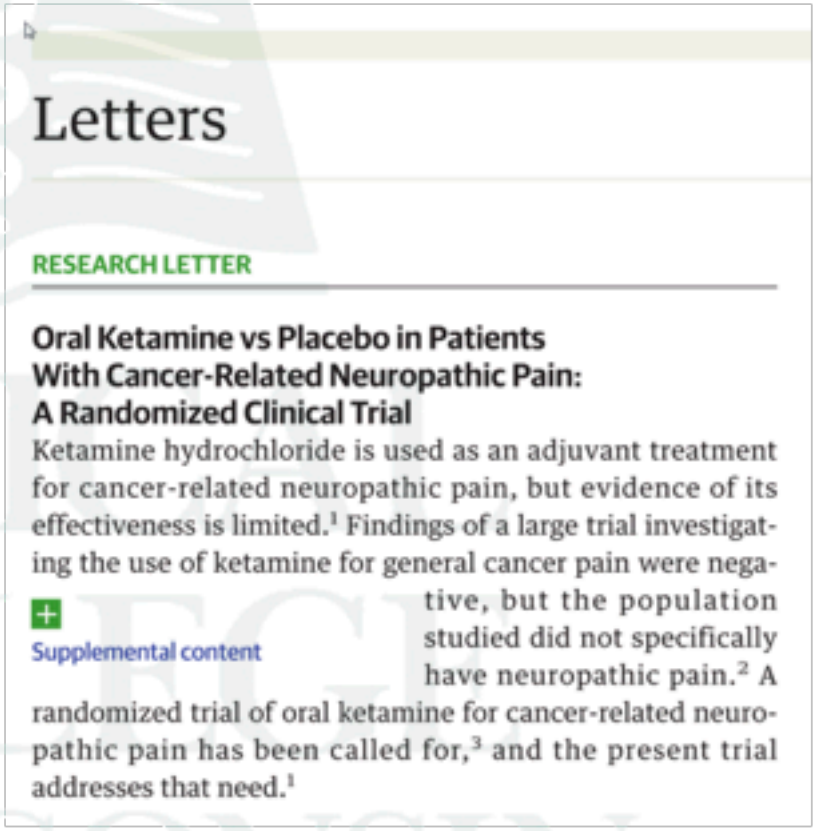
- Ketamine equivalent to placebo for cancer-related neuropathic pain
- Hypothesized that Ketamine may be more helpful in those with central sensitization



Letters

RESEARCH LETTER

Oral Ketamine vs Placebo in Patients With Cancer-Related Neuropathic Pain: A Randomized Clinical Trial

Ketamine hydrochloride is used as an adjuvant treatment for cancer-related neuropathic pain, but evidence of its effectiveness is limited.[1] Findings of a large trial investigating the use of ketamine for general cancer pain were negative, but the population studied did not specifically have neuropathic pain.[2] A randomized trial of oral ketamine for cancer-related neuropathic pain has been called for,[3] and the present trial addresses that need.[1]

Supplemental content

QUESTIONS?

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