OUTPATIENT KETAMINE INFUSIONS FOR REFRACTORY CHRONIC PAIN, A PATIENT INTERVIEW

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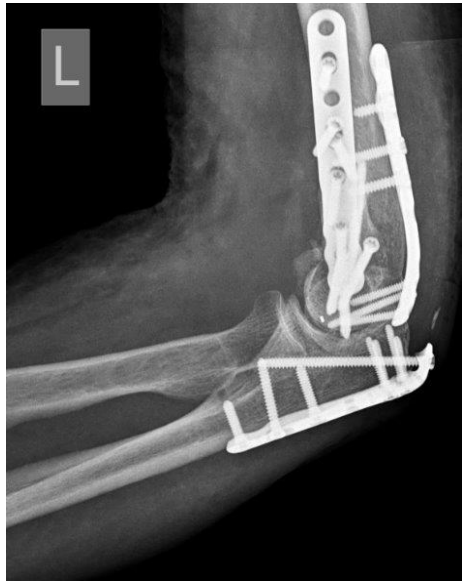
AGENDA

- Introduce Patient
- Treatments over past few years, with commentary from Patient, prior to ketamine
- Review of central + peripheral neuropathic pain syndrome etiologies, treatments
- Review of ketamine for pain
- Ketamine treatment experience + results, per Patient
- Q&A

PATIENT

TREATMENT HISTORY

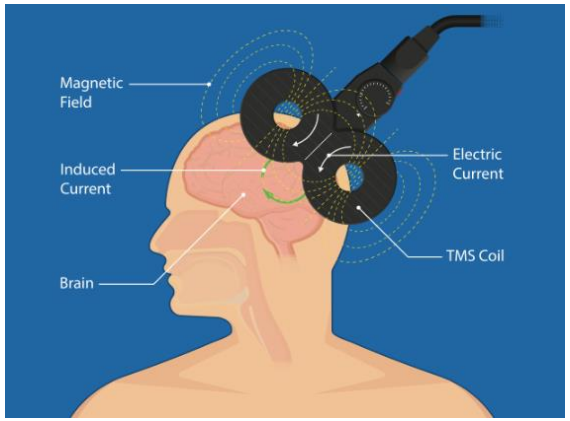
- First meeting in early 2022
- Past medical history: Fibromyalgia, trigeminal neuralgia, depression, and anxiety –all well generally controlled
- Past surgical history: Left arm fracture surgical repair in 2020. Course complicated by ulnar nerve palsy, treated in 2021 with nerve release, tendon transfer.
- How referred to UCSF Pain Medicine?
- Pain experience in 2022?



TREATMENT HISTORY

- MR neurogram: Long segment signal abnormality of the ulnar nerve
- EMG/NCS: Mild ulnar neuropathy
- UCSF ortho: Surgery not certain to help

- Psychiatry, pain psychology (individual, group CBT)



- Medications: Gabapentin, pregabalin, carbamazepine, duloxetine, more
- TMS for pain with Center for Pain Medicine faculty
- Ulnar nerve block with steroid
- Peripheral nerve stimulation, left ulnar nerve

- Benefit from these treatments?

CHRONIC NEUROPATHIC PAIN

- "Chronic neuropathic pain is chronic pain caused by a lesion or disease of the somatosensory nervous system. The pain may be spontaneous or evoked, as an increased response to a painful stimulus (hyperalgesia) or a painful response to a normally nonpainful stimulus (allodynia). "

Narrative Review

PAIN

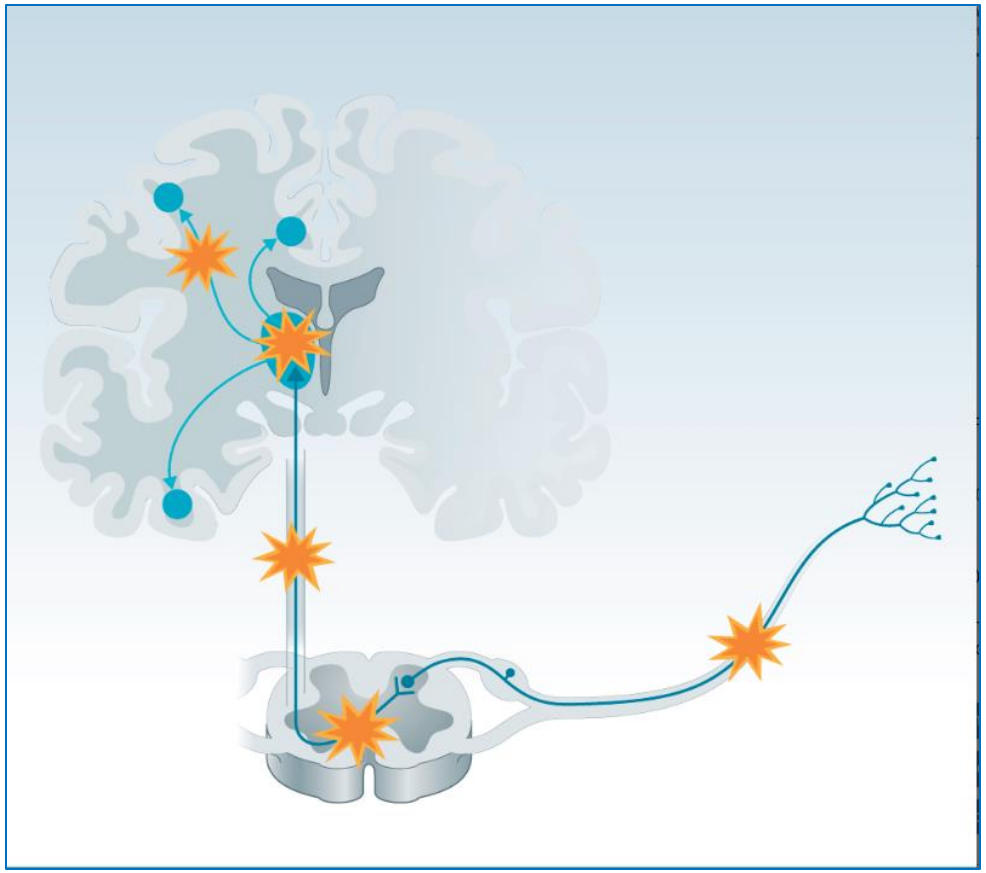
ICD-11

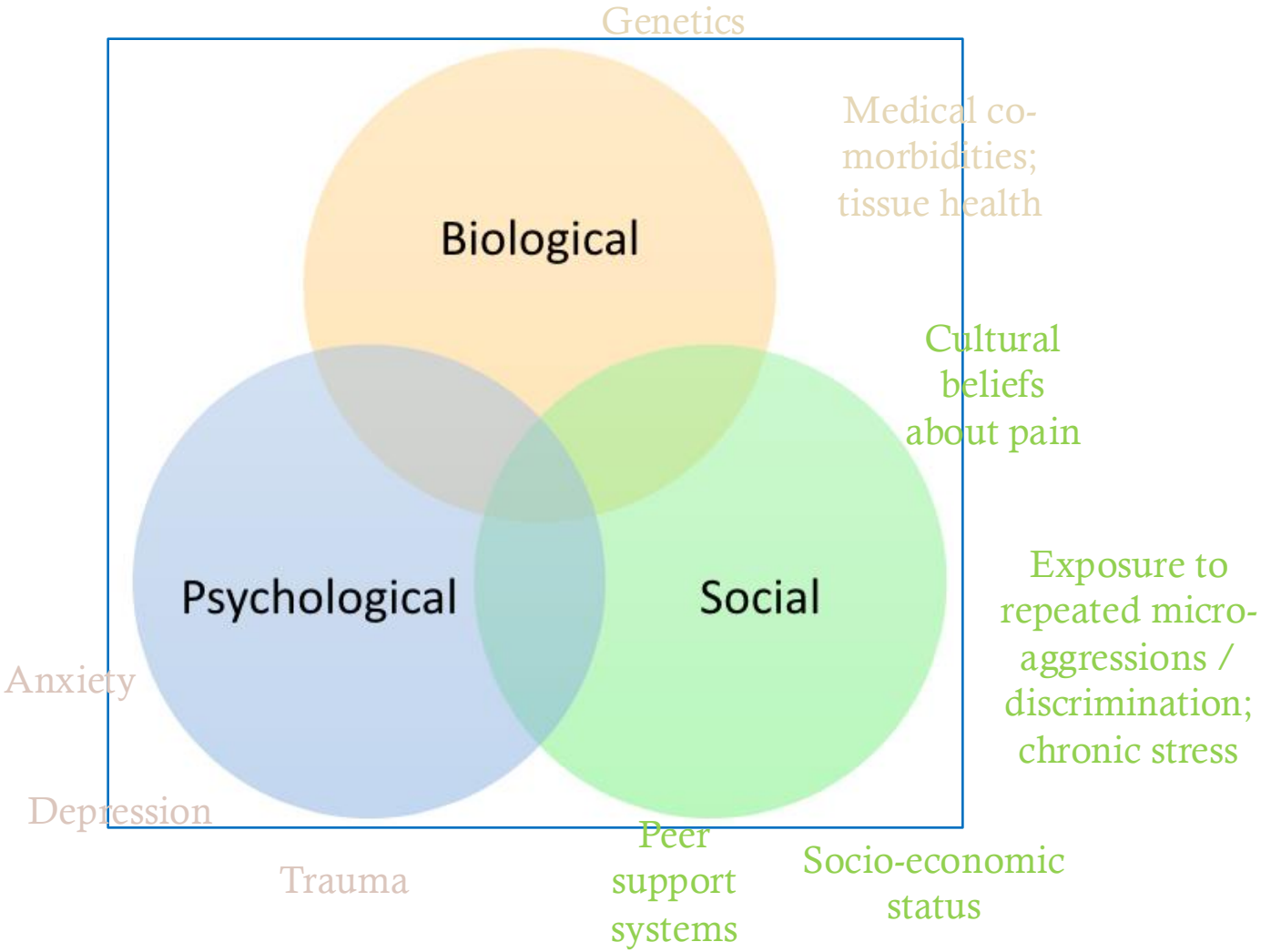
The IASP classification of chronic pain for *ICD-11*: chronic neuropathic pain

Joachim Scholz[a,b], Nanna B. Finnerup[c,d], Nadine Attal[e,f], Qasim Aziz[g], Ralf Baron[h], Michael I. Bennett[i], Rafael Benoliel[j], Milton Cohen[k], Giorgio Cruccu[l], Karen D. Davis[m,n], Stefan Evers[o,p], Michael First[q], Maria Adele Giamberardino[r], Per Hansson[s,t], Stein Kaasa[u,v,w], Beatrice Korwisi[x], Eva Kosek[y], Patricia Lavand'homme[z], Michael Nicholas[aa], Turo Nurmikko[bb], Serge Perrot[cc], Srinivasa N. Raja[dd], Andrew S. C. Rice[ee], Michael C. Rowbotham[ff], Stephan Schug[gg], David M. Simpson[hh], Blair H. Smith[ii], Peter Svensson[jj,kk], Johan W.S. Vlaeyen[ll,mm], Shuu-Jiun Wang[nn,oo], Antonia Barke[x], Winfried Rief[x], Rolf-Detlef Treede[pp,*], Classification Committee of the Neuropathic Pain Special Interest Group (NeuPSIG)

- Chronic neuropathic pain prevalence ranges between 6.9% and 10% of the general population
- When present, neuropathic pain frequently causes major suffering and disability

CHRONIC NEUROPATHIC PAIN





"Many experts consider the distinction between different pain types to be a continuum, rather than discrete classification categories." -ASRA

KETAMINE FOR PAIN

KETAMINE FOR PAIN

CHRONIC AND INTERVENTIONAL PAIN

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‡‡‡*

2018

"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."

KETAMINE FOR PAIN

- "Anesthetic agent": hypnotic, analgesic, amnestic
- Antagonist at phencyclidine binding site at NMDA receptor whose major agonist is excitatory glutamate; ketamine activity --> decrease neuronal activity
- Also, MOR, nicotinic, muscarinic cholinergic, D2 receptors, more

- For pain, depression, seizures, more
- Sympathetic nervous system stimulation, while negative cardiac inotrophic effect
- Neuroplasticitiy thought to relate to NMDA
- Dissociative effect from reduced thalamocortical and increased limbic + hippocampus activity

- **"Resets the CNS"**; reverses central sensitization

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) • Blurry vision or diplopia CV: Tachycardia, hypertension; anxiety	• Unlikely to occur with intraoperative use alone; may occur if used postoperatively • If they occur, discontinuation of infusion often improves symptoms; benzodiazepines or α2 agonists may be effective • Reported incidence 6.2% • Dose-response relationship unclear at subanesthetic doses • 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 • Reported upper incidence 9.8% • Typically presents with elevated liver enzymes • Mechanism may be cholestatic • 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 • At higher doses, serious causes such as elevated intracranial pressure should be considered • Considered a treatment for headaches
Morgan,[190] 2011; Jhang,[191] 2015; Shahani,[192] 2007; Chen,[193] 2011	• Cystitis	• Occurs mostly in ketamine abusers • Typically presents with painful hematuria, dysuria, increased frequency, and pain postmicturition • 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 • 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 • Weak evidence exists in animal studies; unknown effects in humans • Toxicity may be more likely if preservative used but may still occur with preservative-free formulation

KETAMINE FOR PAIN

Different for acute pain or psychiatric

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

Category	Contraindication/Precaution "Relative"
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

KETAMINE FOR PAIN

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

KETAMINE FOR PAIN

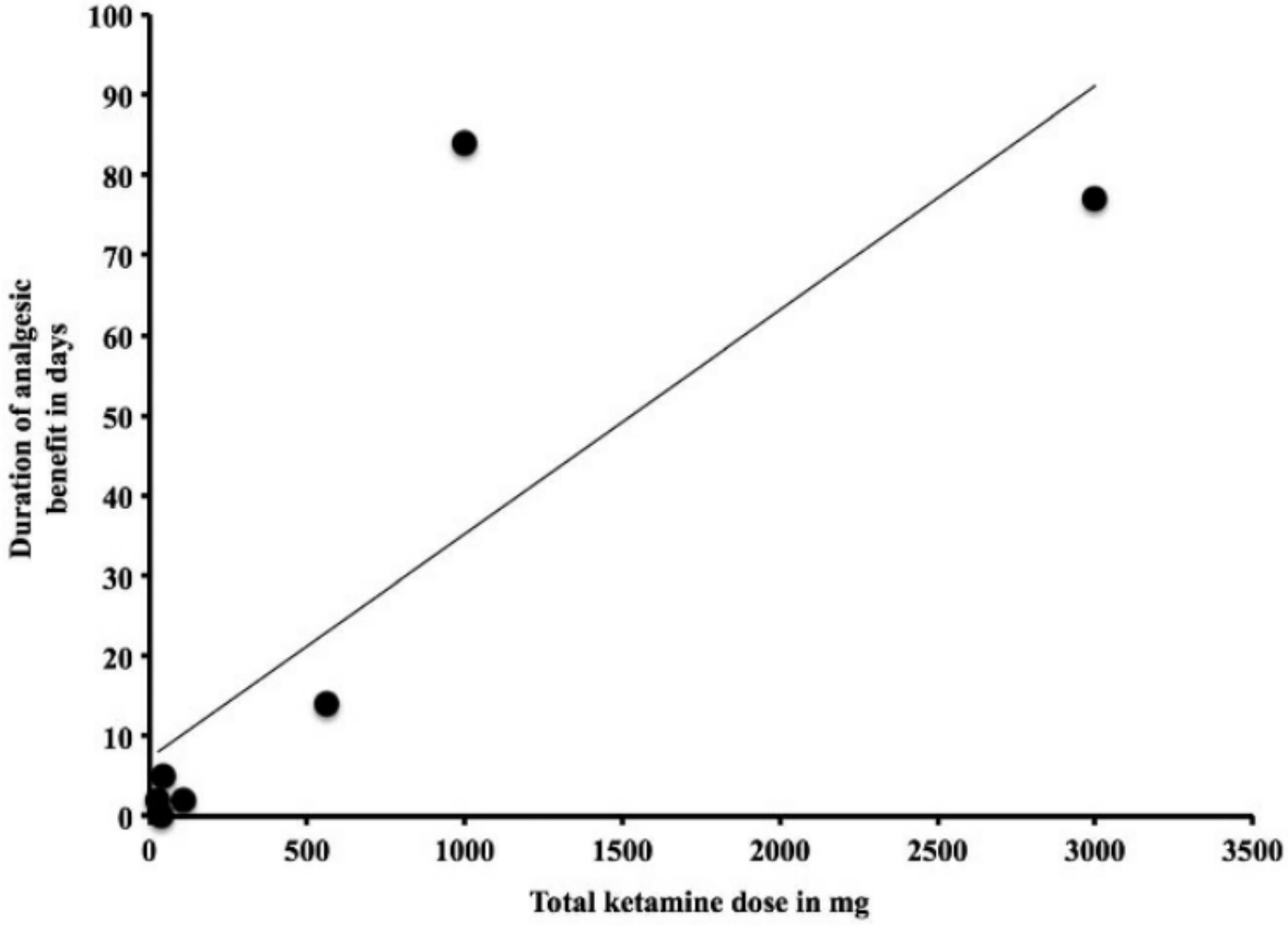


FIGURE 1. Graphical depiction of the relationship between ketamine dose and duration of analgesic benefit in randomized placebo-controlled trials that evaluated IV ketamine for chronic pain with a minimum of 48 hours' follow-up.[117,123,155,160–162,164] A trend line is been plotted to indicate the nature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

KETAMINE FOR PAIN

TREATMENT HISTORY

- Summer 2023: Ketamine gtt in clinic. ~60mg / 2 hours, with mild sedation. What was your experience?

- Summer 2024: Clinic visit. Noted improvement in neuropathic arm pain and trigeminal nerve pain, NRS 4/10 --> 1-2/10, tapered off carbamazepine. Relief was >6 months

- Fall 2025: Ketamine gtt in clinic. ~60mg / 2 hours., with some but less experience than the first infusion. What was your experience?

Q&A

With me and Patient.