Treatment of MH Disorders with Ketamine in AKUHN

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Ketamine, A Breakthrough?

"Ketamine is that breakthrough in mental health. It immediately improves mood & regenerates lost neural pathways while creating an opening for therapeutic discussions to take hold. It's a fast-acting relief, with long-lasting healing. It's safe, FDA-approved, and about to turn the field of MH on its head"

The Ketamine Breakthrough (Dr. Mike Dow & Ronan Levy)

A Short History of Ketamine

- **FDA** approved as a general anesthetic in 1970
- Safe anesthetic & analgesic agent for adults & children: on the WHO Essential Drugs List in 1985
- 1st heard of its indication for TRD in 2015
- FDA approval of esketamine (Spravato) in 2019
- **2019: Commencement of ketamine infusion for MH Disorders in AKUHN**

AKUHN Qualifications for Non-Anesthesiologist Clinicians Involved with Procedural Sedation

- Doctors who have **Sedation Training & ACLS Certification**
- Nurses with **critical care training, Sedation Training, ACLS Certification**

Qualifications for Clinicians Involved with Ketamine Sedation

- **APA Consensus : Doctors who deliver ketamine should be prepared to deal both with clinical & psychiatric emergencies**
  - Should be familiar with procedures to manage potential **cardiorespiratory** events & should have ACLS certification.

Gustavo H. Vasquez, Carlos A. Zarate, et al.

Ketamine for Treatment: Neurobiology and Applications

Ketamine Sessions & Patients in AKUHN: 2019-2023

Year	No. of Sessions	No. of Patients*
2019	14	09
2020	88	32
2021	229	98
2022	221	56
2023	101	35
Totals	**653**	**230**

*** TRD/Suicidal**

Neuropsychiatric Conditions In Which Ketamine May Be Useful

- **TRD, Severe depression with suicidality**
- **Severe GAD/Social Anxiety**
- Severe OCD
- **PTSD**
- **Substance use disorders**
- Eating disorders
- **Migraine headache**

Ketamine Mechanisms of Action

- Antagonism of NMDAR on GABA-mediated (GABA-ergic) inhibitory interneurons causing disinhibition of downstream glutamatergic neurons, which results in increased glutamatergic activity in pyramidal neurons in the PFC or **"glutamate burst"**
  - *This can be inhibited by benzodiazepines, Z-drugs & lamotrigine*
- The glutamate burst causes an increase in brain-derived neurotrophic factor (**BDNF**), which is important for both dendrite growth or synaptogenesis – neuroplasticity
- Opioidergic agonist activity via μ, k, and σ, opioid receptors (*antagonized by **naltrexone**)*
- Monoamine agonist activity at Dopamine D_2 & Serotonin $5HT_2$ receptors and norepinephrine receptors & **antagonists** at cholinergic receptors

Ketamine for Depression

*In summary, we can view a depressive illness as a disease of disconnection at a **personal** & **social** level & even more profoundly at the **cellular** level. Ketamine, through its actions- on the glutamate system, induces changes in both the quality & quantity of connections between neurons, and this in turn improves the function of critical brain circuits impaired by depression, thus freeing people to deal with their problems more effectively.*

Dr. Stephen J. Hyde (Ketamine for Depression)

Ketamine Efficacy

- Response rates for ketamine are approximately 60%-70%

Gustavo H. Vasquez, Carlos A. Zarate, et al

Ketamine for Treatment -Resistant Depression: Neurobiology & Applications

Expected Duration of Effect from Multiples of the Ketamine Dose

Non-overlapping doses of 0.5mg/kg over 40 min.	Expected duration of freedom from depression
1	10-12 days
2	3 weeks
4	6 weeks
6	12 weeks

Robert C. Hiemstra MD
KISSD: Ketamine Intramuscular Stepped System for Depression

Racemic Ketamine Isomers & Efficacy in Depression

- Racemic Ketamine is a mixture of both S-ketamine (**esketamine**) & R-ketamine (**Arketamine)**
- **Spravato** (esketamine), is the intranasal form of ketamine that received FDA approval for TRD IN 2019, it has greater anethetic, analgesic, & sedative effects
- **Arketamine** has greater & longer-lasting, rapid antidepressant effects in animal models of depression
- A 2021 review & analysis of 24 randomized controlled trials showed that racemic ketamine was more effective than Spravato

Journal of Affective Disorders 278 (2021): 542-555

Ketamine Pharmacokinetics

- Bioavailability varies with the route of administration: IV (100%), IM (93%), Intranasal (50%) **Sublingual (30%), Oral (20%).**
- Ketamine is mainly administered via IV. Other routes include IM, lozenges, nasal spray, rectal, subcutaneous
  - *Oral & IM administration allows for a broader spectrum of dosing & may allow concurrent psychotherapy*
- **The α-distribution phase half-life varies from 10-20 minutes, while the ß-elimination phase is varies from 1.5-2.5 h**

Ketamine Pharmacokinetics

- Ketamine is metabolized in the liver to **norketamine & hydroxynorketamine (HNK):** both are active metabolites
- Metabolism is via multiple cytochrome P450 isoforms especially CYP3A4: Ketamine causes **auto-induction** of these isoforms - chronic administration may require higher doses to achieve a therapeutic effect
- **Liver impairment** is an absolute contraindication

Ketamine Primary Adverse Events

- **Apnea, glottic spasm, hypertension (***these 3 can be fatal***) & emergence reactions**
- May occur with more rapid administration (especially IV) or high doses (IV/IM)
- **One near -fatal incidence in AKUHN** (June 2019)

Ketamine – Induced Hypertension

- Ketamine –induced hypertension usual during IV infusion and following IM injection (dose-dependent)
  - Systolic & diastolic BP peaks 10-50% above the baseline levels
- Prevention of extreme BP rise: **Clonidine, Midazolam, or Labetalol**
- **One near-fatal incidence in AKUHN (Feb 2023)**

Mode of Ketamine Administration & Adverse Events

- **IM route does not allow a rapid rise in ketamine blood levels**

- *The IM route is like a **speed-governor** on a vehicle: the drug first enters a muscle, where it is **slowed** as it diffuses through the tissue before trickling into the bloodstream with little of the shock of the concentration gradient generated by the **"open firehose" of an IV ketamine line***

Robert C. Hiemstra MD

KISSD: Ketamine Intramuscular Stepped System for Depression

The Ketamine Emergence (Psychedelic) Reactions

- **Positive** (euphoria/spiritual experience in the context of a dissociative episode)
- **Negative** (panic attacks, dysphoria): ketamine blood level dependent (**midazolam IV/IM** helps)
- **Bad trip or freak-outs** in the context dissociative episodes: **going into a no-return dark hole**

Other Common Ketamine Side Effects

Other common side effects

- Nausea & vomiting (NPO for 4-6h, **Premedications:** ondansetron (4-8mg) SL or IV, promethazine IV/PO
- Dizziness (**falls risk** up 4 hours after ketamine)
- Visual hallucinations of people, heightened **colors**
- Blurred vision (**anticholinergic)** double-vision **photophobia, phonophobia**
- **Tachycardia** (may need **clonidine** for control)
- Headache

Ulcerative Cystitis (Ketamine bladder syndrome)

- May occur after chronic ketamine use - ketamine drug abusers
- Painful hematuria
- Urinary urgency & urge incontinence

The Ketamine for Depression Protocol in AKUHN

Patient eligibility

- Patients, who are American Society of Anesthesiologists ASA 1 category, and maybe ASA 2
- Patients with moderate to severe depressive symptoms who have failed to respond to at least two adequate antidepressant trials.
- Depressed patients with acute suicidal ideation, deemed by the psychiatrist to be at high risk for suicide.

American Society of Anesthesiologists Physical Status (ASA PS) Classification System

Classification	Description
ASA 1	Healthy patients
ASA 2	Mild to moderate systemic disease caused by the surgical condition or by other pathological processes, and medically well controlled
ASA 3	Severe disease process which limits activity but is not incapacitating
ASA 4	Severe incapacitating disease process that is a constant threat to life
ASA 5	Moribund patient not expected to survive 24 hours with or without an operation
ASA 6	Declared brain-dead patient whose organs are being removed for donor purposes

The Ketamine for Depression Protocol in AKUHN

Exclusion Criteria

- Active psychotic symptoms, manic symptoms, (***or a history of a primary psychotic disorder?***
- Known hypersensitivity to Ketamine.
- **Uncontrolled hypertension**
- Pregnant woman or breastfeeding mother
- **Ischemic heart disease**
- **Cardiac arrhythmias**
- **Liver impairment**
- **Hyperthyroidism**

Baseline Investigations Before Ketamine Infusion / Injection Treatment

- CBC
- U/E, Cr
- LFTs
- TSH
- Urinalysis / UDS
- ECG (where indicated)

The Ketamine Protocol for Depression in AKUHN

Personnel

- Psychiatrist with **ACLS certification** and **Sedation training**
- Registered Nurse (RN) with certifications in **ACLS, Sedation** and **Critical Care Training.**

The Ketamine for Depression Protocol in AKUHN

Consent

- A patient or guardian/parent/spouse, **with capacity**, will give consent, following psychoeducation regarding the **benefits** and **potential common side effects** including nausea, drowsiness, dizziness, dissociative symptoms, hallucinations, tachycardia and increased BP.
- For patients under 18 years of age, a parent or guardian will give consent

The Ketamine for Depression Protocol in AKUHN

Location

- **Critical care units** including **Cath Lab,** HDU, ICU,CCU
- Initial ketamine dose is 0.5mg/kg
- The total ketamine calculated at 0.5mg/kg is infused in 50ml normal saline over 40min with continuous monitoring

OR

- Given IM in 2 doses, 30 min. apart, with continuous monitoring

The Ketamine for Depression Protocol in AKUHN

Patient monitoring is by:

- The **psychiatrist** (or designee) & **critical care nurse**
- All patients are connected to a critical care monitor showing **ECG, heart rate**, **blood pressure**, **respiratory rate** and **oxygen saturation**
- The psychiatrist (or designee) supervising Ketamine infusion must be readily available for the entire duration of the procedure in case of **abnormalities (HTN, tachycardia, decreased SPO2, agitation (emergence reactions).**

Post Ketamine Infusion / Injection Patient Monitoring

The patient must be monitored until recommended recovery criteria are met:

- Vital signs and pulse oximetry within normal limits
- The patient is easily aroused, oriented, with appropriate speech
- In-patients are transferred back to their ward
- Day care patients are discharged home in the company of a relative or friend.
- No physical activity including driving for up 6 hours after the ketamine

In Conclusion:
Will Ketamine Go Through The Seige Cycle?

- Seige Cycle was coined by Dutch medical historians Snelders, Kaplan, and Pieters to describe the dynamic phases of the career of psychiatric drugs.
- Max Seige, German Psychiatrist, proposed the concept that psychotropic drugs have a cyclical livelihood: ***"initial enthusiasm & therapeutic optimism; subsequent negative appraisal; and finally, limited use."***
- Will ketamine be a victim of this cycle?

Time Will Tell