Ketamine and the Evolving Psychopharmacologic Pipeline for Depression

A Carlat Webinar

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Conflicts and Disclosures

None

Learning Objectives

After the webinar, clinicians should:

1. Understand ketamine and esketamine's unique history, antidepressant properties, hypothesized mechanism of action, and potential side effects when used as an antidepressant

2. Demonstrate proficiency in evidence-based protocols, monitoring techniques, risk mitigation strategies, and appreciate select clinical and logistical elements crucial for effective care delivery

3. Recognize one example of an agent from the evolving pipeline under investigation in anticipation of related new interventions

Disease Burden

- MDD is the leading cause of disability worldwide, with suicide growing at an alarming pace.
- From 1999 through 2018, the age-adjusted suicide rate in the United States increased by 35%.

Hedegaard H, Curtin SC, Warner M. Increase in Suicide Mortality in the United States, 1999-2018. NCHS Data Brief. 2020;(362):1-8.

Treatment Stasis

I. The monoamine hypothesis of depression

For 3 decades, drug development resulted in agents thought to primarily modulate 3 neurotransmitters: Dopamine, Norepinephrine, Serotonin.

II. Limited novelty since the introduction of SSRIs

Many of these drugs—the SSRIs and SNRIs—are molecular permutations of each other, with few agents engaging novel mechanisms, and most requiring greater than 6 weeks to elicit meaningful clinical response.

Key point: new agents / interventions that leverage novel mechanisms and achieve efficacy rapidly are needed.

What Are Ketamine and Esketamine?

- Ketamine is a synthetic, racemic mixture created in an effort to produce a General Anesthetic
- Esketamine is a synthetic compound that is exclusively of the “s” enantiomer. It is the sole ketamine that carries FDA approval for psychiatric indications
- Esketamine was approved with a specific dosing and administration schedule and requires participation in a risk mitigation system (REMS)

Ketamine Historical Context

1960s: Calvin Stevens synthesizes Cl-581 in a Park Davis Laboratory

1964: Domino and Corssen study anesthetic effects (prison population) effects

1970: FDA approved for anesthetic use

Conflict zones and veterinary medicine use rises

1985: Added to WHO Essential Medication list

2017: *JAMA* Consensus Statement

2018: Esketamine FDA approved as augmentiation in the treatment of treatment-resistant major depressive disorder

Wei Y et al, Pharmacol Biochem Behav 2020;190:172870
Sancora G et al, JAMA Psychiatry 2017;74:399-405

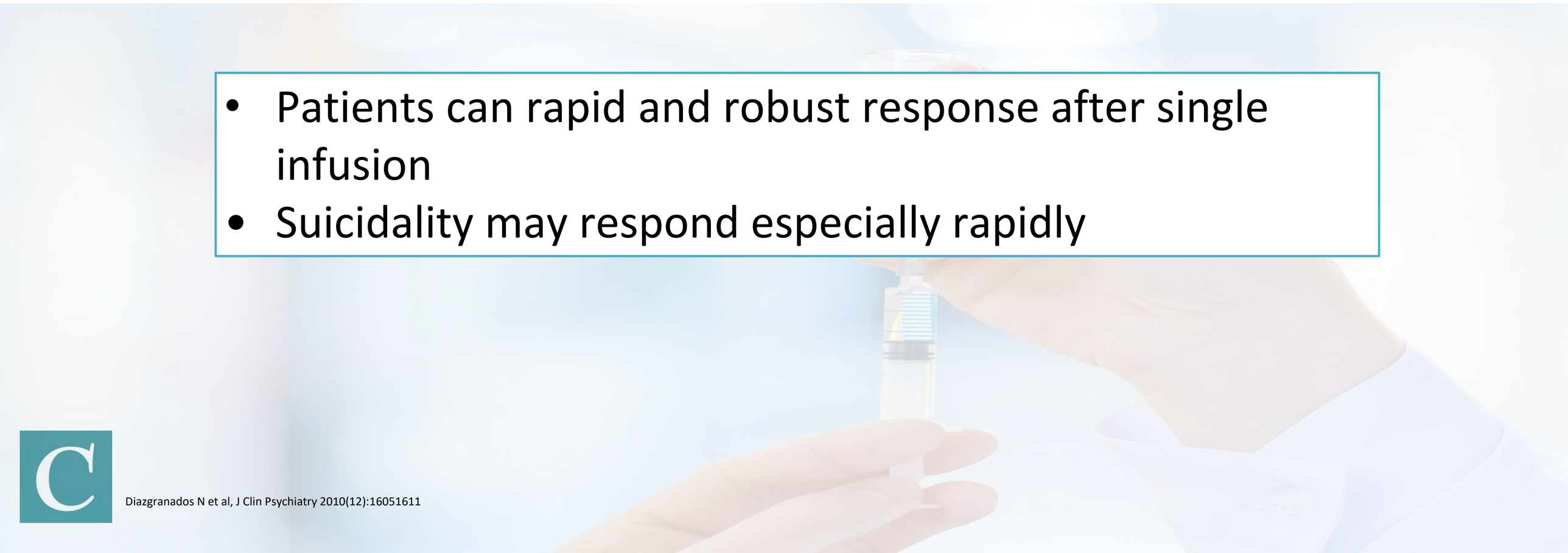
The Evidence Base: Early Interest

- Ketamine can decrease depressive symptoms within hours of administration instead of weeks
- A single infusion may only yield a few days of response

Berman RM et al, *Biol Psychiatry* 2000;47(4):351-354

The Early Evidence Base, 2000 and forward: Berman, Zarate and Diazgranados and others

- Patients can rapid and robust response after single infusion
- Suicidality may respond especially rapidly



Diazgranados N et al, J Clin Psychiatry 2010(12):16051611

The Evidence Base: The Ionesco Study (2016)

- Repeating infusion can yield a more sustained response
- The decrease in suicidal ideation was observed for at least three months after final infusion in some patients.

Ionesco et al, J Clinical Psychiatry 2016;77; 6.
See also Vande Voort et al, J. Affective Disorders 208 (2016) 300.

The Mechanism of Action:

Many receptor and second messenger cascades have been implicated:

N-methyl-D-aspartate (NMDA) glutamate receptor antagonism

- AMPA and mTOR
- BDNF: Brain Derived Neurotrophic Factor
- eEF2: Inhibiting eEF2 increases BDNF
- IGF-1: Insulin-like Growth Factor 1

Li et al, Science 2010;329(5994):959-964
Dwyer JM and Duman RS, Biol Psychiatry 2013;73(12):1189-1198
Drewniany E et al, J Clin Pharm Ther 2014;40(2):125-130

The Mechanism of Action (cont'd)

Of key importance in the antidepressant response:

- Glutamate regulation ("glutaminergic surge")
- Neuroplasticy vs Synaptogenesis

Dwyer JM and Duman RS. 2013 Jun 15;73(12):1189-1198

Patients may experience the following side effects during treatment:

- Transient increase in blood pressure and heart rate
- Nausea/vomiting
- Headache
- Dizziness / Vertigo
- Dissociation
- Sedation
- Anxiety, restlessness, or disorientation
- Loss of sense of time
- Difficulty with word recall, slurred speech

Potential Adverse Events and Toxicities

Liver / hepatobiliary injuries

Transaminitis

Ulcerative or interstitial cystitis

Urinary tract / kidney

Cognitive impairment

Substance Abuse

Zhu W et al, Neurosci Bull 2016;32(6):557-564

Esketamine and Ketamine: Key Distinction in Practice Settings

Esketamine is approved for trMDD and SI in the context of depression.

Racemic ketamine does not have a psychiatric FDA approval.

Esketamine and Ketamine: Key Distinctio in Practice Settings (cont'd)

Cost:

Esketamine: active patent

Racemic ketamine: off-patent

Hence, racemic in theory can be less costly

Esketamine and Ketamine: Key Distinction in Practice Settings (cont'd)

Logistics / Oversight

-Racemic ketamine protocols widely vary; there is concern for insufficient oversight and for non-evidence-based uses.

-Esketamine is administered through a specific protocol with two dose options at established time points. Administration is monitored via REMS.

Ketamine 2.0: Emerging Pipeline Therapie

Psilocybin is one example of a “pipeline” agent actively being studied for its anti-depressant potential (GAD, OCD, EtOH Dep, MDD among potential indications)

Psilocybin carries “Breakthrough Therapy” designation from the FDA

https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy

Ketamine 2.0: Emerging Pipeline Therapie

Psilocybin: Example of Related Pipeline Agent

Small sale feasibility study (response rate = 67% one week after administration)

7 of 8 patients met criteria for “Remission”

58% of patients maintained Response status for 3 months

Carhart-Harris et al, Lancet Psychiatry 2016;3(7):619-627

Psilocybin: Example of Pipeline Agent

Initial aggregate data and consensus suggest that psilocybin and other next-generation agents, esp when paired with psychotherapy, may achieve robust antidepressant effects with less frequent dosing.