Ketamine for Unipolar and Bipolar Depression

Christoph Kraus
Outline

Pharmacology

Rapid Acting Antidepressant Efficacy

Novel Antidepressant Mechanisms & Insights into Glutamate in Mood Disorders

Indication, Safety Profile, Clinical Application

Paradigm Shifting Properties
Ketamine in Medicine

- **Anesthesiology**
  - Narcosis Start i.v. 1-4.5 mg/kg KG, maintenance: 1-2mg/min
  - Used in children/ER surgeries

- **Pain Therapy**
  - p.o., i.n., i.v., 0.5-1 mg/kg KG

- **Psychiatry**
  - Dissociative antidepressant: i.v., i.n. (0.5 mg/kg KG)

- **Pharmacocinetics**
  - CYP3A4 Conjugation to Hydroxynorketamine, Norketamine, Dehydronorketamine, Hydroxyketamine, and Hydroxynorketamine (HNK)
  - Renal Elimination, $T_{1/2}=80-180$ min
Pharmacology

- Phencyclidin derivative
- non-competitive antagonist of NMDA receptors (ionotrop, Na/Ca, K), phencyclidin-binding Site
- Moderate opioid affinity
- Weak inhibitor of monoamine transporter (SERT)
- GABA-A, D2, Ach, Sigma, and others

en.wikipedia.org/wiki/Ketamine#Pharmacodynamics

Zhou, et al., 2016
Ketamine – Serotonin Transporter Occupancy

- No significant differences between Ket>Plac (a)
- KET plasma levels are correlated with occupancy

Spies, et al., 2017
Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal
Meta-analyses

McGirr et al, 2014; Coyle et al, 2015, Newport et al, 2015 , Caddy et al, 2015 (Cochrane)
Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in TRD

Daly et al., 2017

FDA–Approved for TRD on March 4th, 2019
# Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in TRD

## Table 2. Response and Remission Rates for Participants Who Completed the OL and Follow-up Phases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo/Placebo/OL Esketamine (n = 10)</th>
<th>Placebo/Esketamine/OL Esketamine (n = 20)</th>
<th>Esketamine/Esketamine/OL Esketamine (n = 27)</th>
<th>Total (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response Rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OL end point, day 74, No.</td>
<td>6</td>
<td>10</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>≥50% Improvement, No. (%)</td>
<td>6 (100)</td>
<td>5 (50)</td>
<td>11 (61)</td>
<td>22 (65)</td>
</tr>
<tr>
<td>Week 8 (follow-up), No.</td>
<td>7</td>
<td>12</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>≥50% Improvement, No. (%)</td>
<td>5 (71)</td>
<td>3 (25)</td>
<td>15 (68)</td>
<td>23 (56)</td>
</tr>
<tr>
<td><strong>Remission Rate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OL end point, day 74, No.</td>
<td>6</td>
<td>10</td>
<td>18</td>
<td>34</td>
</tr>
<tr>
<td>No, No. (%)</td>
<td>4 (67)</td>
<td>6 (60)</td>
<td>13 (72)</td>
<td>23 (68)</td>
</tr>
<tr>
<td>Yes, No. (%)</td>
<td>2 (33)</td>
<td>4 (40)</td>
<td>5 (28)</td>
<td>11 (32)</td>
</tr>
<tr>
<td>Week 8 (follow-up), No.</td>
<td>7</td>
<td>12</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>No, No. (%)</td>
<td>3 (43)</td>
<td>9 (75)</td>
<td>12 (55)</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Yes, No. (%)</td>
<td>4 (57)</td>
<td>3 (25)</td>
<td>10 (46)</td>
<td>17 (42)</td>
</tr>
</tbody>
</table>

Daly et al., JAMA Psy 2017
Ketamine for „Treatment Resistant Depression“

FDA – Approved for TRD on March 4th 2019

<table>
<thead>
<tr>
<th>SPRAVATO™ (esketamine) nasal spray, CIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1: Recommended Dosage for SPRAVATO</td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td><strong>Induction Phase</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Maintenance Phase</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.</td>
</tr>
</tbody>
</table>
Glutamate (Glu)

Synthesized in glia cells

60% of all Neurons express Glu

Most important excitatory neurotransmitter

Nearly all brain functions involved

Specifically important for: synaptic homeostasis

Motor projection pathways: basal ganglia and premotor cortex

Hippocampus and prefrontal cortex: cognitive functions
Depression: Glutamate-GABA Dysbalance

Modified from Wieronska & Pilic, Neurochem Int 2009

- **Glutamate decrease** leads to Depression
- **Glutamate increase** to Treatment*
- **GABA decrease** to Treatment**
- **GABA increase** to Depression

*Glutamate-GABA excitatory inhibitory balance with glutamatergic modulators
  *prototype: Ketamine, ** prototype: pregnenolone
Glutamate Receptors

Ion channel-associated

**Ionotrophic (iGluR)**

- NMDA
  - NR1 (A,B,C,D)
  - NR2 (A,B,C,D)
  - NR3 (A,B)
- AMPA
  - GluR1
  - GluR2
  - GluR3
  - GluR4
- Kainate
  - KA (1,2)
  - GluR5
  - GluR6
  - GluR7

**Fast excitatory**

G protein-coupled

**Metabotropic (mGluR)**

- Group I
  - mGluR1
  - mGluR5
- Group II
  - mGluR2
  - mGluR3
- Group III
  - mGluR4
  - mGluR6
  - mGluR7
  - mGluR8

**Slow excitatory**

**Slow inhibitory**
• Disinhibition of GABA-ergic inhibitory interneurons
• Rapid BDNF release
• Inhibition of lateral habenula (LHb) neurons
• Activation of mammalian target of rapamycin complex 1 (mTORC1)
• AMPA – Activation (by active metabolite HNK)
A. Major Depressive Disorder

B. Healthy Control

Nugent, et al MolPsy 2017
Ketamine vs. Placebo in HC

Average BOLD response across all subjects

BOLD response [a.u.]

0 60

Time [min]

Ketamine
Placebo

Hoflich et al, Int J Neuropsychopharmacol. 2015

T = 3.39-10
k = 591 voxel
p<0.05 FWE
Global Brain Connectivity Reduction

After Ketamine

middle cingulate, $z=4.7$, $p<0.05$, Type I corrected

Kraus et al, unpublished

Anticevic Lab
medicine.yale.edu/lab/anticevic/

Ours
Adverse Events of Ketamine-Infusion

Kraus et al., 2017; Data from Morrough et al., 2013
### Reported Lifetime Use of Ketamine and Related Drugs

<table>
<thead>
<tr>
<th></th>
<th>12 or older</th>
<th>12-17</th>
<th>18 or older</th>
<th>18-25</th>
<th>26 or older</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ketamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reporting lifetime use</td>
<td>1.3</td>
<td>0.2</td>
<td>1.4</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Estimated number (thousands)</td>
<td>3463.0</td>
<td>46.0</td>
<td>3417.0</td>
<td>632.0</td>
<td>2785.0</td>
</tr>
<tr>
<td><strong>Ecstasy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reporting lifetime use</td>
<td>7.0</td>
<td>1.0</td>
<td>7.7</td>
<td>12.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Estimated number (thousands)</td>
<td>19173.0</td>
<td>257.0</td>
<td>18915.0</td>
<td>4105.0</td>
<td>14811.0</td>
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<tr>
<td><strong>LSD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reporting lifetime use</td>
<td>9.6</td>
<td>1.5</td>
<td>10.4</td>
<td>9.1</td>
<td>10.6</td>
</tr>
<tr>
<td>Estimated number (thousands)</td>
<td>26069.0</td>
<td>364.0</td>
<td>25705.0</td>
<td>3125.0</td>
<td>22581.0</td>
</tr>
</tbody>
</table>
Ketamine Treatment Algorithm

1. Unipolar or bipolar treatment-resistant depression
   - Obtain patient history
   - Physical examination
   - Routine laboratory tests
   - Urine test strip
   - Electrocardiogram (ECG)

2. Quantify baseline severity (MADRS, HDRS or BDI)

3. Severe illness and/or suicidal patient, requires rapid response?
   - No
     - No response to guideline-recommended TRD treatments, e.g. augmentation or ECT?
       - No → Guideline-based care
       - Yes → Consider ketamine treatment

4. Yes → Consider ketamine treatment

Kraus et al., IJNP 2017
Stage 1 – monotherapy / dose escalation
- SERT, NET, DAT reuptake inhibitors – multiple
- Mirtazapine
- Amitriptyline
- Vortioxetine

Stage 2 – augmentation / switch
- Augmentation, (quetiapine, olanzapine, Aripiprazole, Lithium)
- Combination - complementary mechanisms
- Switch – reuptake inhibitors
- ECT / Ketamine in severe MDD

Stage 3
- Tranylcypromine
- ECT

Stage 4 – experimental
- Repetition of previous stages
- Experimental treatments (DBS)
- Augmentation (buprenorphine,...)
- Consider clinical trials for novel substances

Sequential Treatment Optimization Scheme

Stage 1
- Monotherapy
- Dose Escalation

Stage 2
- Augmentation Switch

Stage 3
- Third Stage

Stage 4
- Repetition Experimental
- Remission
- Response
- worse response

Kraus, et al., TranslPsy 2019
Start Illness Specific Psychotherapy
Evaluate Initial Diagnosis
Check Medication Interaction
Pharmacogenomic Testing (CYP450)
Consider Pseudo-resistance
Reduce Ongoing Stressors
Treat Comorbidities
Reduce Side Effects
Check Dose and Duration of Trial

Strategies for Patients Without Improvement Despite State of the Art Therapy

Kraus, Kadriu, Lanzenberger, Zarate, Kasper: Transl Psy 2019
Paradigm Shifts in Clinical Treatment and Basic Science of Mood Disorders

Introducing Rapid-acting Antidepressant Mechanisms

Stimulating Suicide Research

Opening the Field for Hallucinogens

Stimulating Basic Research and Translational Approaches

May Enable Subgroup Stratification (TRD) & Staging
<table>
<thead>
<tr>
<th>Compound</th>
<th>Primary Outcome</th>
<th>Phase</th>
<th>Mechanism</th>
<th>#N</th>
<th>Results</th>
<th>Dosages</th>
<th>Rapid acting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glutamatergic Modulatory Treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-CI-KYN (AV-101)</td>
<td>HDRS</td>
<td>II</td>
<td>NMDAR Glycine Site Partial Agonists</td>
<td>25</td>
<td>Negative</td>
<td>1,080mg or 1,440mg daily</td>
<td>N</td>
</tr>
<tr>
<td>Esketamine</td>
<td>MADRS</td>
<td>III</td>
<td>NMDAR antagonist</td>
<td>30</td>
<td>Positive</td>
<td>0.20 mg/kg and 0.40 mg/kg IV</td>
<td>Y</td>
</tr>
<tr>
<td>Ketamine</td>
<td>HDRS</td>
<td>IV</td>
<td>NMDAR antagonist</td>
<td>99</td>
<td>Positive</td>
<td>0.1, 0.2, 0.5, and 1.0mg/kg</td>
<td>Y</td>
</tr>
<tr>
<td>Nitrous Oxide</td>
<td>HDRS</td>
<td>II</td>
<td>NMDAR antagonist</td>
<td>40</td>
<td>Ongoing</td>
<td>50% / 50% for 1 hour</td>
<td>Y</td>
</tr>
<tr>
<td>GLYX-13 (Rapastinel)</td>
<td>HAM-D</td>
<td>II</td>
<td>NMDAR glycine site functional partial agonist</td>
<td>116</td>
<td>Positive</td>
<td>1, 5, 10, or 30 mg/kg</td>
<td>Y</td>
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<tr>
<td>Sarcosine</td>
<td>HDRS</td>
<td>II</td>
<td>glycine transporter-I inhibitor</td>
<td>40</td>
<td>Positive</td>
<td>500mg to 1500mg</td>
<td>Y</td>
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<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ALKS 5461</td>
<td>MADRS</td>
<td>III</td>
<td>combination of a μ- and κ-opioid partial agonist and a μ-opioid antagonist</td>
<td>790</td>
<td>Positive</td>
<td>high dose or low dose (sublingual)</td>
<td>N</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>MADRS</td>
<td>III</td>
<td>Mu receptor modulator</td>
<td>13</td>
<td>Negative</td>
<td>0.2mg to 1.6mg sublingual</td>
<td>N</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>MADRS</td>
<td>II</td>
<td>Mu receptor modulator</td>
<td>15</td>
<td>Positive</td>
<td>0.2mg to 1.6mg</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Psychodelics and other serotonergic modulators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ayahuasca</td>
<td>HAM-D</td>
<td>II</td>
<td>5-HT2A receptor agonist and MAOI</td>
<td>35</td>
<td>Ongoing</td>
<td>-</td>
<td>N/A</td>
</tr>
<tr>
<td>Lysergic Acid</td>
<td>IDS</td>
<td>II</td>
<td>5-HT2 receptor agonist and modulation of the 5HT2C and 5HT1A receptors</td>
<td>Ongoing</td>
<td>25, 100 or 200 μg</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Psilocybin</td>
<td>QIDS</td>
<td>II</td>
<td>5-HT2A receptor partial agonist</td>
<td>12</td>
<td>Positive</td>
<td>10 mg and 25 mg</td>
<td>Y</td>
</tr>
<tr>
<td>Psilocybin</td>
<td>LTP</td>
<td>II</td>
<td>5-HT2A receptor partial agonist</td>
<td>18</td>
<td>Ongoing</td>
<td>-</td>
<td>Y</td>
</tr>
</tbody>
</table>
Ketamine in Depression - Summary

Strong antidepressant effects in TRD in uni- and bipolar depression

Rapid efficacy and antisuicidal properties

Booster-therapy – repeated administration possible

Imaging correlates: hints for differential effects in HC vs. MDD

Possible RR-increase (RR-Monitoring during infusion), otherwise good safety profile, post market observation important

Approval in Europe pending – inpatient vs. outpatient?