The Role of Glutamatergic Signaling in MDD: Implications for Treatment-Resistant Depression

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Faculty

Rakesh Jain, MD, MPH
Clinical Professor
Department of Psychiatry
Texas Tech University School of Medicine
Midland, Texas
Faculty Disclosure

- **Dr. Rakesh Jain**: Advisory Board—Addrenex, Alkermes, Avanir, Forum, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, Teva; Consultant—Addrenex, Allergan, Avanir, Janssen, Lilly, Lundbeck, Merck, Neos Therapeutics, Neurocrine Biosciences, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Supernus, Takeda, Teva; Consultant (spouse)—Lilly, Otsuka, Pamlab, Sunovion; Grant/Research Support—AstraZeneca, Allergan, Lilly, Lundbeck, Otsuka, Pfizer, Shire, Takeda; Speakers Bureau—Addrenex, Alkermes, Allergan, Lilly, Lundbeck, Merck, Neos Therapeutics, Otsuka, Pamlab, Pfizer, Rhodes, Shionogi, Shire, Sunovion, Takeda, Tris Pharmaceuticals.
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – The off-label or investigational use of ketamine, esketamine, rapastinel, D-cycloserine, riluzole, CP-101,606, CERC 301, basimglurant, JNJ-4011813, ceftriaxone, nitrous oxide, dextromethorphan-quinidine, and AVP 786 for the treatment of depression will be discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Learning Objectives

• Define treatment-resistant depression (TRD) and the clinical and socioeconomic consequences of inadequate response to traditional antidepressant treatment

• Outline the neurobiologic processes regulated by glutamate and how glutamatergic dysfunction contributes to major depressive disorder (MDD) pathophysiology

• Apply an understanding of the role of glutamatergic signaling in MDD to evaluate emerging pharmacotherapies with distinct glutamatergic mechanisms of action

• Assess how the emerging knowledge base regarding glutamate in MDD can be translated to improve clinical outcomes for patients with TRD
Why Bother Learning about Glutamate?
Here’s Why …

The Magnificent 7 Reasons Why

It is the single most potent neurotransmitter in the entire brain.
It is the single most commonly found neurotransmitter in the brain.
It plays an exceptionally large role in learning, cognition, and mood.
It is the major contributor to increased synaptogenesis and neuronal plasticity.
It is the major source of creation of its single greatest antagonist – GABA.
It can be quite neurotoxic in excess.
It isn’t as well understood as it should be.

It was only about 25 years ago that Glutamate’s role as a neurotransmitter was discovered.
Well ...

Does Glutamate Now Have Our Attention???
Disorders where Astrocyte / Glutamate Pathology Plays a Role:

1. Neurological Disorders
   - Autism
   - Down Syndrome
   - Fragile X Syndrome
   - Brain Trauma (CTE)

2. Neurodegenerative Disorders
   - Wernicke and Korsakoff
   - Stroke

3. Psychiatric Disorders
   - Schizophrenia
   - Addictive Disorders
   - Major Depression

CTE = chronic traumatic encephalopathy.
Why Understanding Glutamate is So Critical – It Plays A Central Role in Psychiatry

But... Some Things are Just Complicated – Glutamate’s Life Cycle is Complex. There’s No Getting Around This Fact of Life...
The glutamatergic synapse. Glutamate is an amino acid, a building block for proteins, therefore, it is abundant in all cells of the body. It is also the most important excitatory neurotransmitter in the CNS. Glutamate is synthesized in axon terminals of glutamatergic neurons. It can be produced from α-ketoglutarate—a TCA-cycle intermediate—or from glutamine. For glutamate synthesis from glutamine, the enzyme glutamine synthase is transported to the axon terminal. In the cytosol, it converts glutamine into glutamate. Transporters then concentrate glutamate in vesicles. Release of glutamate is triggered by influx of calcium (Ca\(^{2+}\)) into the presynaptic neuron. The synaptic vesicles fuse with the cell membrane and release glutamate into the synaptic cleft. Glutamate is taken up by the postsynaptic neuron, by glia, or it is recycled in the presynaptic neuron.
Glutamate is packaged into presynaptic vesicles by VGLUT proteins and synaptically released in a voltage-dependent manner through vesicular interactions with SNARE proteins.

Synaptically-released Glutamate is recycled from the extracellular space by EAATs expressed predominantly on astroglia.

In astrocytes, Glutamate is converted to Glutamine by Glutamine synthetase and exported extracellularly to be taken up again by neurons.

Glutamate receptors are present on presynaptic and postsynaptic neurons as well as on glial cells.

These include both ionotropic receptors (NMDA, AMPA/KA) and metabotropic receptors (mGluRs). The effect of Glutamate is determined by the receptor subtype, localization (synaptic, perisynaptic, and extrasynaptic), and interactions with various scaffolding and signaling proteins (not shown) in the postsynaptic density. Glutamate receptor stimulation results not only in rapid ionotropic effects but also in synaptic plasticity, eg, long-term potentiation and long-term depression, via cognate signal transduction cascades.

VGLUT = vesicular glutamate transporter; EAATs = excitatory amino acid transporters; NMDA = N-methyl-D-aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; KA = kainite.

Glutamate is a Firm Believer in the System of Checks and Balances: 
*It Gives Birth to Its Greatest Opposer – GABA*

- THE greatest excitatory neurotransmitter 
in the brain is – GLUTAMATE

- It produces, THE greatest inhibitory 
  neurotransmitter in the brain – GABA

- A comedy of errors, or is this the ultimate 
  system of checks and balances in the 
  human brain?

Glutamate is one of the 20 amino acids in human 
beings. It’s non-essential and the body can create its 
own glutamate

Glutamate may be synthesized in 2 separate ways:

1. Through the Krebs cycle: Firstly, it may be 
synthesized from α-ketoglutarate, by either 
glutamate dehydrogenase or by a variety of amino-
transferases

2. Secondly, glutamate may be synthesized from other 
amino acids; the “glutamate family” of amino acids 
comprise glutamine, arginine, proline, and histidine

3. Taste buds: Umami tastants, particularly glutamate, 
are thought to mediate appetitive responses to 
protein-rich foods. As such, they play a fundamental 
role in evaluating the nutritional value of foods

GABA = gamma-aminobutyric acid. 
Glutamate / Astrocyte Interactions and Its Importance in Health and Psychiatric Disorders

**Molecular homeostasis**
- Ion homeostasis (K⁺, Cl⁻, Ca²⁺)
- Regulation of pH
- Water transport and homeostasis
- Neurotransmitter homeostasis (glutamate, GABA, adenosine, monoamines)

**Systemic homeostasis**
- Chemosensing (O₂, CO₂, pH, Na⁺, glucose)
- Regulation of energy balance and food intake
- Sleep homeostat

**Organ homeostasis**
- Control over blood-brain barrier
- Operation of the lymphatic system

**Cellular & network homeostasis**
- Neurogenesis
- Neuronal development and neuronal guidance
- Defining cyto-architecture of the CNS
- Synaptogenesis, synaptic maintenance and synaptic elimination
- Synaptic plasticity

**Metabolic homeostasis**
- Formation of neuro-glio-vascular unit and glial-vascular interface
- Regulation of local blood flow
- Metabolic support
- Glycogen synthesis and storage

Glutamate Interventions are So Much More than Just Glutamate Interventions – *The Quartet of Other Effects and Benefits*

Glutamate as a Great “Concert Master”: The INTRAcellular Players That Listen to Glutamate’s Commands


PSD-95 = postsynaptic density protein – a major scaffolding protein for both neurons and dendrites

BDNF = brain-derived neurotrophic factor

mTOR = modulation (mammalian target of rapamycin)
“The Party is in Here”: The Real Action from Glutamate-Based Interventions is Intracellular

NMDA = N-methyl-D-aspartate receptor

GABA = γ-aminobutyric acid receptor

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid receptor

VDCC = voltage dependent calcium channel

BDNF = brain-derived neurotrophic factor

PSD-95 = (postsynaptic density protein) – a major scaffolding protein for both neurons and dendrites

mTOR = modulation (mammalian target of rapamycin)

And Let’s Now Focus on Glutamate’s Targets: Its Army of Receptors
NMDA receptors are among the most tightly regulated in the mammalian brain and unique in requiring co-agonists for activation.

At least 6 binding sites have been identified that regulate the probability of ion channel opening, viz., sites for 2 obligatory co-ligands (glutamate and glycine), polyamines, and cations (Mg$^{2+}$, Zn$^{2+}$, and H$^+$). NMDA receptor ligands are short-chain dicarboxylic amino acids (NMDA, glutamate, aspartate, etc.).

Glutamate, the most potent neurochemical agonist identified in the CNS.

Ionotropic and Metabotropic Glutamate Receptors

Role of Neurons and Astrocytes

2 Types of Glutamate Release – “Burst” Release vs “Drip-Drip” Release

Extracellular glutamate in the nervous system may thus be divided into 2 functionally and spatially distinct pools:

1) “Synaptic glutamate,” a transient (few milliseconds) burst of high (0.5–5 mM) glutamate that appears in the synaptic cleft when glutamate-filled synaptic vesicles in neurons fuse with the presynaptic membrane

2) “Ambient extracellular glutamate,” a relatively steady background of glutamate, mostly from glia, that fills most of the extracellular space at lower concentration (1–5 uM)

Oh, Magnificent NMDA Receptor

NMDA receptors are among the most tightly regulated in the mammalian brain and unique in requiring co-agonists for activation.

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Glutamate / NMDA Receptors

- NMDARs contain 4 subunits which are a combination of: NR1, NR2, and NR3
- There is consensus that NMDARs are tetramers composed of 2 NR1 subunits and 2 NR2 subunits, less commonly including NR3 subunits
- The combination of NR1 with different NR2 subunits results in diverse electrophysiological and pharmacologic responses
- There is a binding place in the channel pore for Mg$^{2+}$, and at resting membrane potential, Mg$^{2+}$ is attached to this binding site, blocking ion flow through the channel
- They are mostly located on dendrites

AMPARs are activated in the presence of glutamate, thus inducing a fast excitatory synaptic signal involved in early glutamatergic effects in the synapse.

These effects play a crucial role in calcium metabolism, synaptic strength, and oxidative stress. Indeed, AMPAR activation opens the pore permitting the inward flow of sodium, which results in the depolarization of the neuronal membrane.

At mature synapses, AMPARs can be co-expressed with NMDARs, thereby contributing to synaptic plasticity and neuroprotection.

It is important to note that AMPARs have a lower affinity for glutamate than NMDARs, which allows for a more rapid dissociation of glutamate and a fast deactivation of the AMPAR.

Ketamine-induced BDNF release is dependent on activation of glutamate-AMPA receptors and L-type VDCCs. (A) Cortical neurons were incubated with NBQX (50 µM) 20 min prior to ketamine, and medium was collected 15 min later (after ketamine). Incubation with the AMPA receptor antagonist completely blocked ketamine-induced BDNF release (n=6; drug x drug interaction, \( F_{1,20} = 13.209, *P<.01 \))

Incubation of primary neuronal cultures with ketamine rapidly increases BDNF release.

15 min (n=12; \( t_{22} = 3.10, **P<.01 \)), 60 min (n=6; \( t_{10} = 3.33, **P<.01 \)), and 6 hours (n=3; \( t_{4} = 3.14, *P<.05 \)) incubations.

NMDA Receptor and Glycine
Another Important Player in the Glutamate Homeostasis

NMDA Receptor and Its Various Ligands

Schematic diagram of NMDA receptor complex. The NMDA receptor is an ionotropic glutamate receptor for controlling synaptic plasticity and memory function. Glutamate (and NMDA) binds to the agonist site on the NMDA receptors. PCP, ketamine, and dizocilpine bind to the PCP receptor in the inside of the NMDA receptors. Glycine and D-serine bind to a glycine modulatory site on the NMDA receptors. The NMDA receptor is blocked by Mg\(^{2+}\) in a voltage sensitive manner. Activation of NMDA receptor by binding of both glutamate and glycine results in the opening of the channel. This allows voltage-dependent flow of Na\(^+\) and small amounts of Ca\(^{2+}\) ions into the cell and K\(^+\) out of the cell. The symbol (−) denotes inhibitory effect.

PCP = phencyclidine; 7-CK = 7-chlorokynurenic acid; L689,560 = trans-2-carboxy-5,7-dichloro-4-phenylaminocarboxyl; AP5 = 2-amino-5-phosphonovaleric acid; CGS-19775 = cis-4-phosphonomethyl-2-piperidinecarboxylic acid.

Glycine – (an NMDA Agonist)  
Another Way to Modulate the Glutamate System

Glycine, an important amino acid released by both glial cells and glutamatergic neurons, elicits persistent bidirectional modifications in NMDAR-mediated synaptic responses.

Activation of GlyR by glycine has additional contributions to the glycine-induced NMDAR endocytosis as well as suppression of NMDAR function.

Net effect mediated by glycine is a depression of the NMDA response.

GlyR = glycine receptor; GlyT1 = glycine transporter type 1.
Glutamate Modulation (in this case NMDA Antagonism via Ketamine) Enhances Synaptogenesis

Glutamate / NMDA Functioning: 
A Tale of Two Extremes

Shifting Our Focus to Glutamate and Its Role in Psychopathology
What Goes Wrong with Glutamate in Psychiatric Disorders? *Answer: Multiple Things*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Astrocyte Dysfunction</th>
<th>Impact on Glutamate Homeostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive disorder</td>
<td>Functional asthenia and morphological atrophy</td>
<td>Decrease in number of astrocytes and GFAP expression, associated with decreased glutamate uptake and secretion of growth factors and cytokines as well as impaired glutamine synthesis, altered gap junctional connectivity in glial syncytia, which all may contribute to abnormal connectivity in neural networks and neurotransmission disbalance</td>
</tr>
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GFAP = glial fibrillary acidic protein.
Glutamate and Depression

**Stress Disrupts Glutamate at Multiple Levels**

1. Presynaptic release of glutamate
2. Postsynaptic ionotropic receptors for glutamate (NMDA and AMPA receptors)
3. Reuptake of glutamate by glial glutamate membrane transporters
4. Glutamate metabolism and recycling by the glutamate/glutamine cycle

- Increased glutamate release
- Altered trafficking/expression/function of ionotropic glutamate receptors
- Altered clearing of glutamate from the synapse
- Reduced glutamate/glutamine cycling and glial cell density

Evidence of Abnormal Glutamate Trafficking in Depression: Meta-Analysis of Peripheral Blood Glutamate Levels and Major Depression

Systematic review and meta-analysis of 12 association studies between blood glutamate levels and MDD in a total of 529 MDD patients and 590 controls

**Results:**
Blood glutamate levels were significantly higher in MDD patients than in controls (standardized mean difference = 0.54, 95% CI = 0.27–0.82, P=8.5×10^{-5}

**Authors’ Conclusion:**
Findings suggest that altered glutamate levels may be implicated in MDD, which provides further evidence of glutamatergic dysfunction in MDD

MDD = major depressive disorder.
Glutamate and Inflammation: A “Brain–Body” Link

Glutamate disruptions adversely affect production of IL-6, TNF-α etc. from microglia and macrophages.

Examining Treatment-Resistant Depression
In the only empirical test of the Thase–Rush vs MGH Staging Methods, the 2 methods were similar, but MGH showed superior ability to predict nonremission to antidepressant treatment.

TRD = treatment-resistant depression; TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor; ECT = electroconvulsive therapy.

Patients with TRD – More Severely Impaired Than Non-TRD Patients

TRD Definition:
Non-responders to ≥ 2 treatments

<table>
<thead>
<tr>
<th></th>
<th>Non-TRD Patients (n=65)</th>
<th>TRD Patients (n=42)</th>
</tr>
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<tbody>
<tr>
<td><strong>Duration of Current Episode (mean in weeks)</strong></td>
<td>15</td>
<td>32.6</td>
</tr>
<tr>
<td><strong>Total number of Hospitalizations (mean)</strong></td>
<td>0.9</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Job Loss Individuals Reporting (%)</strong></td>
<td><strong>38.1</strong></td>
<td><strong>42.9</strong></td>
</tr>
<tr>
<td><strong>Financial Distress Individuals Reporting (%)</strong></td>
<td>*</td>
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*P≤.05; **P≤.001.
Factors Associated with Treatment Resistance in MDD

- Recurrent episodes vs single episode
  - Odds Ratio: 1.5
  - P = .009

- Melancholic features
  - Odds Ratio: 1.5
  - P = .018

- No. of hospitalizations > 1
  - Odds Ratio: 1.6
  - P = .003

- Nonresponse to 1st AD treatment lifetime
  - Odds Ratio: 1.6
  - P = .019

- Severe intensity vs moderate intensity
  - Odds Ratio: 1.7
  - P = .001

- Personality disorder (DSM-IV criteria)
  - Odds Ratio: 1.7
  - P = .049

- Age at onset before 18 y
  - Odds Ratio: 2
  - P = .009

- Social phobia
  - Odds Ratio: 2.1
  - P = .008

- Current suicidal risk
  - Odds Ratio: 2.2
  - P < .001

- Comorbid anxiety disorder
  - Odds Ratio: 2.6
  - P < .001

- Comorbid panic disorder
  - Odds Ratio: 3.2
  - P < .001

AD = antidepressant.
Factors to Consider in Patients Who Fail Trials of Antidepressant Therapy

Treatment-Refractory Patient

- Correct Diagnosis
- Comorbid Psychiatric Conditions
- Appropriate Drug Therapy
- Severity of Illness
- Treatment Adherence
- Comorbid Medical Conditions
- Adequate Dose
- Adequate Duration

Finally, We Shift Our Attention to Glutamate-Centric Interventions
There are Many, Many Correct Roads to Rome!
Similarly, There are Many, Many Paths to Glutamate Modulation
Glutamate Targets in Psychiatry – Where are They? 

**Answer: Literally, Everywhere!**

1) NMDA receptor antagonists (ketamine, NR2B subunit antagonists, memantine, magnesium, and zinc)

2) Positive modulators of AMPA

3) Group I mGluR antagonists, group II mGluR antagonists and agonists, and group III mGluR agonists

4) EAAT2 enhancer (ceftriaxone)

5) Possible indirect NMDA receptor modulator (minocycline)

6) Inhibitor of glutamate release, antagonist of NMDA, AMPA, and kainate receptors, and potentiatior of glutamate uptake (riluzole)

Let’s Meet Target #1 in Glutamate-Based Therapies

**NMDA Receptor**

- Ketamine subunit selectivity for GluN1/GluN2A and GluN2B has been discovered

- The psychotomimetic effects of ketamine are produced by GluN1/GluN2A subunits rather than GluN1/GluN2B

A Tale of Two Cities – *Agonism AND Antagonism of Glutamate NMDA are Both Clinical Approaches to Treating Major Depression*

NMDA Receptor Partial Agonism
- eg – Rapastinel
- D-cycloserine

NMDA Receptor Antagonism
- eg – Ketamine
- Esketamine

Glutamate Activity

How Ketamine Works

1) Proposed mechanism of ketamine’s antidepressant action, whereby ketamine, through a blockade of tonic GABAergic inhibition …

2) causes a surge in glutamate release and cycling.

3) The resulting increased glutamatergic transmission through AMPARs (whose surface expression may be independently upregulated by the suppression of spontaneous NMDAR-mediated neurotransmission) …

4) leads to increased BDNF-dependent levels of synaptogenesis …

5) that ultimately contribute to the rapid and sustained antidepressant effects.

How NMDA Antagonism Works: A Receptor and Intracellular Cascade Story

- NMDA receptor blockade …
- Lead to increased glutamate release from pyramidal neurons
- Activation of postsynaptic AMPARs by increased glutamate transmission …
- release of BDNF. This neurotrophic factor binds to related kinase B (TrkB) receptors, and mTOR is activated …
- Leading to transphosphorylation and downstream activation of the extracellular signal-related kinase (ERK) and suppression of glycogen synthase kinase 3 (GSK-3)

This is to illustrate that the “real action” of the pharmacologic manipulation of glutamate is intracellular. It shows the importance of the mTOR system, GSK-3, BDNF, scaffolding proteins, and synaptogenesis.

“It is important to note that, within four hours to one day, a single infusion of ketamine in TRD patients achieved response rates comparable to that seen following eight weeks of treatment with monoaminergic-based antidepressants in non-TRD patients.

The fact that ketamine is capable of inducing remission in approximately one-third of TRD patients within a single day is in stark contrast to the effectiveness of monoaminergic-based approaches, which usually require 10–14 weeks of chronic use to produce similar remission rates.”

Remarkable, Iconoclastic Things with Ketamine

- Rapidity of antidepressant activity onset
- Many studies demonstrate 4 hours to 1 day onset of action
- Ability to induce remission in one-third of patients with TRD
- No significant challenges for use in bipolar depression (low switching rates)
- Improvement in 3 domains that were particularly vexing challenges with SSRIs
  - Anhedonia
  - Fatigue
  - Suicidal ideations (ketamine’s ability to reduce suicidal-ideation measures may occur independently of its antidepressant effects)

**DOWNSIDE:** Ketamine while rapid, had transient antidepressant effects and caused brief dissociative and psychotomimetic effects

SSRI = selective serotonin reuptake inhibitor.
Modulating Glutamate May Impact Both “Poles”: Impact on Depression and Wellness

Note:
Early antidepressant action from Glutamate NMDA antagonism and AMPA agonism

AND

Later, but substantial increase in Wellness traits such as Happiness, Energy, Calmness, Self-Esteem

14 participants completed 6 IV infusions of 0.5 mg/kg ketamine over 40 minutes on a Monday–Wednesday–Friday schedule.

Glutamate Interventions Can Be Rapidly Anti-Suicidal Even with One Dose: *Results from a Meta-Analysis*

This meta-analysis investigated studies of single-dose IV ketamine for the treatment of any psychiatric disorder; only comparison intervention trials (using saline placebo or midazolam as a control). 10 trials were included.

**Clinician-Rated Change**

**Patient-Rated Change**

*P*<.05, ***P*<.001.

Intranasal Esketamine
A Promising Glutamate-Based Therapy

What is Esketamine?
• Ketamine = racemic mixture of (R) and (S) enantiomers
• Esketamine = isolated (S)-enantiomer of ketamine
  • 4-fold greater affinity for NMDA receptor
  • 2-fold greater potency
  • Rapid clearance/recovery
  • Less lethargy, cognitive impairment, agitation

28 placebo-treated participants with moderate-to-severe symptoms were rerandomized (1:1:1:1) to 1 of the 4 treatment arms; those with mild symptoms continued receiving placebo. Participants continued their existing antidepressant treatment during the study. During the open-label phase, dosing frequency was reduced from twice weekly to weekly, and then to every 2 weeks.

A significantly greater improvement in MADRS score was observed in the esketamine group compared with the placebo group at 4 hours (least-square mean difference = -5.3, SE = 2.10; effect size = 0.61) and at ~24 hours (least-square mean difference = -7.2, SE = 2.85; effect size = 0.65), but not at day 25 (least-square mean difference = -4.5, SE = 3.14; effect size = 0.35).

Significantly greater improvement was also observed in the esketamine group on the MADRS suicidal thoughts item score at 4 hours (effect size = 0.67), but not at 24 hours (effect size = 0.35) or at day 25 (effect size = 0.29).

MADRS = Montgomery–Åsberg Depression Rating Scale.
Therapeutic Effects of Glutamate Intervention Through Ketamine

Glutamate
(ketamine modulation of NMDA and AMPA)

- TRD
- Anti-suicidal
- PTSD/?OCD
- Bipolar Depression

PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder.

Ketamine: A Glutamate NMDA Receptor Antagonist, in Refractory Anxiety Disorders

Anxiety is a Common Comorbidity of TRD

- Open-label, 10 women (50%) and 10 men (50%); 15 patients (75%) met criteria for GAD and 18 (90%) for SAD
- Patients received 1 or 2 weekly ketamine doses of 1 mg/kg injected subcutaneously for 3 months

**Results:**
- Fear Questionnaire ratings decreased by ~50%, as did Hamilton Anxiety ratings
- The most common adverse events were nausea, dizziness, and blurred vision. Of the 20 patients, 18 reported improved social functioning and/or work functioning during maintenance treatment
- Maintenance ketamine may be a therapeutic alternative for patients with treatment refractory GAD/SAD

GAD = generalized anxiety disorder; SAD = social anxiety disorder.
Rapastinel: An NMDA Receptor Partial Agonist (Through Glycine Receptor Partial Agonism)

A Glycine Receptor Partial Agonist, Working on NMDA Receptor, Quickly Impacts Depression

In this double-blind, randomized, placebo-controlled study, a single IV dose of rapastinel (1, 5, 10, or 30 mg/kg) or placebo was administered to 116 participants with MDD who had not benefitted from a trial of at least one biogenic amine antidepressant during the current episode.

Results. Rapastinel, 5 or 10 mg/kg IV, reduced depressive symptoms as assessed by the HAM-D-17 at days 1 through 7. Onset of action as assessed using the Bech-6 occurred within 2 hours. Rapastinel did not elicit psychotomimetic or other significant side effects.

Which Then is the Better Approach to Treating MDD?

Good news for us clinicians, both approaches are helpful. There are enough similarities and dissimilarities to potentially make both approaches viable –

There are neurobiological similarities and dissimilarities: “The results demonstrate similarities as well as differences in the synaptic and behavioral actions of [rapastinel] compared with ketamine.”

More Glutamate-Based Therapies on the Horizon (maybe!)

- D-cycloserine (FDA approved for tuberculosis) – works on glycine site on NMDA receptor
- Riluzole (FDA approved for amyotrophic lateral sclerosis [ALS])
- CP-101,606 and CERC 301 – both work only on NR2B subunit of NMDA receptor as an antagonist
- Basimglurant and JNJ-4011813 – mGluR5 negative and positive modulators

In a placebo-controlled, double-blind, crossover study examining 20 patients with TRD who received an inhalation of 50% N₂O or 50% nitrogen (placebo), both over 1 hour, those who received N₂O experienced a reduction in depressive symptoms (as measured by the HAM-D) at both 2 hours and 24 hours post-inhalation compared to placebo. Adverse effects included anxiety, headache, and nausea/vomiting, but there were no psychotomimetic effects associated with N₂O inhalation.

Depressive symptoms improved significantly at 2 hours and 24 hours after receiving N₂O compared with placebo (mean HAM-D-21 difference at 2 hours, -4.8 points, 95% CI, -1.8 to -7.8 points, \( P = .002 \); at 24 hours, -5.5 points, 95% CI, -2.5 to -8.5 points, \( P < .001 \); comparison between N₂O and placebo, \( P < .001 \)). 4 patients (20%) had treatment response (reduction \( \geq 50\% \) on HAM-D-21) and 3 patients (15%) had a full remission (HAM-D-21 \( \leq 7 \) points) after N₂O compared with 1 patient (5%) and none after placebo.

“Don’t You Sneeze at Glutamate’s Role in Depression!” – Dextromethorphan in Depression

Dextromethorphan acts on opioid receptors, and at higher doses dextromethorphan acts as a σ-1 receptor agonist and inhibitor of the serotonin and norepinephrine transporters, as well as a non-competitive NMDA receptor antagonist.

Dextromethorphan-Quinidine combination, which is FDA-approved for the treatment of pseudobulbar affect—is currently under investigation as a potential antidepressant agent in patients with MDD.

In addition, AVP 786, a combination of deuterated (d6)-dextromethorphan and an ultra-low dose of quinidine, received fast-track designation for agitation in Alzheimer’s disease; it is currently under investigation for use in depression.

## Our Future with Glutamate-Based Therapies

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### Glutamatergic Modulator
- **Ketamine (+ Metabolites?)**
  - Target: NMDA receptor, AMPA receptor (?)
  - Major Mechanism(s) of Action: NMDA receptor antagonist, AMPA receptor agonist
  - Potential Indication(s): MDD, BD, Suicidality, Anxiety, PTSD, OCD

- **Eskinette (Intranasal Ketamine)**
  - Target: NMDA receptor
  - Major Mechanism(s) of Action: NMDA receptor antagonist, AMPA receptor agonist
  - Potential Indication(s): MDD, Suicidality, PTSD

- **D-cycloserine (DCS)**
  - Target: NMDA receptor
  - Major Mechanism(s) of Action: Partial agonist at glycine site; functional NMDA receptor antagonist
  - Potential Indication(s): MDD, BD

- **Riluzole**
  - Target: Voltage-gated sodium channels
  - Major Mechanism(s) of Action: Increased synaptic glutamate reuptake, blockade of voltage-gated sodium channels
  - Potential Indication(s): MDD, BD, OCD

- **CP 101,606**
  - Target: NMDA-NR2B subunit
  - Major Mechanism(s) of Action: NMDA-NR2B non-selective antagonist
  - Potential Indication(s): MDD

- **CERC-301**
  - Target: NMDA-NR2B subunit
  - Major Mechanism(s) of Action: NMDA-NR2B selective antagonist
  - Potential Indication(s): MDD

- **Basinghurant (RG7090)**
  - Target: mGluR5
  - Major Mechanism(s) of Action: mGluR5 NAM
  - Potential Indication(s): MDD

- **JNJ-40411813 (ADX71149)**
  - Target: mGluR2
  - Major Mechanism(s) of Action: mGluR2 PAM
  - Potential Indication(s): MDD

- **Dextromethorphan**
  - Target: NMDA receptor, Sigma-1 receptor, SERT, NET
  - Major Mechanism(s) of Action: NMDA receptor antagonist, Sigma-1 receptor antagonist, SERT and NET inhibitor
  - Potential Indication(s): BD

- **AVP-786**
  - Target: NMDA receptor, Sigma-1 receptor, SERT, NET
  - Major Mechanism(s) of Action: NMDA receptor antagonist, Sigma-1 receptor antagonist, SERT and NET inhibitor
  - Potential Indication(s): MDD

- **AVP-923 (Nuedexta)**
  - Target: NMDA receptor, Sigma-1 receptor, SERT, NET
  - Major Mechanism(s) of Action: NMDA receptor antagonist, Sigma-1 receptor antagonist, SERT and NET inhibitor
  - Potential Indication(s): MDD

- **Nitrous Oxide (N2O)**
  - Target: NMDA receptor
  - Major Mechanism(s) of Action: NMDA receptor antagonist
  - Potential Indication(s): MDD

- **Rapastinel (GLYX-13)**
  - Target: NMDA receptor
  - Major Mechanism(s) of Action: NMDA receptor glycine site NAM
  - Potential Indication(s): MDD

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Ketamine has also been used in conjunction with SSRIs. In a double-blind study, 30 MDD patients were randomized to receive either a single administration of ketamine or placebo concomitant to daily treatment with escitalopram (10 mg). Improvement in depressive symptoms was greater, and remission rates were higher, in those that received escitalopram plus ketamine vs those that received escitalopram plus placebo for up to 2 weeks (92.3% vs 57.1%, \(P=0.04\) and 76.9% vs 14.3%, \(P=0.001\), respectively), with a significantly shorter time to response (HR 0.04, 95% CI 0.01–0.22, \(P<0.001\)) and remission (HR 0.11, 95% CI 0.02–0.63, \(P=0.01\)). This suggests that ketamine administration may be used to offer more immediate antidepressant relief during the lag time to monoaminergic antidepressant response.

Physical Exercise and Glutamate
Physical Exercise is a Powerful Modulator of Glutamate and GABA

Running also increases the gene expression levels of the NR2B subunit of the NMDA receptor in the dentate gyrus.

Meditation and Glutamate
Meditation Has a Strong Impact on Brain Glutamate Levels


Differences on Glutamate Levels in Left Thalamus between Meditators and Healthy Non-meditators

Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI) are correlated with years of meditation and psychological variables in 10 long-term Zen meditators compared to 10 healthy non-meditator controls.

In Conclusion
Why This In Depth Examination and Understanding of Glutamate Matters …
Consequences of a Narrow, Monoamine-Centric View in Psychiatry is …

“None of the antidepressants have been designed with astrocytes (or glutamate) as target in mind.”

And this may be because of …

“(delayed) new drug development, but this is often a slow process due to adherence to existing dogma by research community and drug companies.”

“Glutamatergic transmission is generally believed to be significantly impaired in the contexts of all major neuropsychiatric diseases.”

“…Glutamate homeostasis are affected in all forms of major psychiatric disorders and represent a common mechanism underlying neurotransmission disbalance, aberrant connectome and overall failure on information processing by neuronal networks, which underlie pathogenesis of neuropsychiatric diseases.”