

# Ketamine for Difficult to Treat Depression

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# Agenda

- Typical Case
- Depression treatment goals and phases of care
- Considering oral pharmacotherapy for depression
- History of antidepressant pharmacotherapy development
  - And comparing this to cancer treatment development
- Ketamine
  - What is it
  - How does it work
  - What is it approved for
  - Use for depression
  - Safety
- Discussion



# A Tale of Difficult to Treat Depression

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- Jane: 54 year-old divorced♀, works as nurse in primary care office.
- Chief complaint: “My depression is back, and I can’t get back on track.”
- Depression symptoms: Sadness, lack of enjoyment, cognitive slowing, insomnia, weight gain, fatigue, thoughts of dying.
- Hypertension, diabetes, obesity, hx breast cancer, post-menopausal. knee arthritis, back pain, fibromyalgia, irritable bowel syndrome. All are worse when stressed. **Total # medications: 9**
- Lives alone. Finances strained. Cares for elderly parents. Three children live out of state. She helps support two of them.
- Nightly use of marijuana “gummies” to relax and sleep.
- Strengths: No alcohol, wants to feel better, has friends, supportive co-workers, and usually enjoys her work.

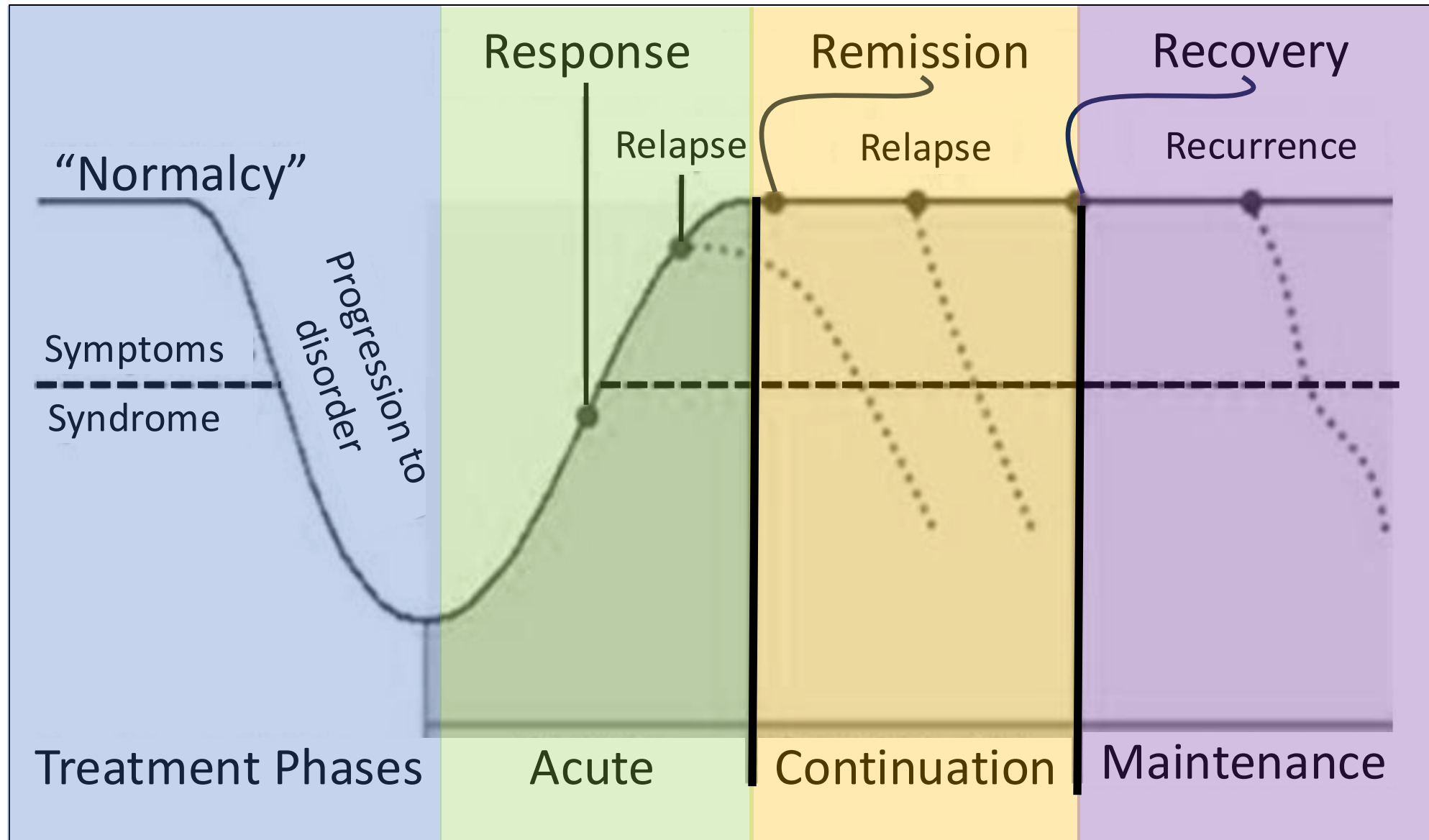
# A Tale of Difficult to Treat Depression



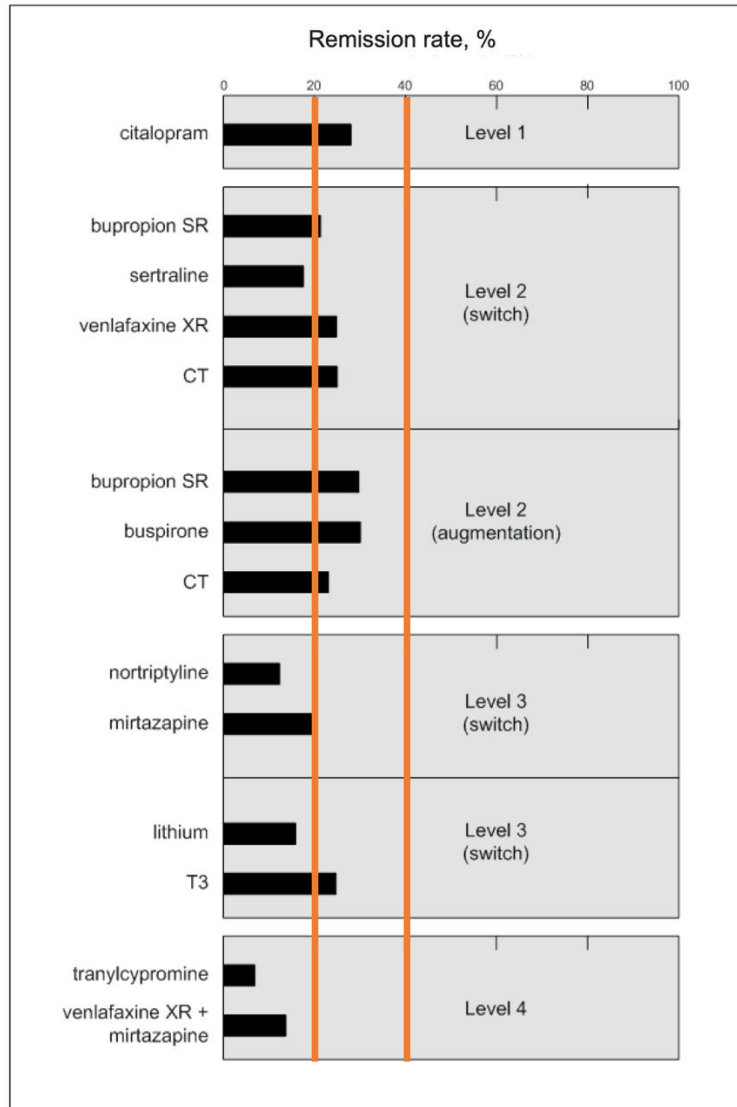
- Depression started age 17. Recurrent episode of depression every 2-3 years. Estimates this is her 8th and most severe episode.
- Psychotherapy on and off for past decade. Currently sees a therapist every other week.
- Adequate trials of Lexapro (escitalopram), Prozac (fluoxetine), Effexor (venlafaxine) and Pamelor (nortriptyline).
- Tried augmentation treatment with Abilify (aripiprazole) and Ritalin (methylphenidate).
- Considered trial of Electroconvulsive Therapy, but she changed mind because of worries about general anesthesia and memory loss.
- **WHAT DO YOU DO NEXT?**



# Five “Rs” of Depression Treatment



Depression remission rates across all 4 treatment levels



14 weeks

14 weeks

14 weeks

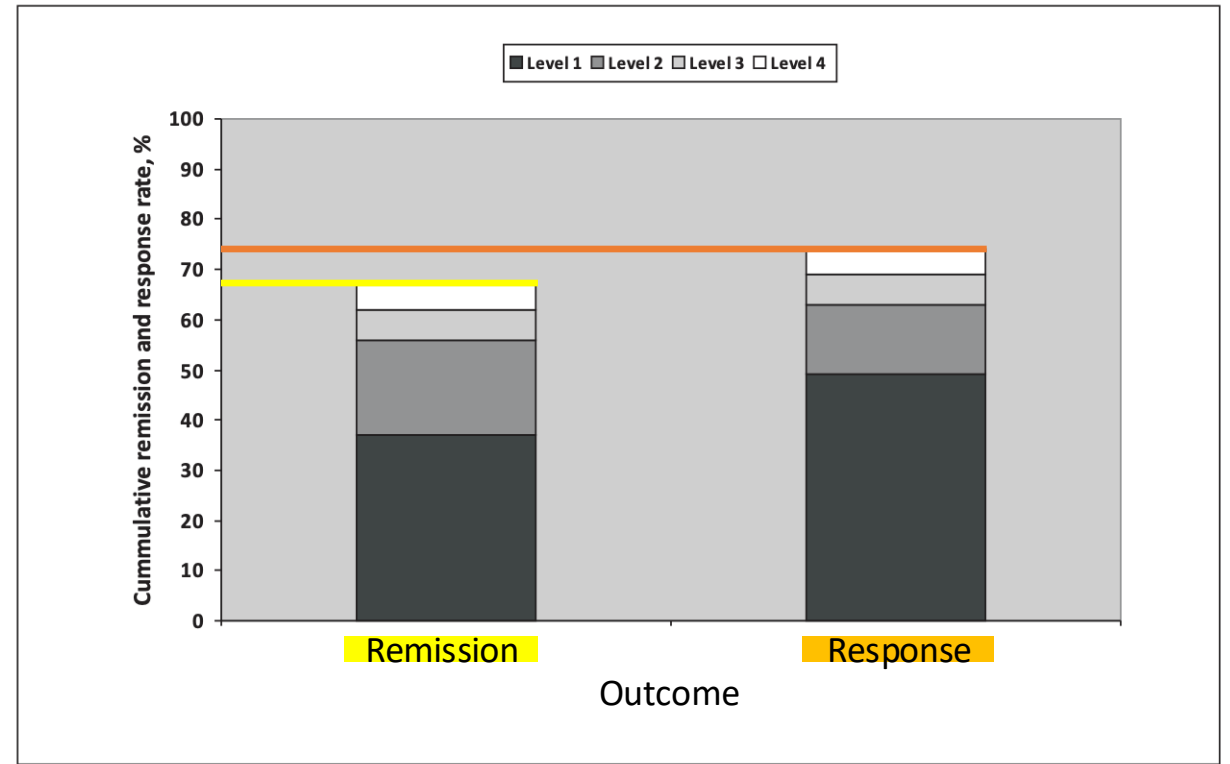
14 weeks

56 weeks

Level 1: n = 2876; Level 2: n = 1893; Level 3: n = 377; Level 4: n = 109  
Differences in remission rates across a particular treatment level were not statistically significant at any of the 4 levels.

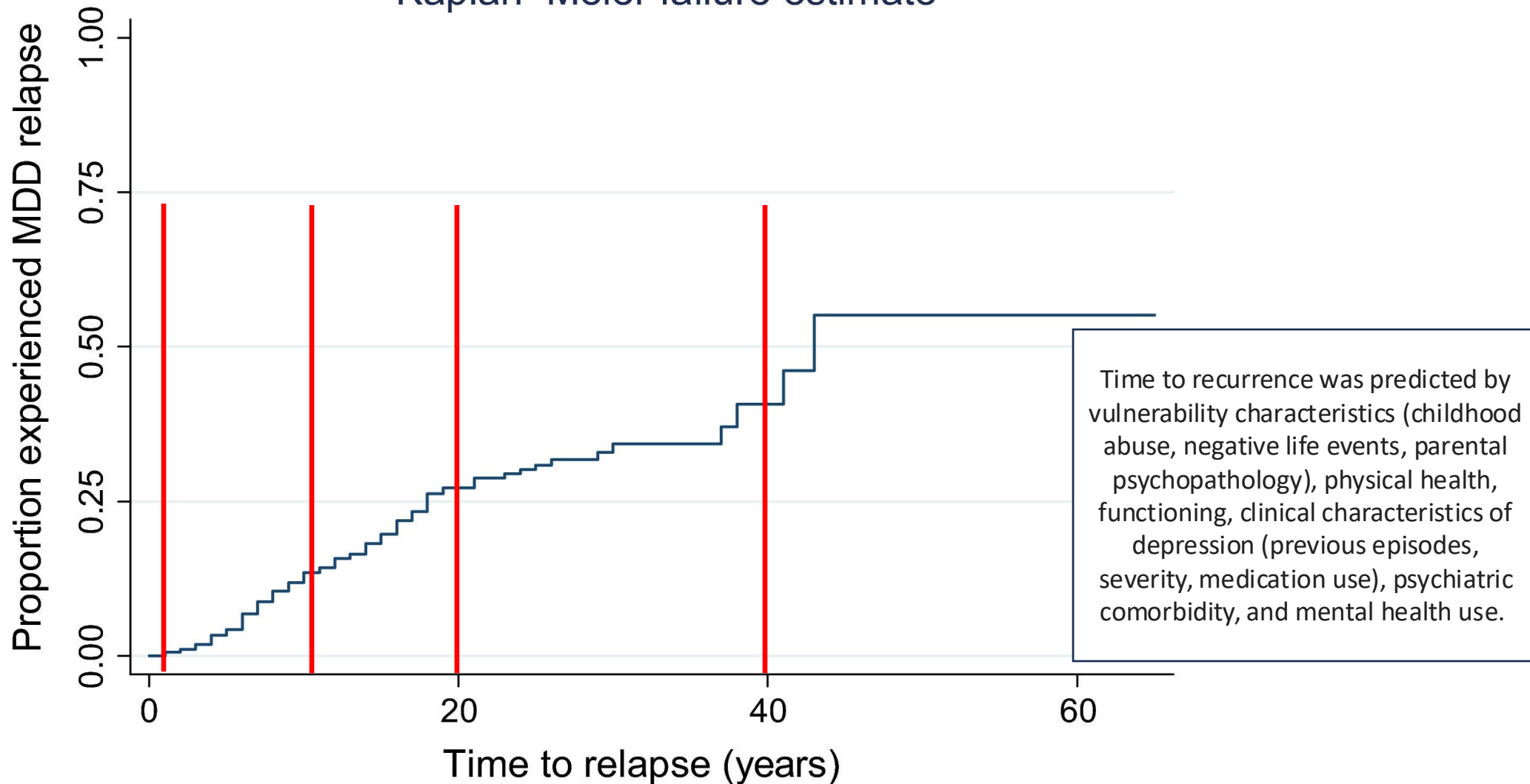
# Most Patients Don't Respond to First Antidepressant

Cumulative remission and response rates across all 4 treatment levels



# Depression is a Recurrent Disorder

Kaplan–Meier failure estimate



Among remitted MDD cases ( $n = 746$ ), the cumulative recurrence rate was 4.3% at 5 years, 13.4% at 10 years and 27.1% at 20 years.

# Reviewing What We've Learned About Depression Treatment So Far

- 5 “Rs” of Depression Treatment

- Response
- Remission
- Recovery
- Relapse
- Recurrence

- 3 Phases of Depression Treatment

- Acute
- Continuation
- Maintenance

- Depression worsens the “bothersomeness” of other medical conditions.
- Most patients don't respond to their first antidepressant.
- Depression is a recurrent condition.





On to Ketamine...



**1958**

**MAOI APPROVED**

*Iproniazid\**

Isocarboxazid\*

Phenelzine

Amitriptyline

Desipramine,  
Nortriptyline

Doxepin

**1959**

**TCA APPROVED**

*Imipramine*

**1981**

**ATYPICAL AD APPROVED**

*Trazodone*

Bupropion

Tianeptine\*

Sertraline

Paroxetine

**1987**

**SSRI APPROVED**

*Fluoxetine*

**1993**

**SNRI APPROVED**

*Venlafaxine*

Citalopram

Escitalopram

Duloxetine

Desvenlafaxine

Agomelatine\*

Vilazodone

Levomilnacipran

**2019**

**FAST-ACTING  
AD APPROVED**

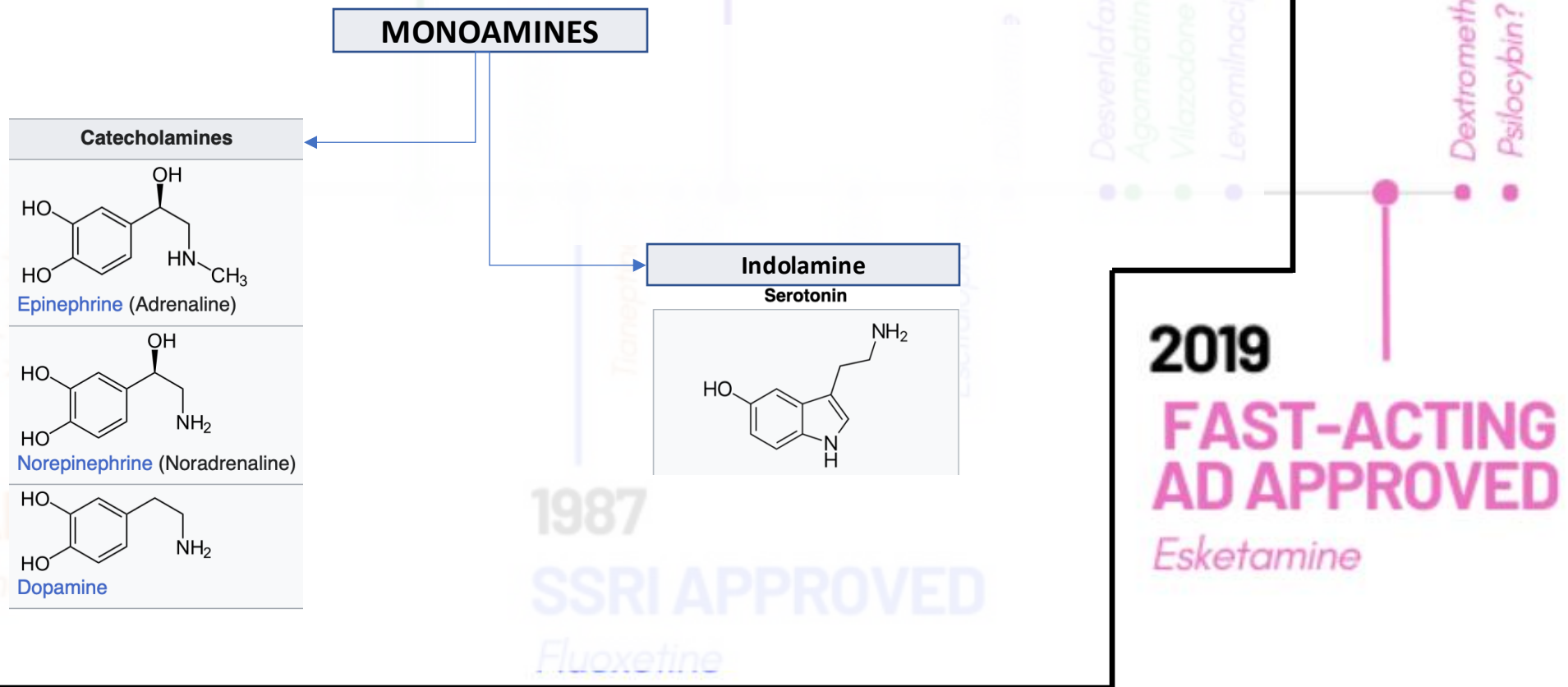
*Esketamine*

Dextromethorphan/bupropion

Psilocybin?

• All these drugs address the monoaminergic system by increasing levels of monoamines in the synapse (where they have a functional effect) by:

- Blocking re-uptake back into the neuron.
- Blocking degradation once released into the synapse.



Desvenlafaxine  
Agomelatine\*  
Vilazodone  
Levomilnacipran  
Dextromethorphan/bupropion  
Psilocybin?

**2019**  
**FAST-ACTING  
AD APPROVED**  
Esketamine

1981

1993

1987

1959

TCA A

Imipramin

SSRI APPROVED

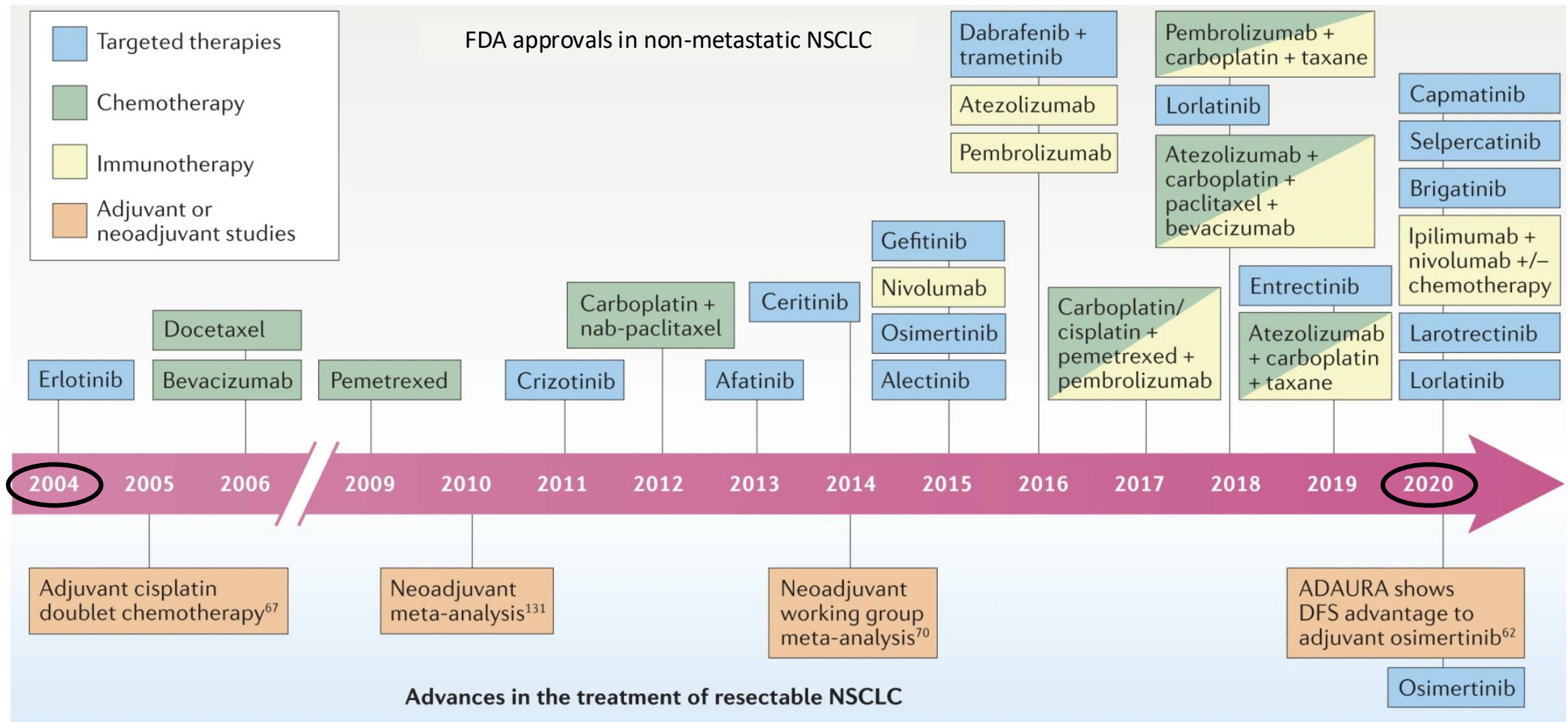
Fluoxetine

Amitriptylin  
Desipramin

Tianeptin

Escitalopram

# Evolution of systemic therapy for stages I–III non-metastatic non-small-cell lung cancer



# Further Consolidated Appropriations Act, 2024 (H.R.2882), Allocated to NIH **\$48.6 billion** (↑of \$300 million above FY2023)



- National Cancer Institute (NCI): \$7.2 billion (↑of \$120 million over FY23)
- National Institute of Mental Health (NIMH): \$2.2 billion (↑of \$75 million over FY23)

# Economic Burden of Cancer vs. Depression



# Economic Burden of Cancer vs. Depression

## Cancer

- **Patient out-of-pocket costs:** In 2019, this was \$16.22 billion.
- **Patient time costs:** In 2019, this was \$4.87 billion, which includes the value of time spent traveling to and from care, waiting, and receiving care.
- **National medical care costs:** In 2015, these were estimated to be \$190.2 billion.
- **Productivity loss:** In 2017, this was estimated to be \$30.3 billion.
- **Premature mortality:** In 2017, this was estimated to be \$150.7 billion.
- **Estimate: \$392.29 billion**

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## Depression

- In 2019, the number of adults with MDD in the USA was estimated at 19.8 million
- **Primary cost drivers:**
  - healthcare costs (\$127.3 billion; 38.1%)
  - household-related costs (\$80.1 billion; 24.0%),
  - presenteeism (\$43.3 billion; 13.0%)
  - absenteeism (\$38.4 billion; 11.5%).
- Total incremental societal economic burden of MDD was **estimated at \$333.7 billion**

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- **Total incremental societal economic burden of MDD was estimated at \$333.7 billion**
- **Hypothetical novel therapy with a 50.0% early response rate was associated with a 7.7% reduction in the economic burden of Depression relative to standard of care over 12 months.**

# Ketamine (finally!)

- What it is
- (Putative) Mechanism of Action
- What is it approved for
- Use for depression
- Safety



# Intravenous and Intramuscular Ketamine: What Is It?

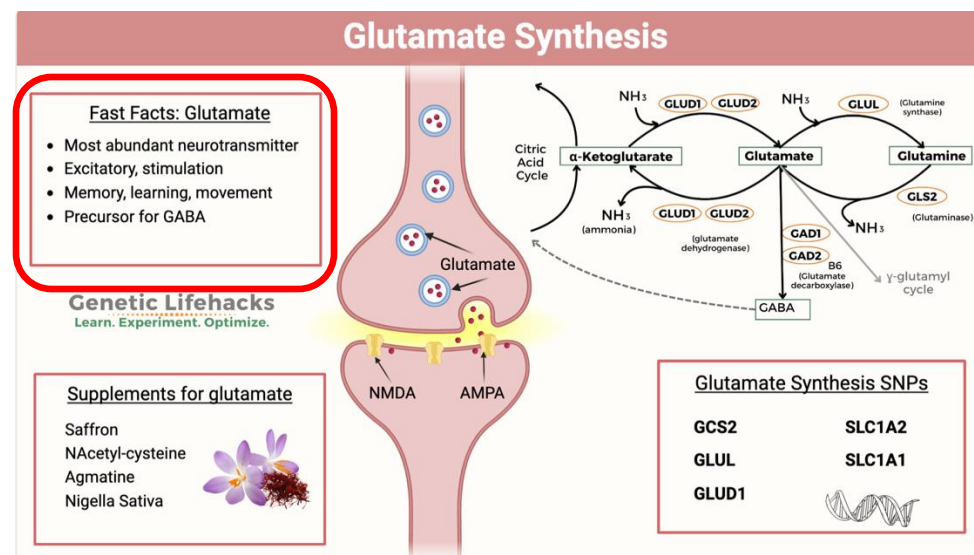
- Rapid-acting general anesthetic producing an anesthetic state characterized by:
  - Profound analgesia
  - Normal pharyngeal-laryngeal reflexes
  - Normal or slightly enhanced skeletal muscle tone
  - Cardiovascular and respiratory stimulation
  - Occasionally a transient and minimal respiratory depression



# Ketamine: Putative Mechanism of Action

## Glutamate and Neuroplasticity

- **Neuroplasticity:** The brain's ability to modify, change, and adapt both structure and function throughout life and in response to experience.
- **Structural plasticity** involves our brains changing its physical structure as we learn new things or form new memories.
- **Functional plasticity** is the brain's ability to move functions from a damaged area of the brain to other undamaged areas.



# Biochemistry, Enantiomers, Drug Development, and Spravato (esketamine)

*(Why isn't IV ketamine approved for depression?)*

- **Enantiomers** are sets of molecules that have the same chemical formula, and the same connectivity, but differ in how their atoms are arranged in space.
- They are a **pair** of molecules that exist in two forms that are mirror images of one another but cannot be superimposed one upon the other.

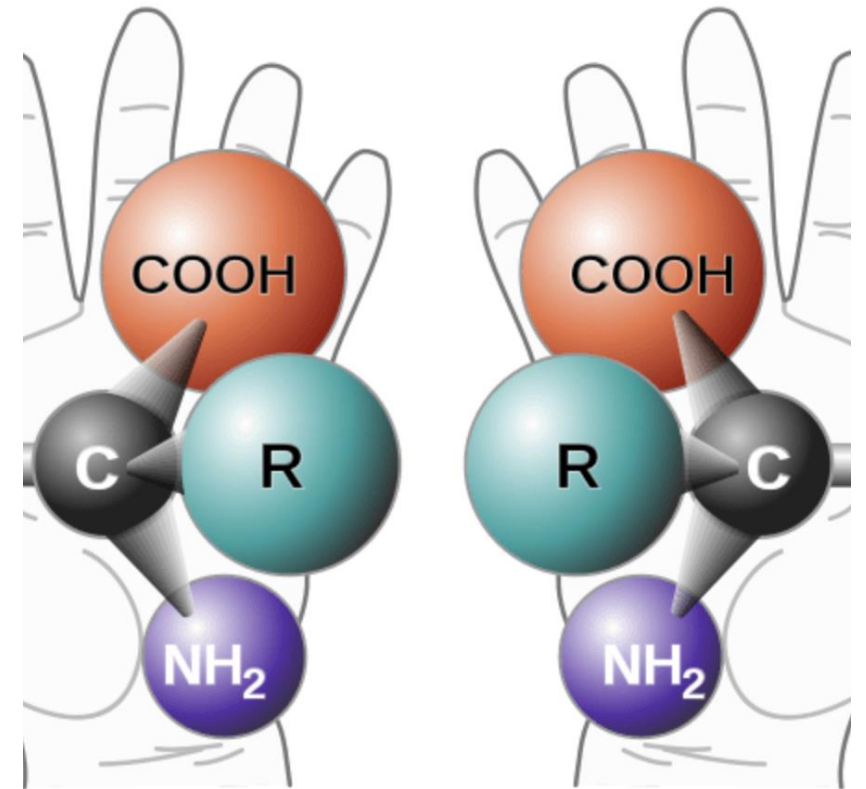


R and S ketamine  
(racemic mixture)



**Spravato**  
(esketamine) ©  
nasal spray

S ketamine



# Ketamine Indications and Administration

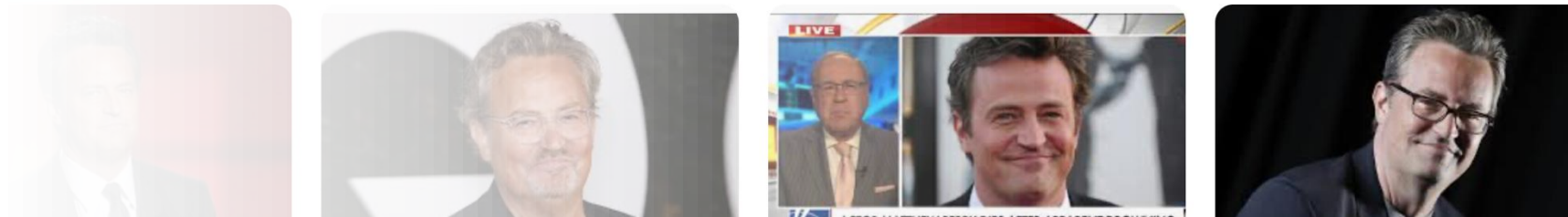
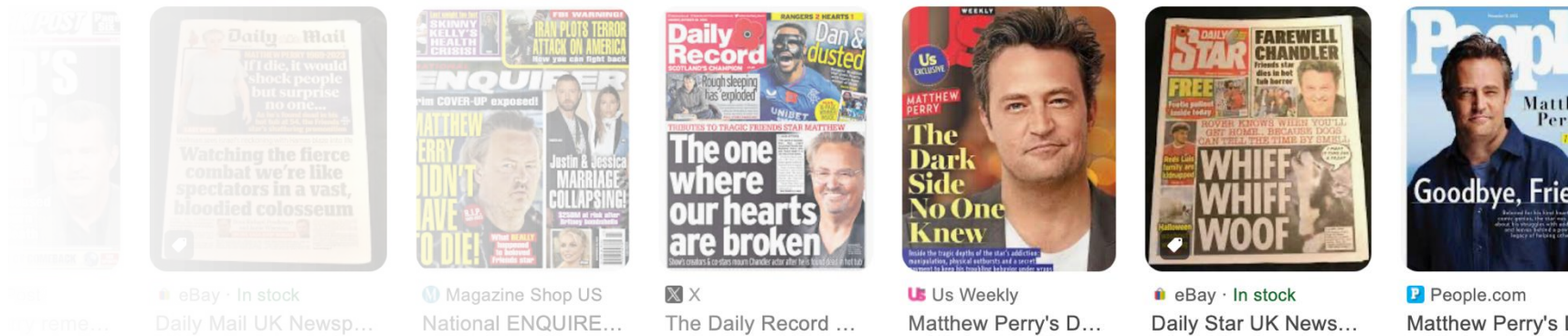
- IV and IM ketamine: No FDA indication, but frequent use off-label.
- Intranasal esketamine (Spravato) is FDA-approved to be used when patients are co-prescribed an oral medication:
  - Adults with treatment-resistant depression (TRD)
  - Depressive symptoms in adults with major depressive disorder (MDD) with suicidal thoughts or actions

**IV ketamine** 0.5 mg/kg infused over 40 minutes.

- Monitored (blood pressure, neuropsychiatric symptoms, sedation) for another hour
- No driving next 24 hours



# Ketamine and Safety: "What About Matthew Perry?"



# Ketamine is Not Without Risks

- Most concerning side effects:
  - Increase in blood pressure
  - Neuropsychiatric
    - Anxiety
    - Depersonalization
    - Psychosis
- Synergistic effects with other sedating medications
- Cystitis
- Misuse



# Internet-Delivered Ketamine and Community-Based Ketamine Infusion Clinics

Joyous and Mindbloom are examples of Internet-based Ketamine Programs

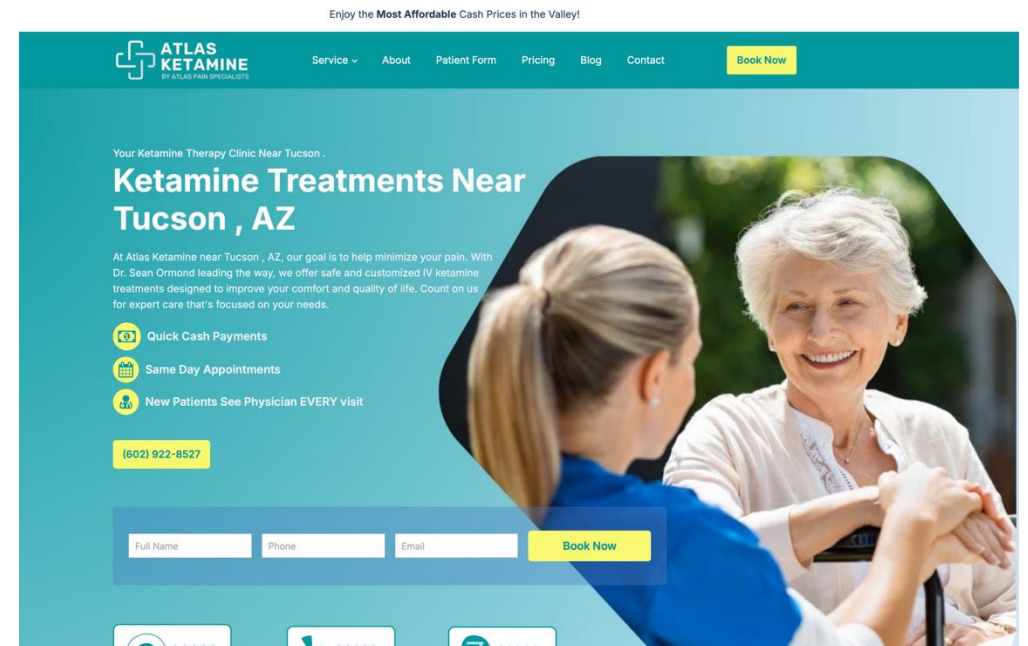
**Joyous Arizona**

← **New Patient Mental Wellbeing**  
👤 Jenny Parker  
📅 Tuesday, January 14, 2025  
🕒 10:45 AM - 11:00 AM (15 min)  
📍 America/Phoenix

Legal first name*	Legal last name*	
<input type="text" value="First name"/>	<input type="text" value="Last name"/>	
Email*	Cellphone*	
<input type="text" value="Email"/>	<input type="text" value="+1 Cellphone"/>	
Date of birth*		
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State *	Zip Code*	
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[Schedule appointment](#)

Atlas Ketamine is an example of many infusion clinics





# Reviewing What We've Learned About Ketamine

- Ketamine is the first FDA-approved medication in 60 years that does not target the monoaminergic neurotransmitter system.
- Increased neuroplasticity (structural and functional) which means tighter neural connectivity and improved ability to learn may be one way that ketamine works for depression.
- IV ketamine and intranasal esketamine (Spravato) both can rapidly improve depression and suicidal thoughts.
- No drug is without some risk.
- We need more research funding for mental health.



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RESOURCES



Patients with difficult-to-treat depression can receive specialized treatment, such as ECT, rTMS, and Esketamine, from our Center for Interventional Psychiatry and Neurotherapeutics.