



**Stanford** | Department of Psychiatry  
MEDICINE | and Behavioral Sciences

**Rodriguez** | LAB  
Translational Therapeutics



# Towards Rapid-Acting Treatments for OCD

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# Funding and Disclosures (Rapastinel)

## Study Drug:

**Rapastinel (formerly GLYX-13) was supplied by Naurex at no cost (since drug donation Naurex has been acquired by Allergan)**

## Funding:

**2014 NARSAD Ellen Schapiro and Gerald Axelbaum Young Investigator Award, Brain and Behavior Research (PI: Rodriguez)**

**New York Presbyterian Youth Anxiety Center**

**K24MH9155 (PI: Simpson)**

**K23MH092434 (PI: Rodriguez)**

**Dr. Rodriguez was reimbursed for time and travel to present these findings at Allergan after submitting for publication.**

**Dr. Moskal founder and owned stock in Naurex.**

**Dr. Burch was an employee of Naurex when rapastinel was donated.**



# Funding and Disclosures

## **NIMH (PI: Rodriguez)**

- K23 Novel Interventions for Adults with OCD
- R01 NMDAR Modulation As A Therapeutic Target and Probe of Neural Dysfunction in OCD

## **Foundations/Donors (PI: Rodriguez)**

- Harold Amos Medical Faculty Development Award, Robert Wood Johnson Foundation
- 2009 & 2014 NARSAD, Brain and Behavior Research Foundation
- Black Family, Graham Arader, Youth Anxiety Center Initiative

## **Other (PI: Rodriguez)**

- New York State Office of Mental Health
- Provost's Grants Award Program
- Irving Institute for Clinical and Translational Research

## **Industry (Consultant: Rodriguez)**

- Allergan
- Rugen Therapeutics
- BlackThorn Therapeutics

# OCD: A Chronic, Disabling Disorder



**2% Lifetime prevalence**

**Half of cases start by age 19**

**Only FDA-approved medication:  
Serotonin-reuptake inhibitors**

*Koran et al., 2007; Koran and Simpson 2013*

**Koran et al., 2007; Koran and Simpson, 2013**

# Imagine you are on a hike...



**...but the only water lies in a toilet bowl.  
Would you drink?**



# Did you pause? Did you grimace?



Wilkerson and Rodriguez, *American Journal of Psychiatry*, 2016

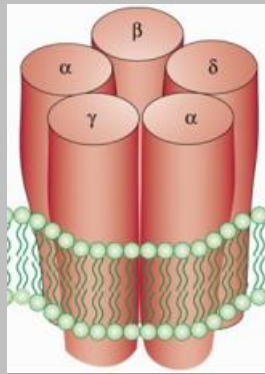
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# OCD: Hyperactive Fronto-Striatal Brain Circuits

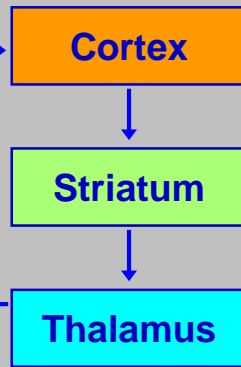


Rosenberg et al., 2000; Pittenger et al., 2011; Maia et al., 2008; Ahmari et al., 2013; Burguiere et al., 2013; Wood and Ahmari, 2015

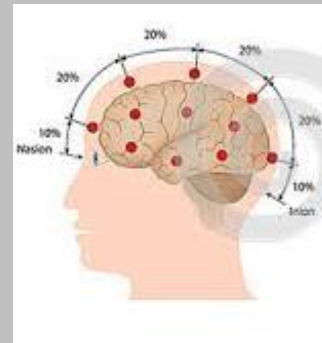




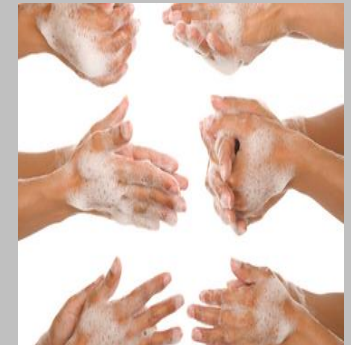
Receptor



Circuit



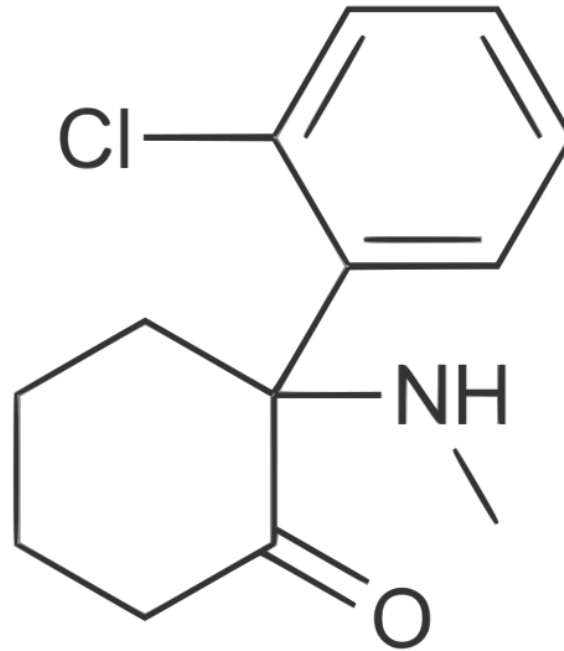
Neural  
Networks



Behavior



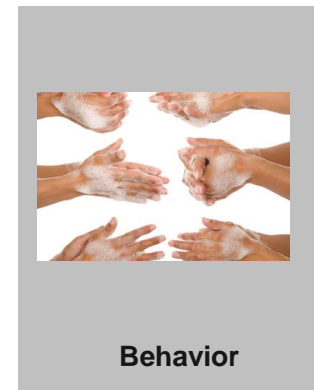
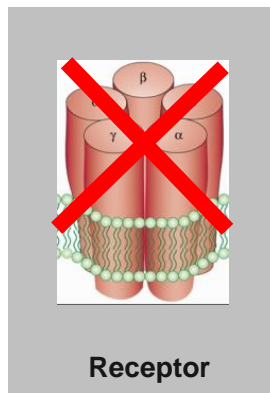
# Ketamine



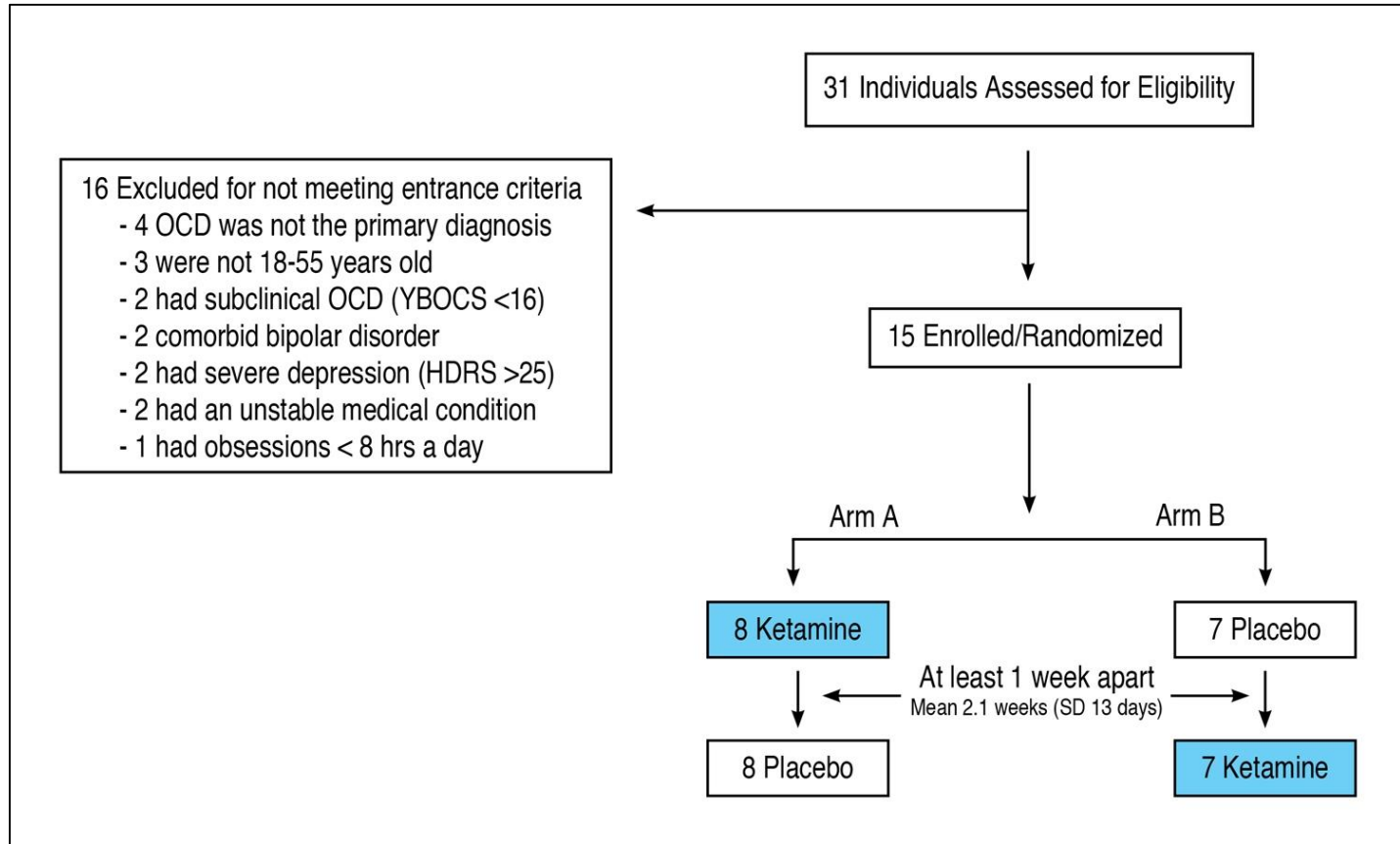
# Ketamine Decreases OCD

**Ketamine: NMDA glutamate receptor antagonist**

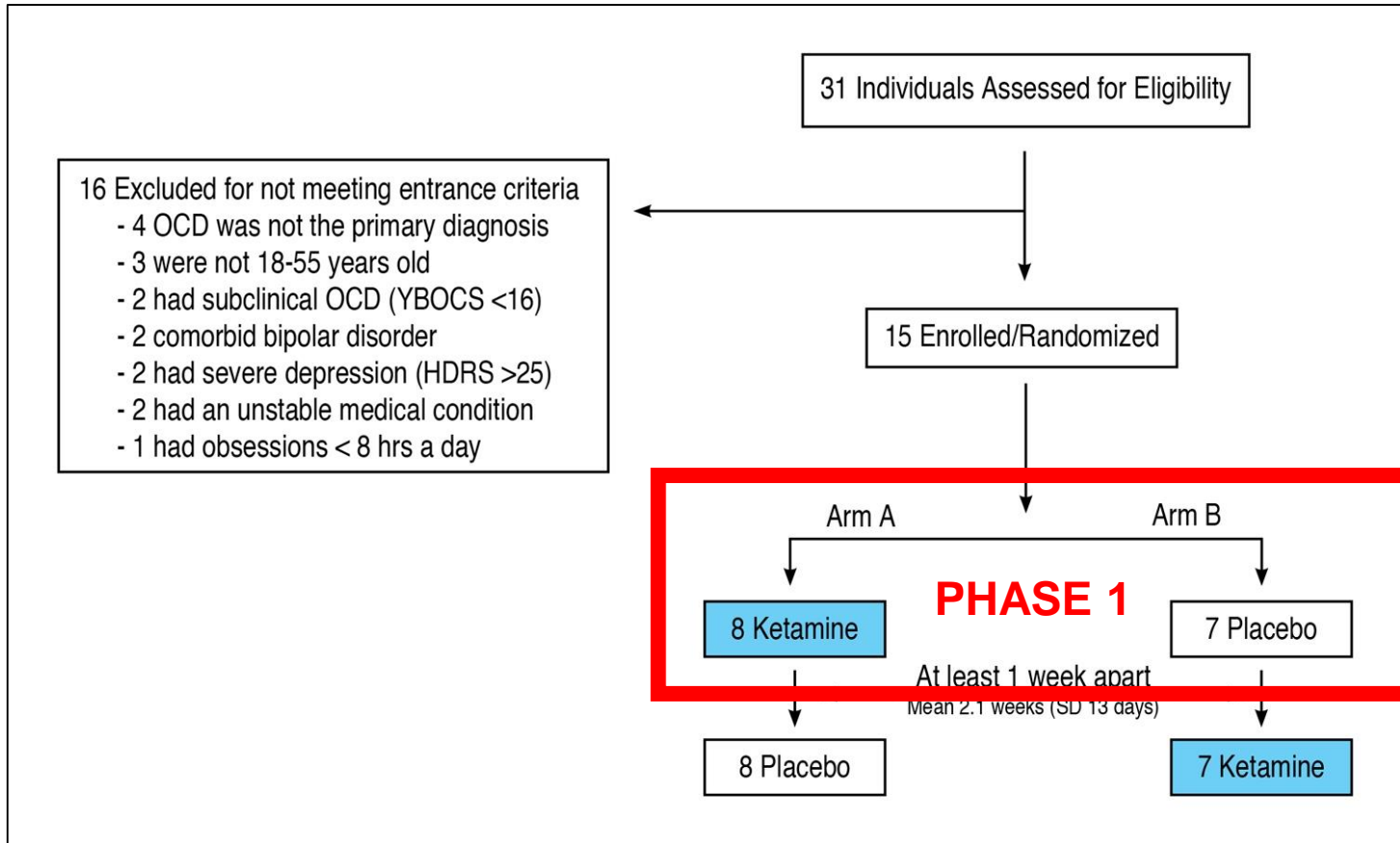
**Individuals with OCD (n=15) randomized to IV ketamine or saline**



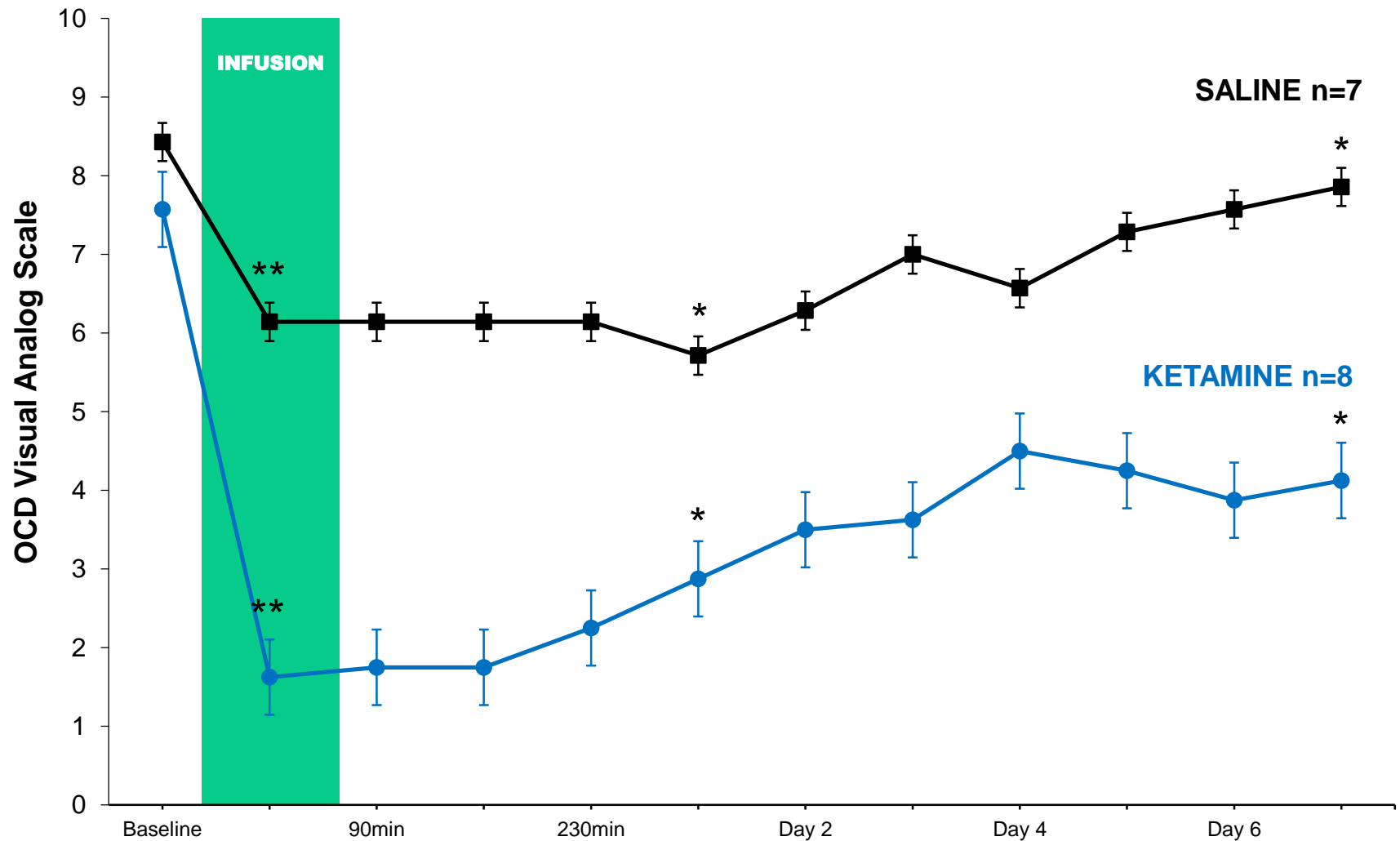
# Study Design (Flow)



# First Phase Only



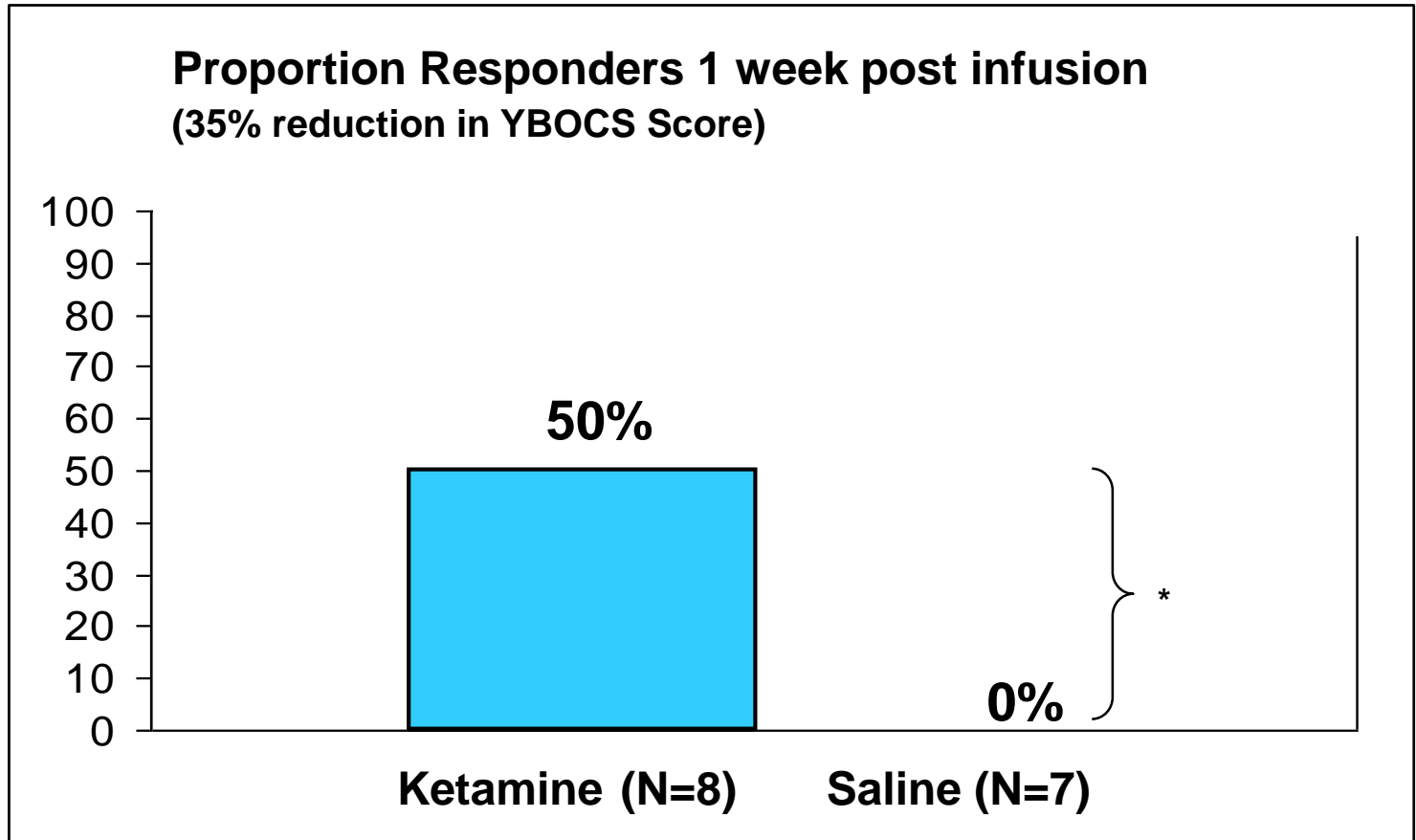
# Ketamine Rapidly Reduces OCD



Rodriguez et al., *Neuropsychopharmacology*, 2013

Stanford University

# First Phase



\*  $p < 0.05$

# Quotes from Responders after Ketamine

## Responders (4 out of 8):

1. “I feel as if the weight of OCD has been lifted...I want to feel this way forever”
2. “I feel like someone is giving me an explanation [for my OCD]”
3. “I don’t have any intrusive thoughts. I was laughing when you couldn’t find the key, which normally is a trigger for me. This is amazing, unbelievable. This is right out of a movie.”
4. “I tried to have OCD thoughts, but I couldn’t”



# Side Effects

Side effects in order of frequency	TOTAL N=15 (8 Ketamine, 7 Saline)			
	<u>n</u>		<u>%</u>	
	Ketamine	Saline	Ketamine	Saline
Feelings of unreality/ Dissociation	8	1	100%	12.5%
Dizziness	2	0	25%	0%
Nausea	1	0	12.5%	0%
Vomiting	1	0	12.5%	0%
Headache	1	0	12.5%	0%

Mild transient changes in blood pressure and heart rate observed on infusion day consistent with MDD studies that show mean change pre/post IV ketamine of less than 20 mm Hg systolic and 10 mm Hg diastolic.

Rodriguez et al., *Neuropsychopharmacology*, 2013  
 Murrough, et al., 2013  
 Stanford University

# Summary #1

**First study** showing ketamine can decrease intrusive thoughts in the absence of SRIs

Glutamate modulation may be a **rapid-acting therapeutic target** for OCD

# Challenge:

## Ketamine Has Side Effects

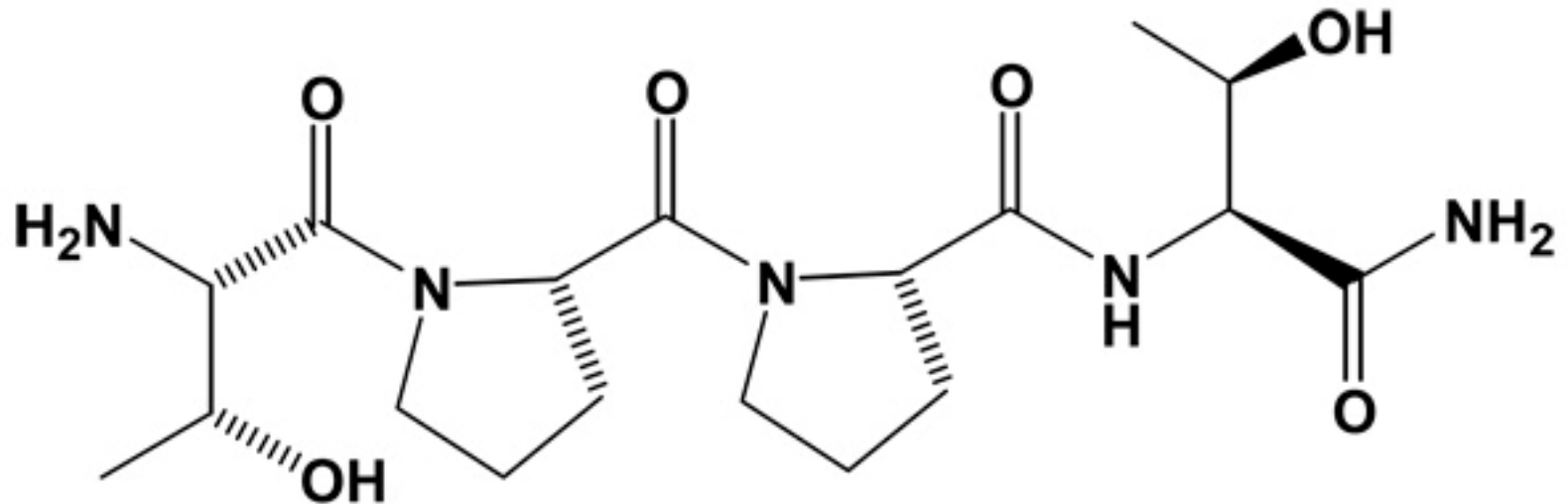


# Rapastinel

Monoclonal antibody-derived neuropeptide (Glyxin family)

Invented by Dr. Joseph Moskal

Putative NMDAR modulator



# Could Rapastinel be an OCD Therapeutic?

**Shows rapid anti-depressant activity without ketamine-like effects in animal models**

**Dosing:**

**Phase IIa randomized, multiple-dose controlled (N = 116)**

**Showed 10 mg/kg had significant anti-depressant effects vs placebo**

**Effect lost at higher dose**

# Study Design

## Method:

**Open-label: Single 3-5 min push IV Rapastinel 10 mg/kg**

## Inclusion:

**OCD at least moderate severity (YBOCS>16)**

**Unmedicated**

**Age 18-55**

## Exclusion:

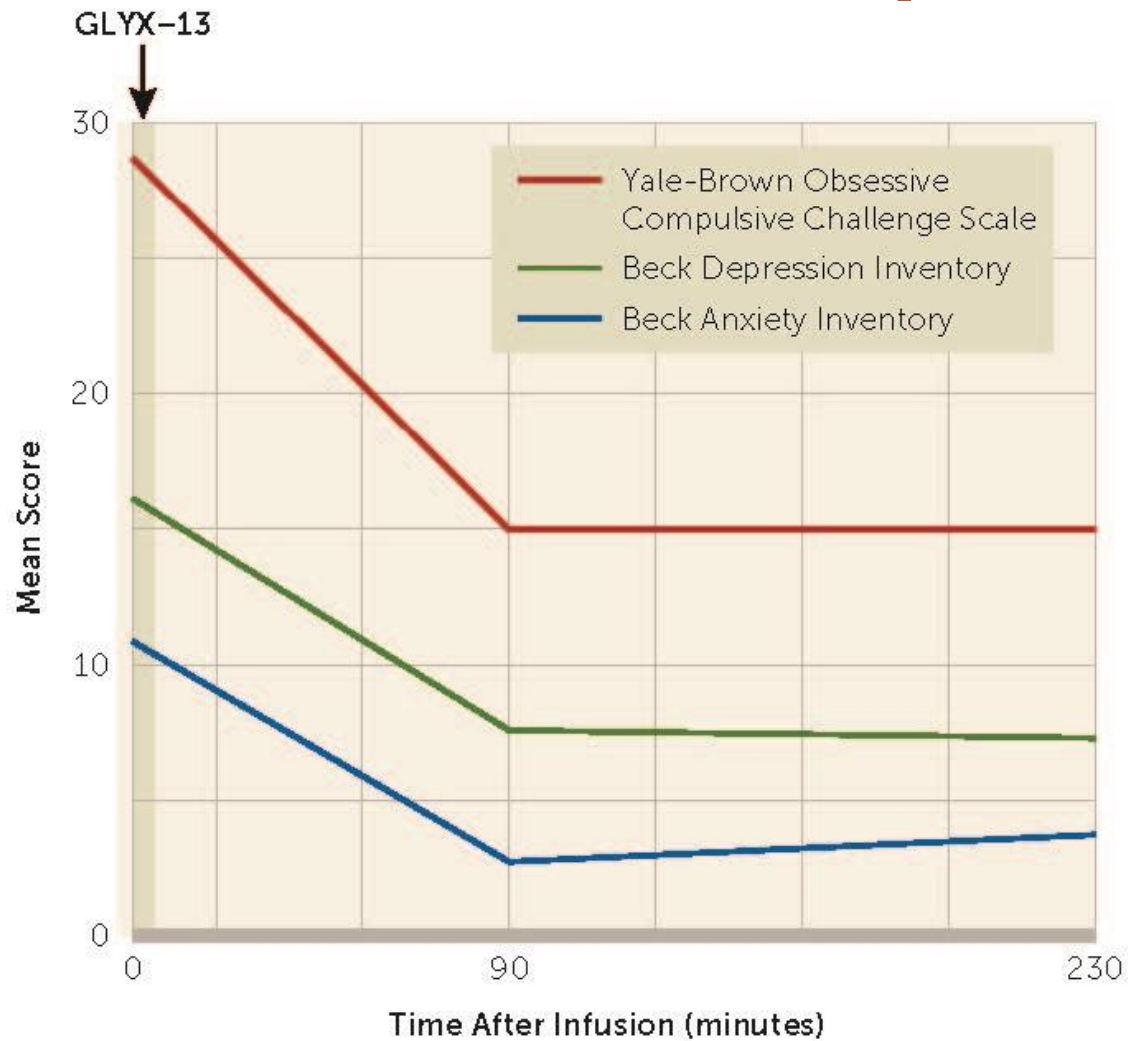
**Severe depression (HDRS>25)**

**Lifetime psychosis, bipolar, substance dependence**

Rodriguez et al, *American Journal of Psychiatry*, 2016

Stanford University

# Acute Effects of Rapastinel



Rodriguez et al, *American Journal of Psychiatry*, 2016

Stanford University



# Assessments of Sustained Effect

**Sustained Effect: YBOCS (independent evaluator)**  
**Measures Obsessions and Compulsions**  
**Assessed over past week**  
**Responder  $\geq$  35% reduction**

**One week post-infusion:**  
**YBOCS = 0 out of 7 met response criteria for OCD**  
**Beck Depression Inventory = not significant (p=0.2)**  
**Beck Anxiety Inventory = significant (p=0.02)**



# Summary #2

**Rapastinel is well tolerated in unmedicated OCD patients, as it is in patients with depression**

**It did not increase psychotomimetic effects, unlike ketamine**

**Acute effects on OCD, anxiety and depression, but no effects on OCD 1 week post infusion**

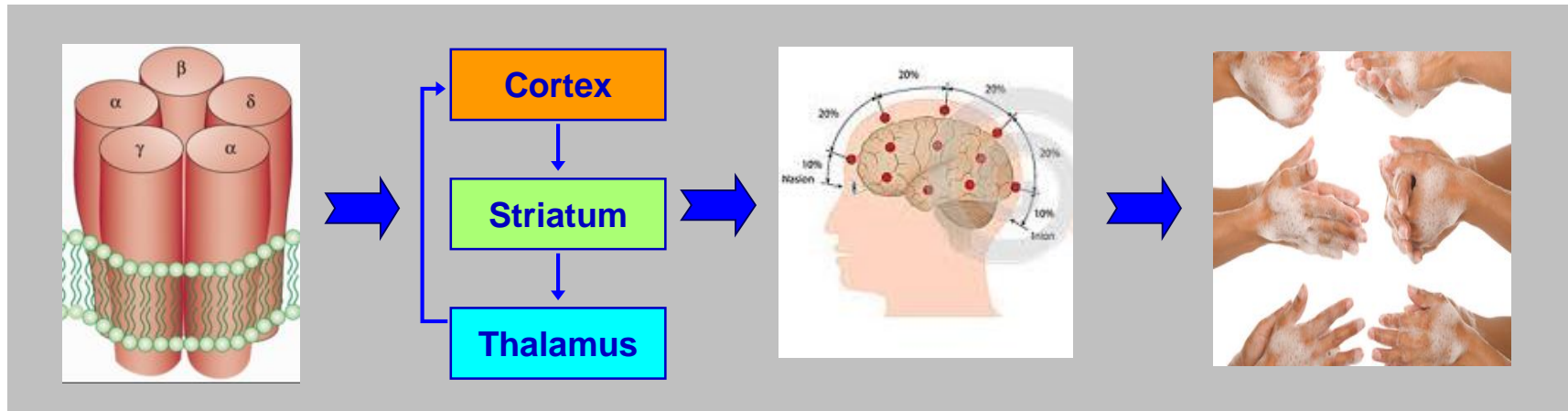
**Next Steps: repeated dosing**

Rodriguez et al, *American Journal of Psychiatry*, 2016

# Future Directions

## Next Generation NMDAR Modulators

### Ketamine's Mechanism of Action (NIMH R01)



### Biomarkers of Ketamine's Effects (Harold Amos – RWJ)

# Rodriguez Lab

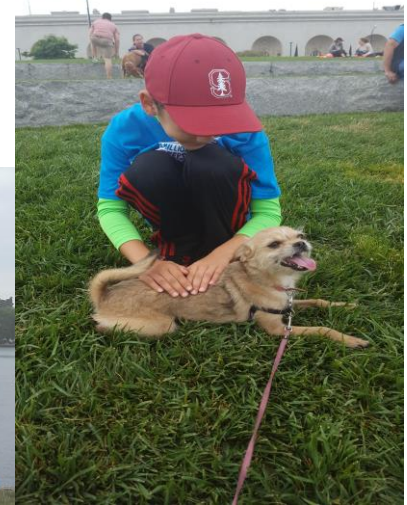


# Impact

Demonstrate Rapidly Acting Tx Possible

Shed light on severity of OCD

Decrease Stigma



1 Million Steps 4 OCD Walk    Oakland, CA, June 4, 2016  
Sacramento, CA, June 10, 2017

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