



Pharmacotherapy of OCD

Michael Jenike, MD

Professor of Psychiatry
Harvard Medical School

Founder, OCD Clinic & Research Unit
Massachusetts General Hospital

Founder, OCD Institute
Mclean Hospital

Disclosures

Neither I nor my spouse has a relevant financial relationship to disclose.



MASSACHUSETTS
GENERAL HOSPITAL

PSYCHIATRY ACADEMY

Jenike@comcast.net

Treatment Options

- Psychotherapy
- ECT
- TMS
- Behavior therapy
- Neurosurgery
- Medications

Medication Treatments

- Documented to be partially effective -> SSRIs
- Probably effective -> SNRIs
- Experimental
- Augmentation

Therapeutic Dosages

- Clomipramine (Anafranil) 250 mg
- Fluvoxamine (Luvox) 300 mg
- Sertraline (Zoloft) 200 mg
- Paroxetine (Paxil) 40-60 mg
- Fluoxetine (Prozac) 40-80 mg
- Citalopram (Celexa) 40 mg
- Escitalopram (Lexapro) 20 mg
- Duloxetine (Cymbalta) 60 mg
- Venlafaxine (Effexor) 375 mg

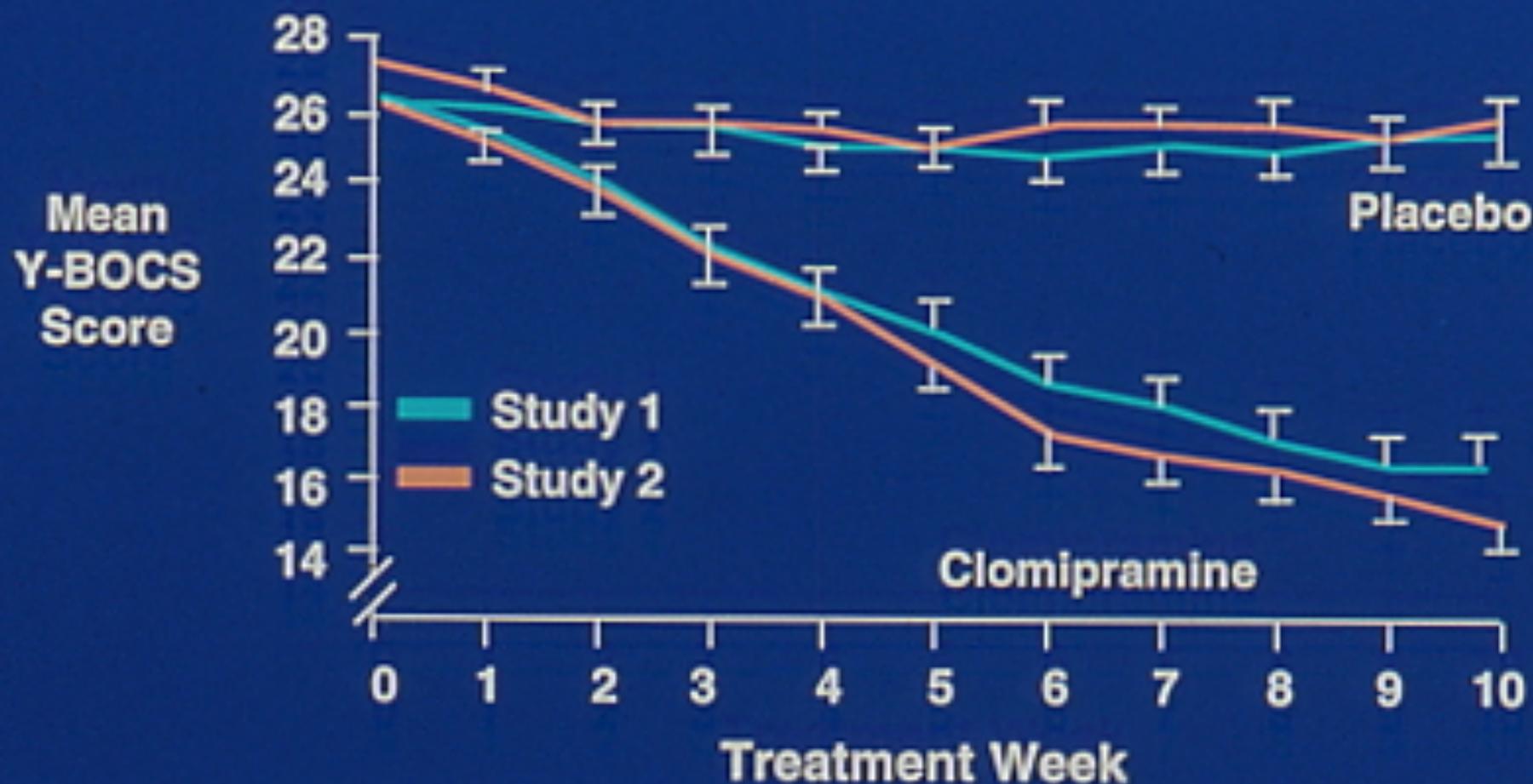
Therapeutic Dosages – Celexa

- Citalopram (Celexa) 40mg
- FDA recommends maximum dosage of 40mg daily due to heart arrhythmias at higher dosage

Paxil – last choice

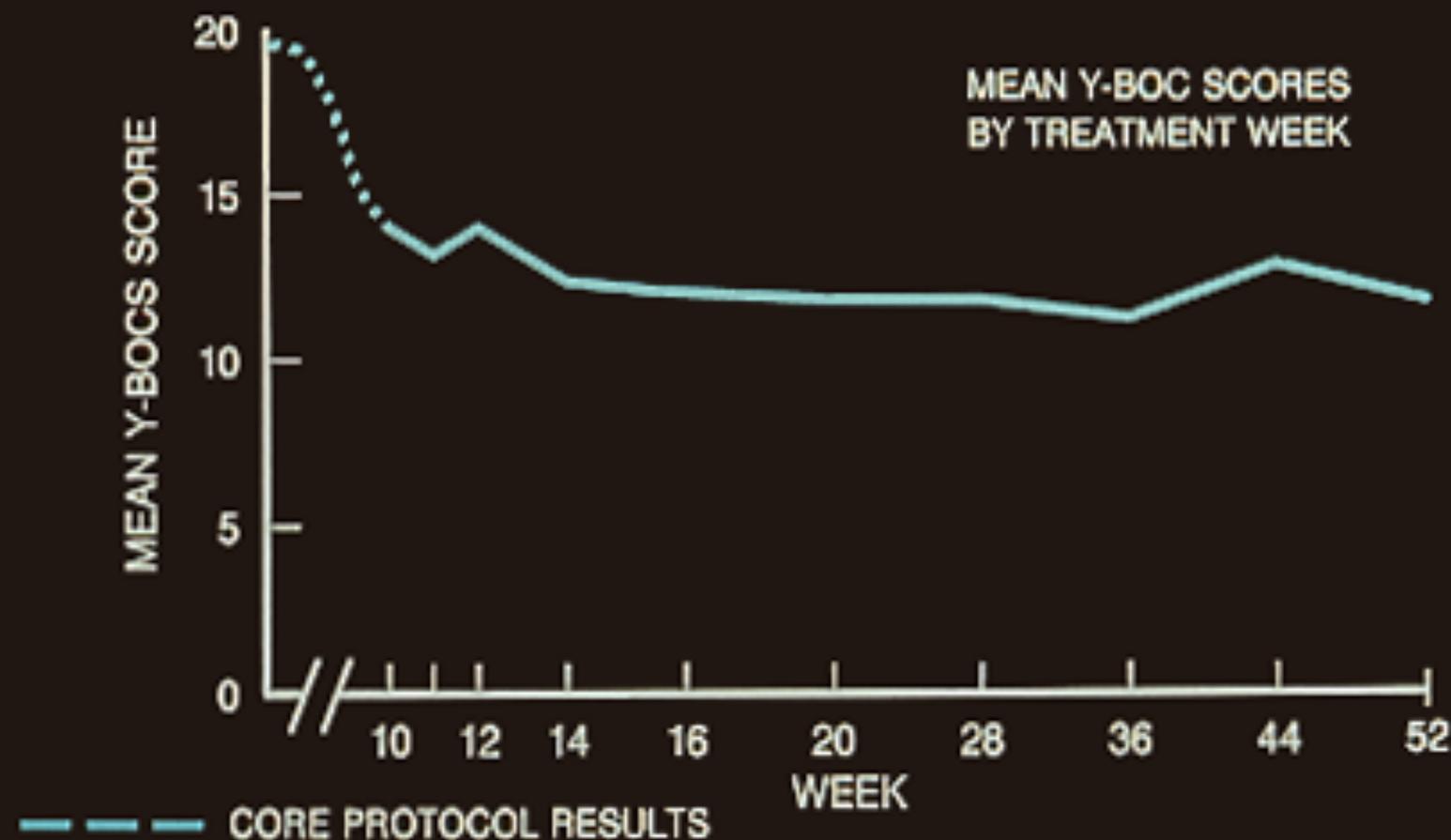
- Paxil has the most sexual and weight gain side effects.
- It is my last choice of SSRIs, but sometimes it works well and patients tolerate it well.

Clomipramine vs Placebo



The Clomipramine Collaborative Study Group. *Arch Gen Psychiatry*, 1991.

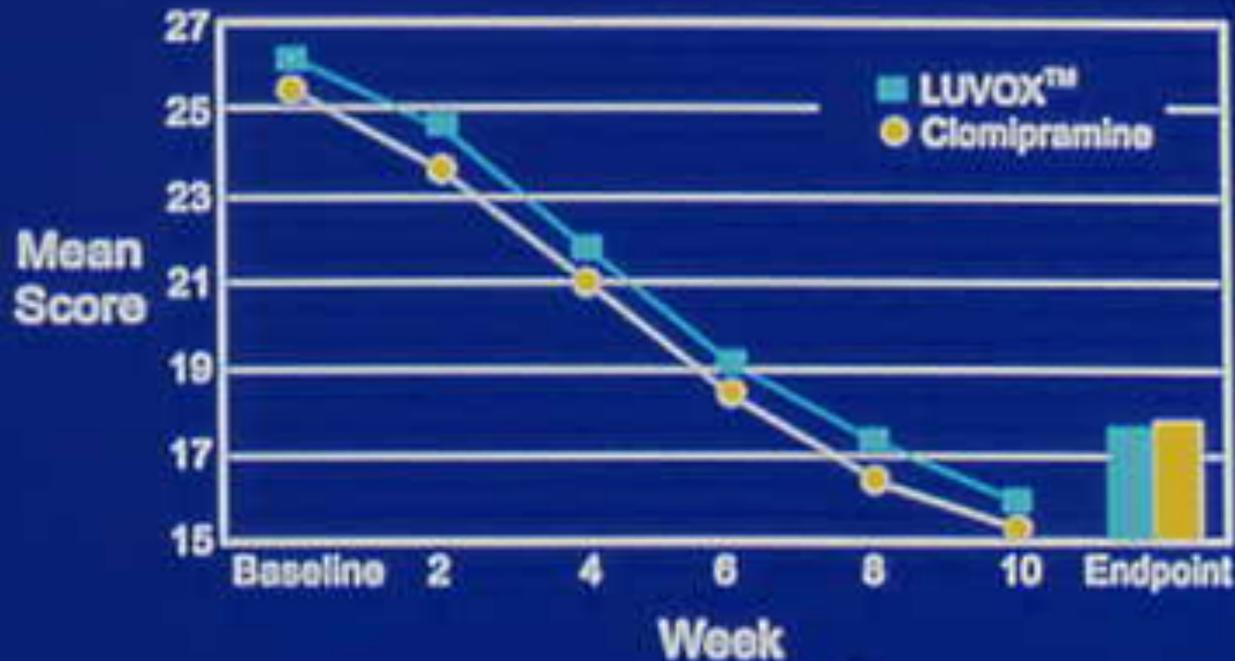
ANAFRANIL® clomipramine HCl EXTENSION TRIAL RESULTS PROTOCOL 61 EXTENSION





Which Is Best OCD Drug?

Y-BOCS Total Score Visit-Wise Analysis



Time Course of Drug Response

- 10-12 weeks for full antiobsessional response

Experimental Medications

Positive Case Reports

- Phenytoin (Dilantin)
- Gabapentin (Neurontin)
- Morphine – 30-45mg once a week
- Ondansetron (Zofran) – 1mg TID

Experimental Medications

Positive Case Reports

- Tramadol (Ultram) - 50-200mg daily
- Pindolol – 2.5mg TID
- Very high dose SSRI – 250-400mg sertraline a day
- Clomipramine + SSRI

Inositol for OCD

- Double-blind, controlled crossover trial
- 18 grams/day of inositol vs. placebo
- 6-week trial
- Subjects receiving inositol had significantly lower scores on the Y-BOCS
- Available from amazon.com

Fux M, Levine J, Aviv A, Belmaker RH. Inositol treatment of obsessive compulsive disorder. *Am J Psychiatry*. 1996;153:1219-1221.

St. John's Wort (hypericum)

- One open trial of 12 patients indicating that it is partially effective for OCD
- No controlled trials

Taylor LVH, Kobak KA. J Clin Psychiatry. August 2000.

Monoamine Oxidase Inhibitors

- Possibly effective when OCD patients have associated panic attacks or symmetry concerns
- *Wait at least 5 weeks between stopping fluoxetine & starting MAOI. Wait 2 weeks for other SSRIs*

Progress Report: The Psilocybin/Obsessive-Compulsive Disorder (OCD) Study Obtains Final FDA Approval!

by Dr. Francisco Moreno (fmoreno@u.arizona.edu)

On May 8, 2001, we learned that the FDA has approved the psilocybin for use in humans. This is the final approval we needed from FDA!

Update

Around April 20, 2001, we submitted additional analytical data to the FDA regarding the purity

of the one gram of psilocybin that MAPS arranged to be synthesized and purchased for our experiment. On May 8, 2001, we learned from the FDA that the psilocybin was approved for human use. We now have final approval from FDA to begin the study! All we need to do now prior to beginning formal recruitment of subjects for the study is to obtain our DEA Schedule 1 licenses to handle the psilocybin, and obtain a DEA certificate of confidentiality (to protect the privacy of our subjects, who are required to have had prior experience with psychedelics). Now that we have final FDA approval for the study, we should be able to obtain our DEA licenses and certificate of confidentiality within a month or two.

History of the Protocol Approval Process

From late 1994 through the beginning of 1995, I treated, under Dr. Pedro Delgado's supervision, a patient who had difficult-to-treat Obsessive-Compulsive Disorder (OCD). Surprisingly, this patient reported that his symptoms had dramatically improved immediately after ingestion of dry psilocybin mushrooms (taken in a recreational context). After chronic exposure to these mushrooms, he noticed that his symptoms remained in remission even when he stopped using psilocybin.

After a brief discussion with Dr. Delgado, in which he indicated that he had heard of similar cases, we conducted a literature search and found minimal direct literature but several supportive reports. We wrote a case report and initiated contact with experienced hallucinogen researchers, including Dr. Rick Strassman, who was then in New Mexico and had expressed interest in collaborating in a prospective study to evaluate this phenomena under controlled circumstances. A number of other researchers including our supporters at MAPS were very enthusiastic about the plan and contributed ideas and feedback to the development of the current protocol.

Our initial task was to work closely with the University of Arizona Human Subjects Committee (HSC) in order to discuss the potential approval of our project. After repeated reviews

and a visit by Dr. Delgado and myself with the HSC, we were able to satisfy their concerns and suggestions by November 1997.

Earlier conversations with Dr. Strassman made it clear that obtaining permission from the FDA and the DEA would be the largest hurdles to overcome once the HSC had approved the protocol. In addition to FDA approval of our protocol for the use of an Investigational New Drug (IND), we need to obtain a DEA schedule I license that is psilocybin-specific. However, the DEA requires an FDA-sanctioned protocol with an approved IND in order to process the application for a DEA license.

Although our protocol design was finally approved by the FDA on September 17, 1998, the FDA placed our IND on clinical hold pending clarification of the source of the drug. Part of the delay in the FDA process is the result of our lack of experience at preparing all the material that is required by the FDA. They accepted our application without a formal protocol written in the format that pharmaceutical companies usually compose. Mistakenly, we had provided the FDA with data on psilocybin existing at NIDA even though NIDA had not yet decided to make that psilocybin available to us. We made the decision to pursue obtaining the drug from NIDA through our in-house collaborators but were unable to do so after about one year of trying. We attempted to import psilocybin from Switzerland but were also unable to arrange for that option.

Hallucinogens for OCD

- Hallucinogens rapidly stimulate 5-HT₂ receptors which may be involved in the mechanism of action of improvement in OCD with SSRIs. SSRIs do this slowly.
- Delgado & Moreno, J Psychoactive Drugs. 1998

Neuroleptics for OCD

- Older neuroleptics rarely helpful
- Helpful as augmenting agents in OCD patients who also have tics
- Newer agents like Risperdal, Seroquel, Geodon, Abilify, and Zyprexa may be helpful in some patients when combined with SSRIs
- May worsen or produce OCD symptoms if used without a SSRI
- Zyprexa – average weight gain is 25 lbs.

Oral Morphine

- Placebo-controlled, double-blind study
- Once weekly morphine – more effective than placebo
- Dose 30-45 mg
- These were SSRI refractory patients

*Koran et al. Double-blind treatment with oral morphine in treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2005 Mar;66(3):353-9.

Tramadol (Ultram)

- Tramadol binds to opioid receptors & inhibits reuptake of serotonin & norepinephrine
- Case reports of tramadol helping OCD patients when they are also on SSRIs

*Goldsmith et al. Rapid remission of OCD with tramadol hydrochloride. Am J Psychiatry. 1999 Apr;156(4):660-1.

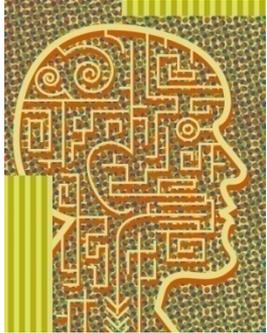
Glutamate Modulating Agents

Glutamate is the most abundant excitatory neurotransmitter in the brain; it is critical to the communication of nerve cells with one another in practically every circuit in the nervous system.

An abnormally high level of glutamate can lead to neuron damage, and glutamate-modulating therapies (medications aimed at affecting or normalizing the actions of glutamate in the brain) have been explored in medical conditions such as “Lou Gehrig’s Disease” (ALS) and in stroke.

Evidence from several sources suggests that abnormal levels of glutamate may contribute to OCD.

Glutamatergic Dysfunction and OCD



Neuroimaging

Animal Studies

CSF Studies

Genetics

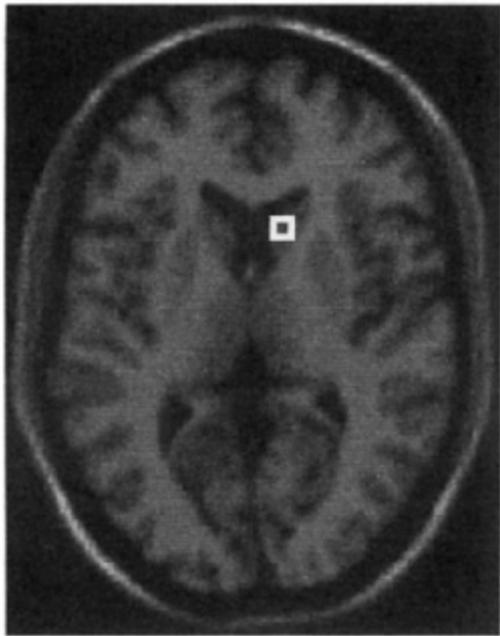
Clinical Studies

with Glutamate Modulating Agents

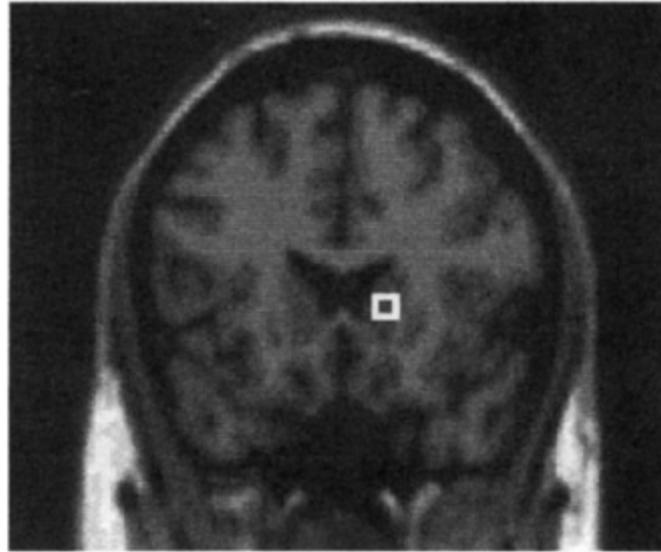


Glutamate and OCD: Neuroimaging Studies

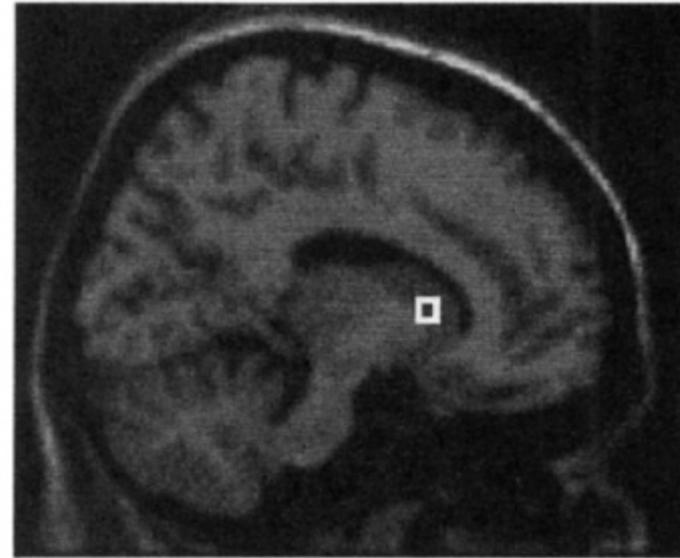
Rosenberg et al, 2000.



Axial



Coronal



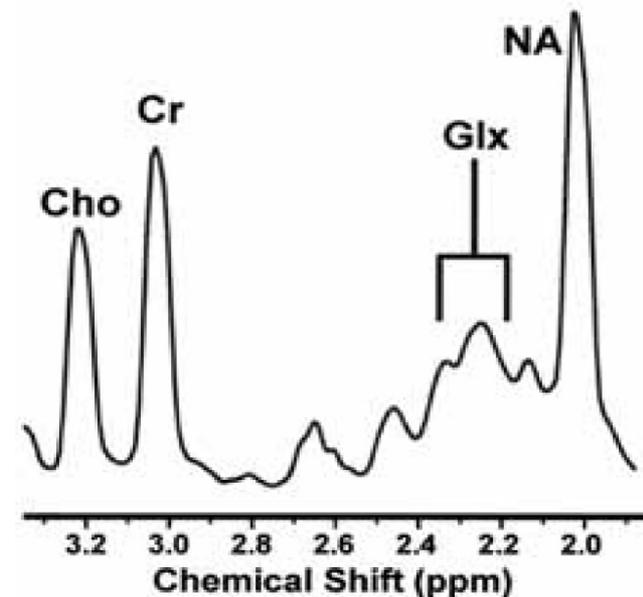
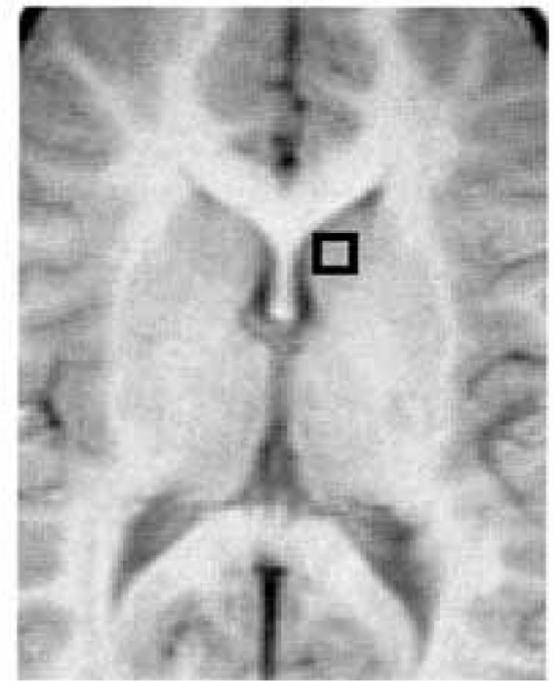
Sagittal

- Proton magnetic resonance spectroscopy (MRS) of left caudate
- 11 healthy controls (ages 8-17)
- 11 psychotropic drug-naïve subjects (ages 8-17) pre- and post-12 weeks of SRI treatment

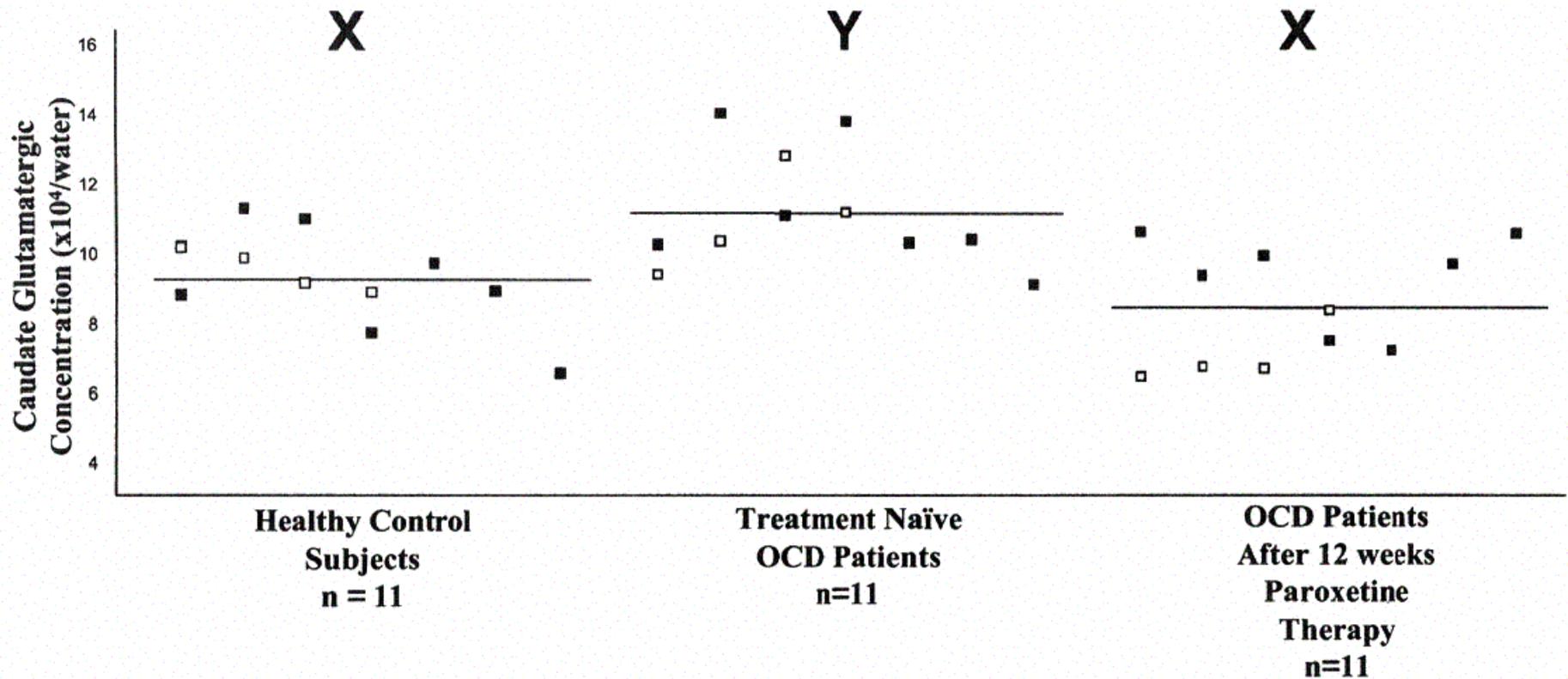
Rosenberg et al, 2000. (cont' d)

Hypothesis: Caudate glutamate is elevated in OCD patients prior to treatment and decreased after effective treatment

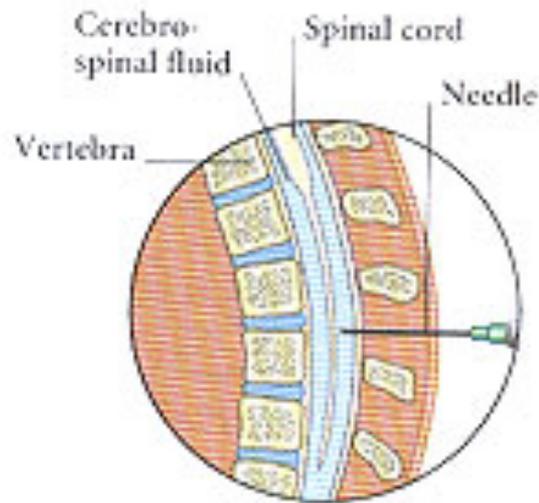
Predicted: Improvement in OCD symptoms is associated with decreased caudate glutamate concentrations



Rosenberg et al, 2000. (cont' d)

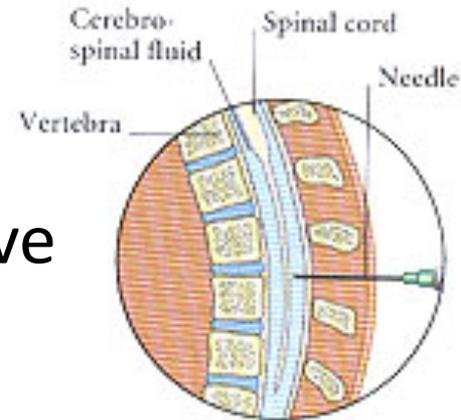


Cerebrospinal Fluid Study: OCD and Glutamate



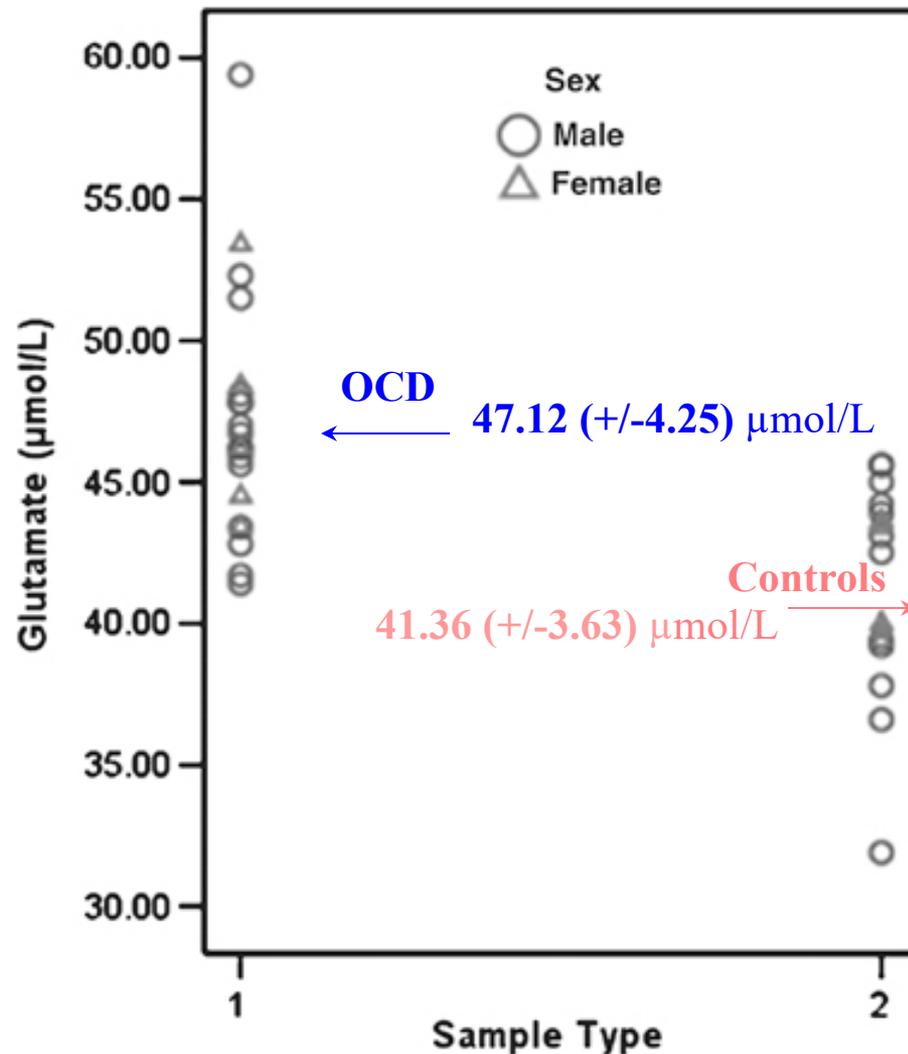
Elevated CSF Glutamate in Patients Diagnosed with OCD

- Chakrabarty et al, 2005.
(*Neuropsychopharmacology*)
- CSF obtained from psychotropic-naïve OCD patients (n = 21) and control subjects (n = 18)
- CSF analyzed for glutamate levels ($\mu\text{mol/L}$)



Elevated CSF Glutamate in OCD (Chakrabarty et al, 2005)

- CSF glutamate level significantly higher in OCD pts vs. controls ($p = 0.014$)
- No effect of gender, age, duration of illness, Y-BOCS score, or CGI-S on glutamate levels



Genetic Studies: OCD

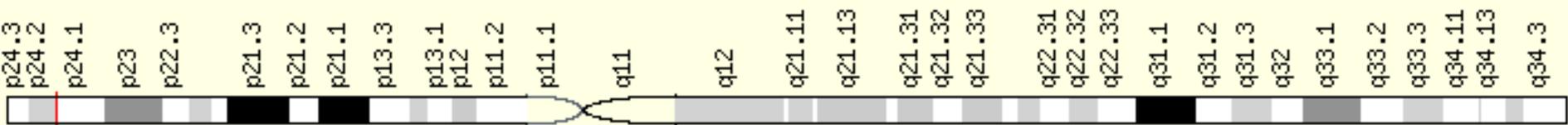
- Strong genetic component associated with OCD
 - Familial pattern
 - Higher concordance rates in *monozygotic* vs. *dizygotic* twins (80-87% vs. 47-50%)
 - Higher rates in 1st-degree relatives with OCD or Tourette's
- Two OCD genetic studies to date have suggested evidence for linkage on chromosome region 9p24



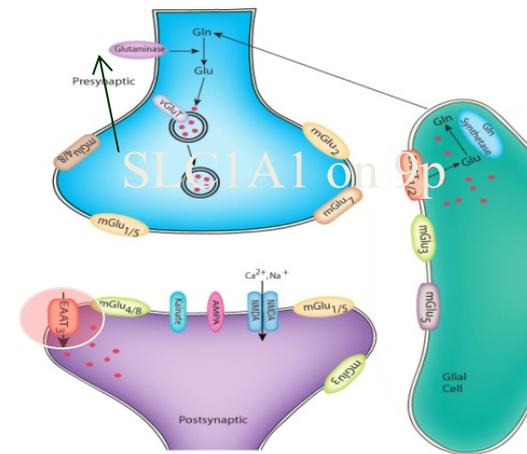
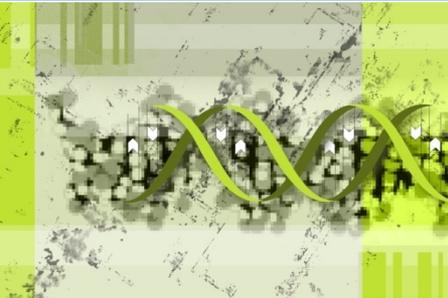
Hanna et al, 2002. Willour et al, 2004.



Chr 9



Genetic Studies: OCD and Glutamate



- Chromosome region 9p24 contains the gene encoding for the glutamate transporter

Mouse Studies (Calakos & colleagues)

- mice who were engineered to lack gene Sapap3 start grooming compulsively
- a brain receptor mGluR5 is overactive in these mice

Mouse Studies (Calakos & colleagues)

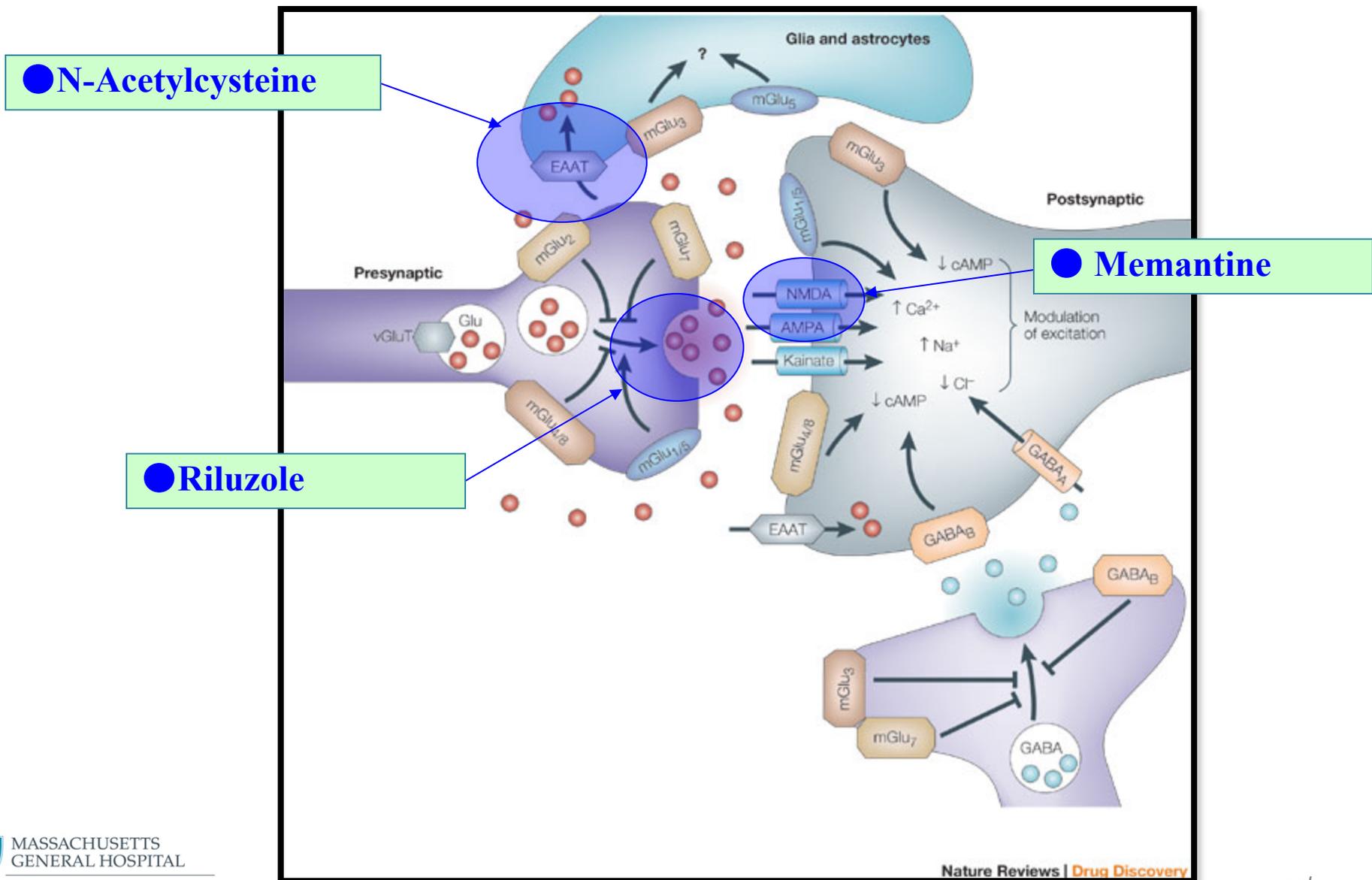
-if mGluR5 is blocked
experimentally, the symptoms
went away **IMMEDIATELY**

Mouse Studies (Calakos & colleagues)

- if mGluR5 is boosted in a normal mouse, OCD-like behaviors appear.
- perhaps mGluR5 blockers could help OCD patients.

Glutamate and OCD: Clinical Studies

Current Clinical Pharmacologic Studies Modulating Glutamatergic Neurotransmission



Namenda (memantine)

- Start at 5 mg per day
- Raise by 5 mg per day per week
- Target dose = 20 mg per day

Namenda (Memantine)

Memantine augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial

Aboujaoude E, Barry JJ, Gamel N.
J Clin Psychopharmacol. 2009

14 OCD patients

Failed average of 2.8 SSRI trials

12 week trial

Namenda 20mg daily

almost half the subjects had a meaningful improvement in OCD symptoms

Namenda (Memantine)

A single-blinded case-control study of memantine in severe obsessive-compulsive disorder.

22 OCD patients and 22 matched controls

All in an intensive residential treatment program

At least 12 week trial

Namenda 20mg daily

OCD symptoms improved in patients vs controls

***Stewart SE, Jenike EA, Hezel DM, Stack DE, Dodman NH, Shuster L, Jenike MA, J Clin Psychopharmacol. 2010*

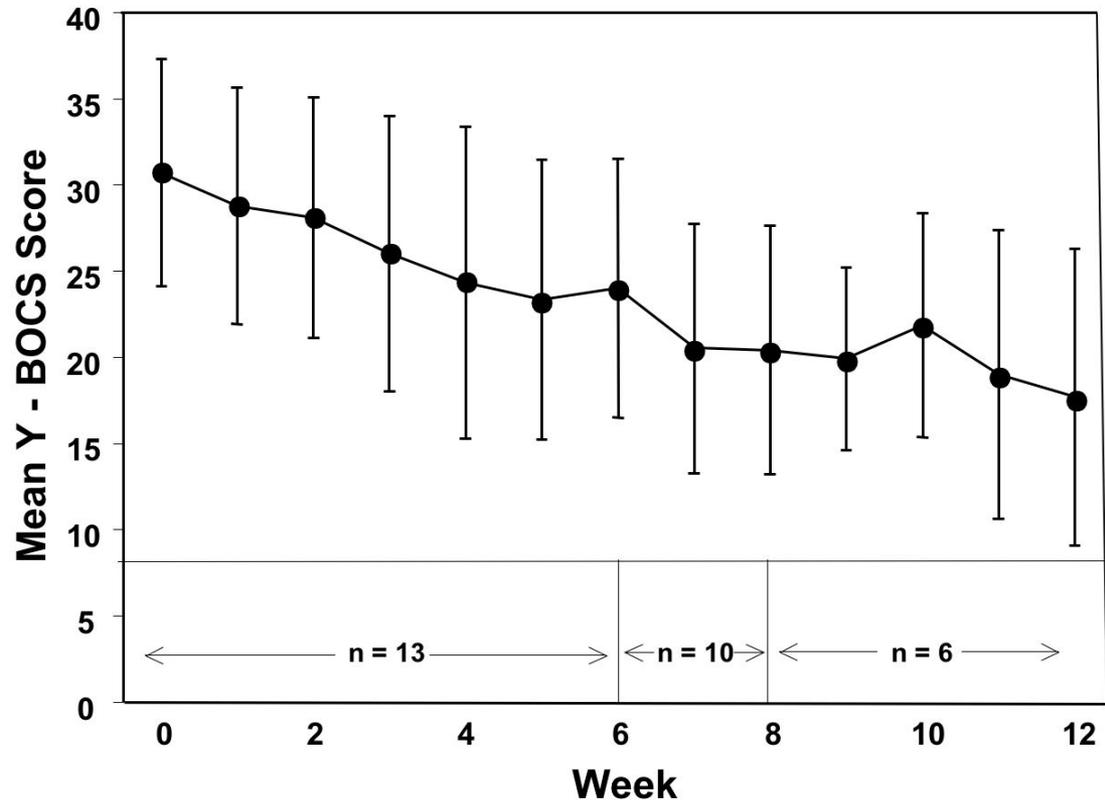
Riluzole

- Used for ALS
- 13 treatment-resistant OCD patients received Riluzole 50 mg twice a day in an **open** trial
- 7 patients had a $> 35\%$ reduction in Y-BOCS
- HAM-D and HAM-A scores also significantly improved
- No serious adverse effects noted

***Coric V et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. Biol Psychiatry. 2005 Sep 1;58(5):424-8.*

Riluzole in OCD

(Coric et al, 2003; Coric et al, 2005)



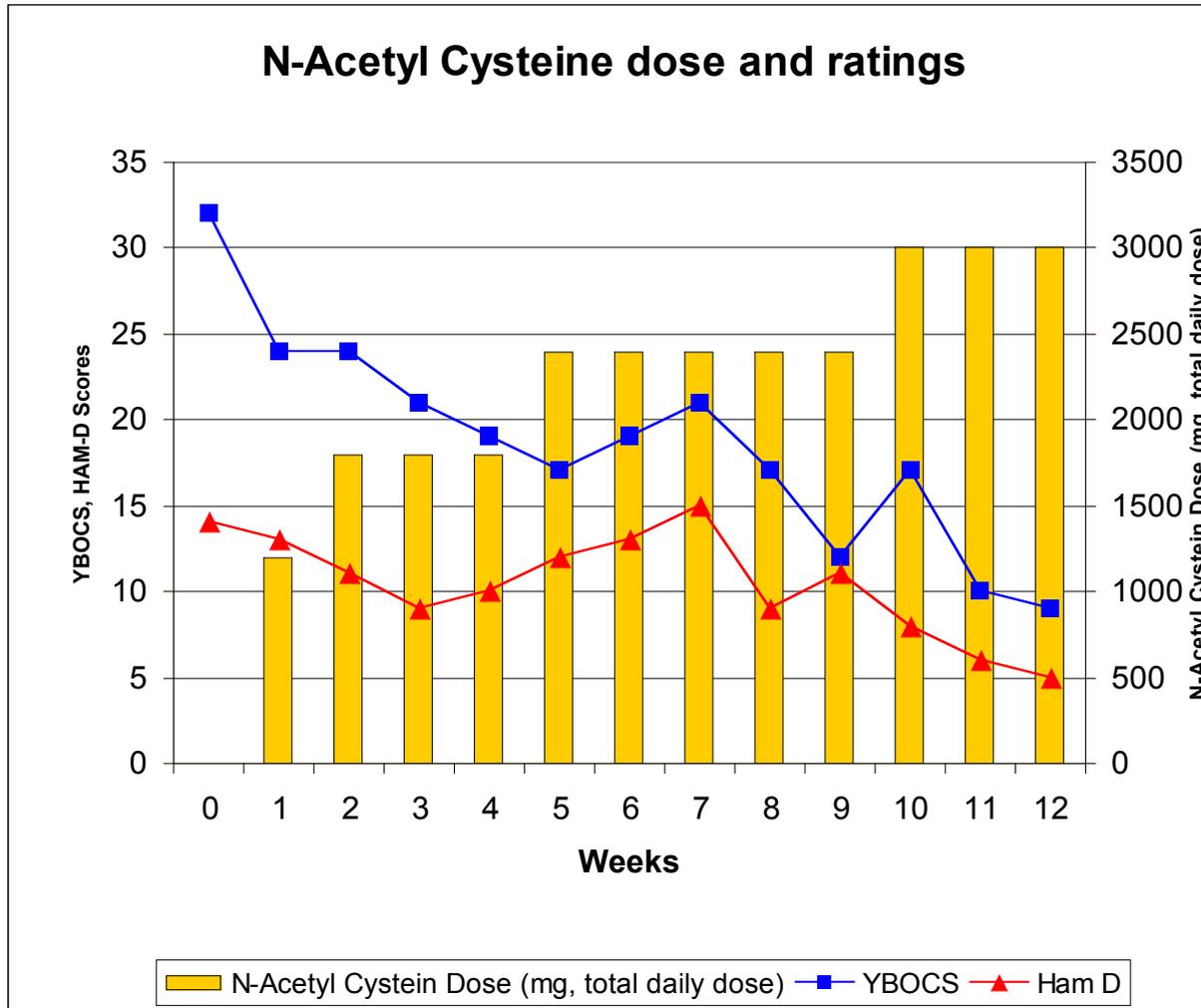
*Y-BOCS scores improved significantly over time ($F_{1,11.1} = 19.78, p = 0.001$)

Troriluzole

Lia Donahue at:

lia.donahue@biohavenpharma.com

Case Report: NAC in OCD



Where to buy NAC

- https://www.amazon.com/Jarrow-Formulas-Sustain-SupportsFunction/dp/B0013OVVK0/ref=sr_1_1_a_it?ie=UTF8&qid=1478034480&sr=81&keywords=nac%2Bjarrow&th=1
-
- https://www.amazon.com/Swanson-Nac-N-Acetyl-Cysteine-Caps/dp/B00068GKC8/ref=sr_1_2_a_it?ie=UTF8&qid=1478034514&sr=8-2&keywords=swanson%2Bnac&th=1
- (this one is often cheaper, fully publishes ingredients, and was used in many studies)

Anticonvulsants

- Blocks glutamate neurotransmission
- ***Lamotrigine*** – 100mg added to SSRI – placebo controlled trial – significant improvement
- ***Topiramate*** – mean dose 180mg added to SSRI – placebo controlled trial - significant improvement

Summary

- Convergent evidence suggests that glutamate is perturbed in OCD
 - MRS studies show elevated glutamate in the striatum of patients with OCD
 - CSF studies show increased glutamate in OCD
 - Genetic linkage studies suggest a dysregulation of glutamate in some familial cases of OCD
 - Clinical studies suggesting efficacy associated with the use of glutamate modulating agents in SRI-resistant OCD

OCD Improves: Depression Persists

- Bupropion (Wellbutrin)
- Lithium
- Thyroid hormone (Cytomel)
- Pindolol (Visken)
- Desipramine (Norpramin)
- Nortriptyline (Pamelor)
- Mirtazapine (Remeron)

Treatment Duration

- Many patients want to stay on medication
- Women who want to get pregnant may want no meds
- Of 35 OCD patients who discontinued fluoxetine after a good response, only eight (23%) relapsed in the first year (Fontaine, Chouinard, 1989)

Treatment Duration

- In a double-blind, placebo-controlled study, 16 of 18 patients (89%) had worsening of OC symptoms during a 7-week placebo period (Pato et al, 1988)
- Clinical wisdom:
 - Taper very slowly over many months
 - Add behavior therapy to prevent relapse



PANDAS/PANS

Sudden onset OCD, anorexia, tics,
or psychosis may have an
infectious etiology



PANDAS/PANS

May be a role for antibiotics, anti-inflammatory agents, ivig, plasmaphoresis

PANDAS/PANS



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May occur in adults as well as
children



Pandas Information and Resources

www.pandasppn.org

latitudes.org/category/conditions/pandas-pans/

www.iocdf.org

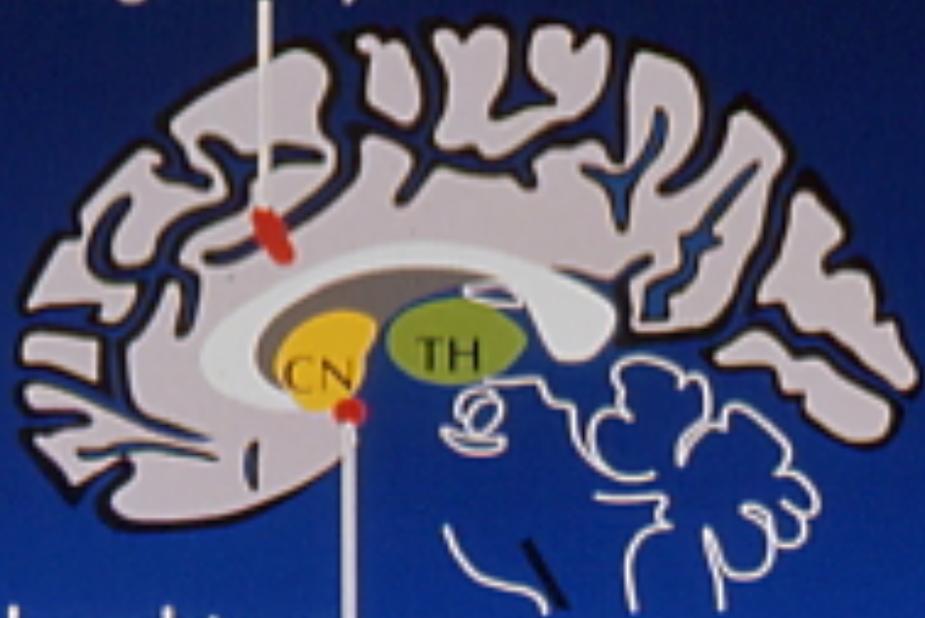
intramural.nimh.nih.gov/pdn/web.htm

Neurosurgery in OCD

Anterior Capsulotomy



Anterior Cingulotomy



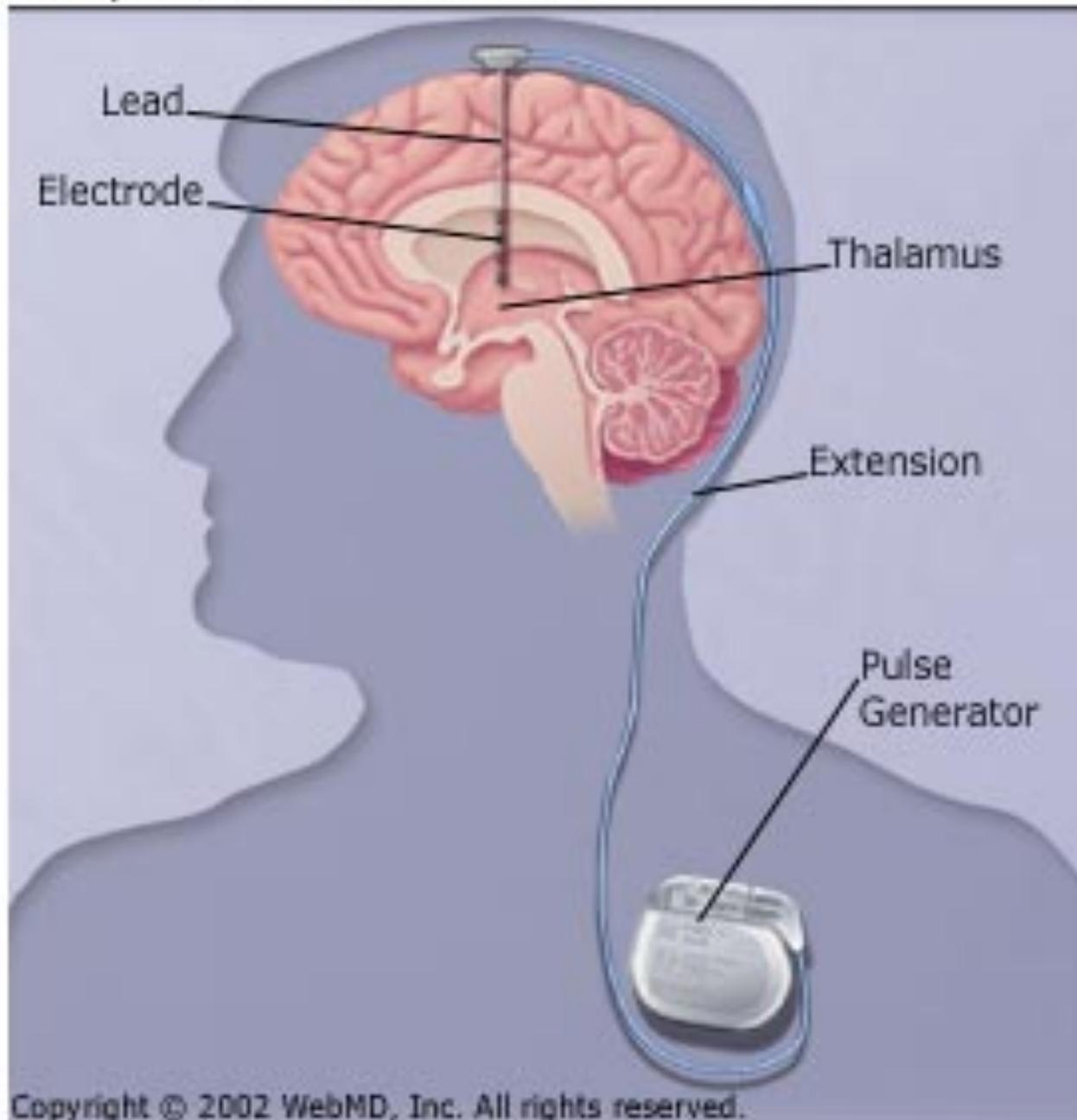
Subcaudate Tractotomy

TH = Thalamus

CN = Caudate Nucleus

Deep Brain Stimulation

Deep Brain Stimulation

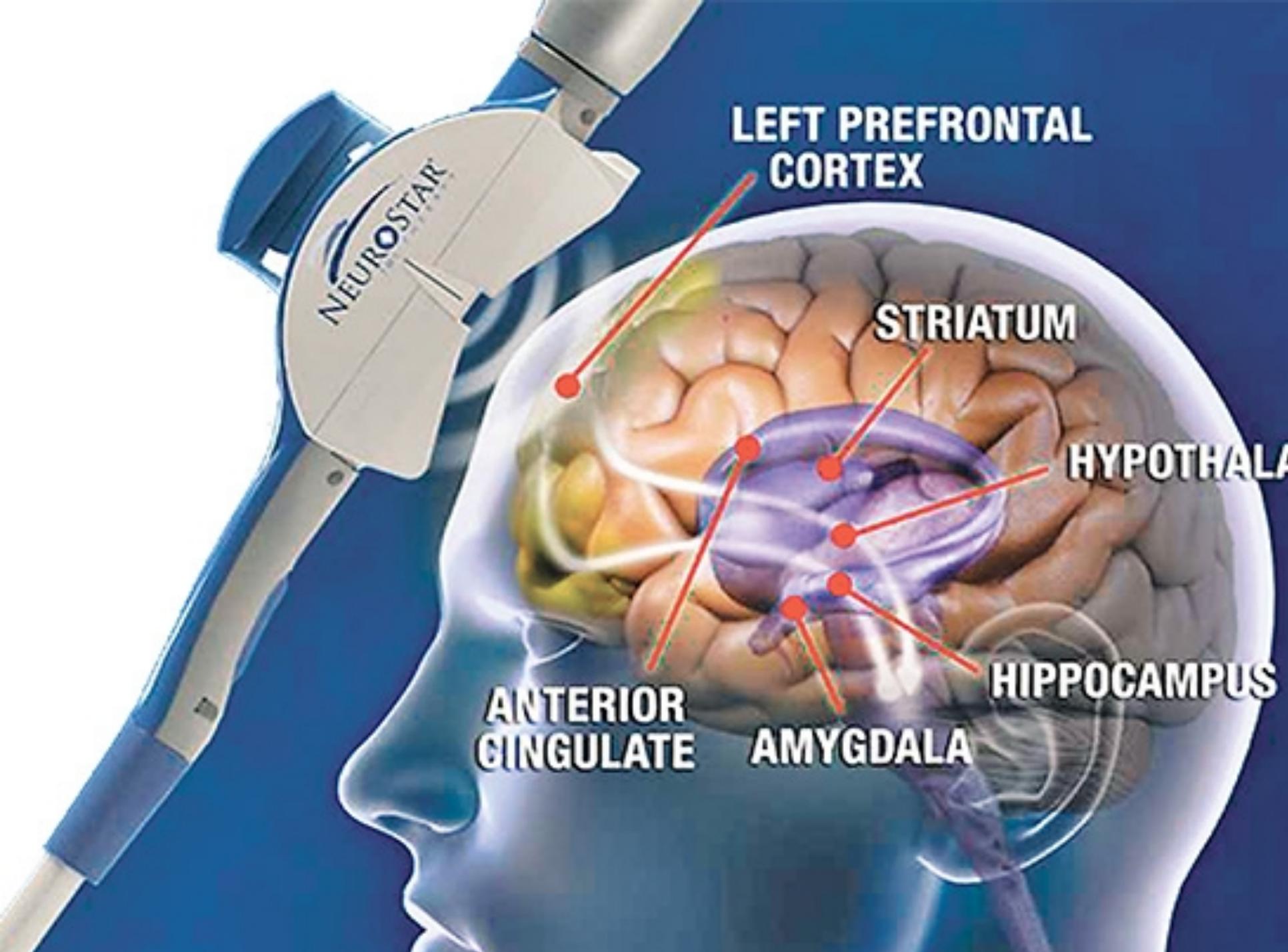


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Transcranial Magnetic Stimulation

While TMS for OCD is in the early stages of development, it is promising for patients and families, and we are certain to see an increasing number of studies published in the next years.



**LEFT PREFRONTAL
CORTEX**

STRIATUM

HYPOTHALAMUS

HIPPOCAMPUS

**ANTERIOR
GINGULATE**

AMYGDALA



Residential Treatment Facilities

1. OCD Institute – near Boston

<http://www.mclean.harvard.edu/patient/adult/ocd.php>

2. OCD House – Houston

<http://houstonocdprogram.com/>

3. Rogers Hospital – Wisconsin

<http://www.rogershospital.org/monroe/content/obsessive-compulsive-disorders>

OC Foundation

Phone: (617) 973-5801

email: info@ocfoundation.org

OCF home page: www.ocfoundation.org

PO Box 961029

Boston, MA 02196



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“What fits your busy schedule better, exercising one hour a day or being dead 24 hours a day?”

Sometimes ... when you cry ... no one sees your tears ...

Sometimes...when you are worried....no one sees your pain...

Sometimes ... when you are happy ... no one sees your smile ...

But fart just one time...







Jenike@comcast.net