Treatment of Obsessive-Compulsive Disorder

Lisa Zakhary, MD PhD
Medical Director, Center for OCD and Related Disorders
Director of Psychopharmacology, Excoriation Clinic and Research Unit
Massachusetts General Hospital
Assistant Professor, Harvard Medical School
10/23/2022

Disclosures

Research Support: Promentis Pharmaceuticals, Inc.

Image not reproduced for copyright reasons

OCD

- >2% prevalence, **10th leading cause of disability** by WHO
- Takes **~14-17 years** to get diagnosed
- Early/accurate dx critical for treatment
- Diagnosis of OCD in DSM-5:
  - Presence of **obsessions, compulsions, or both**
  - Obsessions/compulsions **>1h/day** or cause **distress** or **impairment**
  - Variable insight, may be delusional

"Just checking that I've turned off the lights, dear!"

CartoonStock.com

Obsessions

- Contamination
- Symmetry/exactness
- Harm by carelessness
- Violent
- Sexual (perverse)
- Relationship
- Identity (orientation, gender)
- Religious (scrupulosity)
- Postpartum (accident or harm)
- Suicidal
- Superstitious (color, numbers)
- Many more

Compulsions

- Cleaning/washing
- Ordering/arranging
- Checking (including seeking reassurance)
- Repeating
- Mental
- Others
  - Urge to confess
  - Excessive list-making
  - Eating rituals
  - Superstitious rituals

Adapted from https://iocdf.org/about-ocd/

Treatments

Treatment of OCD

SSRIs and **CBT** are **first-line treatments** for OCD

- **SSRIs**
  - Fluvoxamine, 6 RCTs
  - Fluoxetine, 3 RCTs
  - Sertraline, 6 RCTs
  - Escitalopram, 2 RCTs
  - Citalopram, 1 RCT
  - Paroxetine, 4 RCTs
  - Clomipramine, 4 RCTs (non-selective SRI)

- **CBT**
  - Large **effect size (1.39)** in metanalysis of OCD treatments
  - May **reduce SSRI dosing** needs and can **prevent future OCD relapses**

Reviewed in Bandelow. *World J Biol Psychiatry*. 2008; Reviewed in Fineberg. *Int J Neuropsychopharmacol*. 2005; Mundo. *J Clin Psychopharmacol*. 1997; Bergeron. *J Clin Psychopharmacol*, 2001; Hollander. J Clin Psychiatry 2003; Montgomery. Eur Neuropsychopharmacol 1993; Romano. *J Clin Psychopharmacol* 2001; Stein. *Curr Med Res Opin* 2007; Zohar. *British Journal of Psychiatry 1996;* Olatunji. *Psychiatr Res.* 2013.

Therapy or meds?

CBT alone

- Mild impairment
- Pt refuses medications

CBT + SSRI

- Moderate/severe impairment
- If pt is too distressed to engage in ERP
- Pt has other major comorbidities such as MDD/GAD

SSRI alone

- No access to CBT
- Prior history of failed CBT
- Pt declines CBT

Which SSRI is best?

SSRIs thought to be equally effective but given **high dose** requirements in OCD, SSRIs with **lower side effect profiles typically trialed first**

SSRI

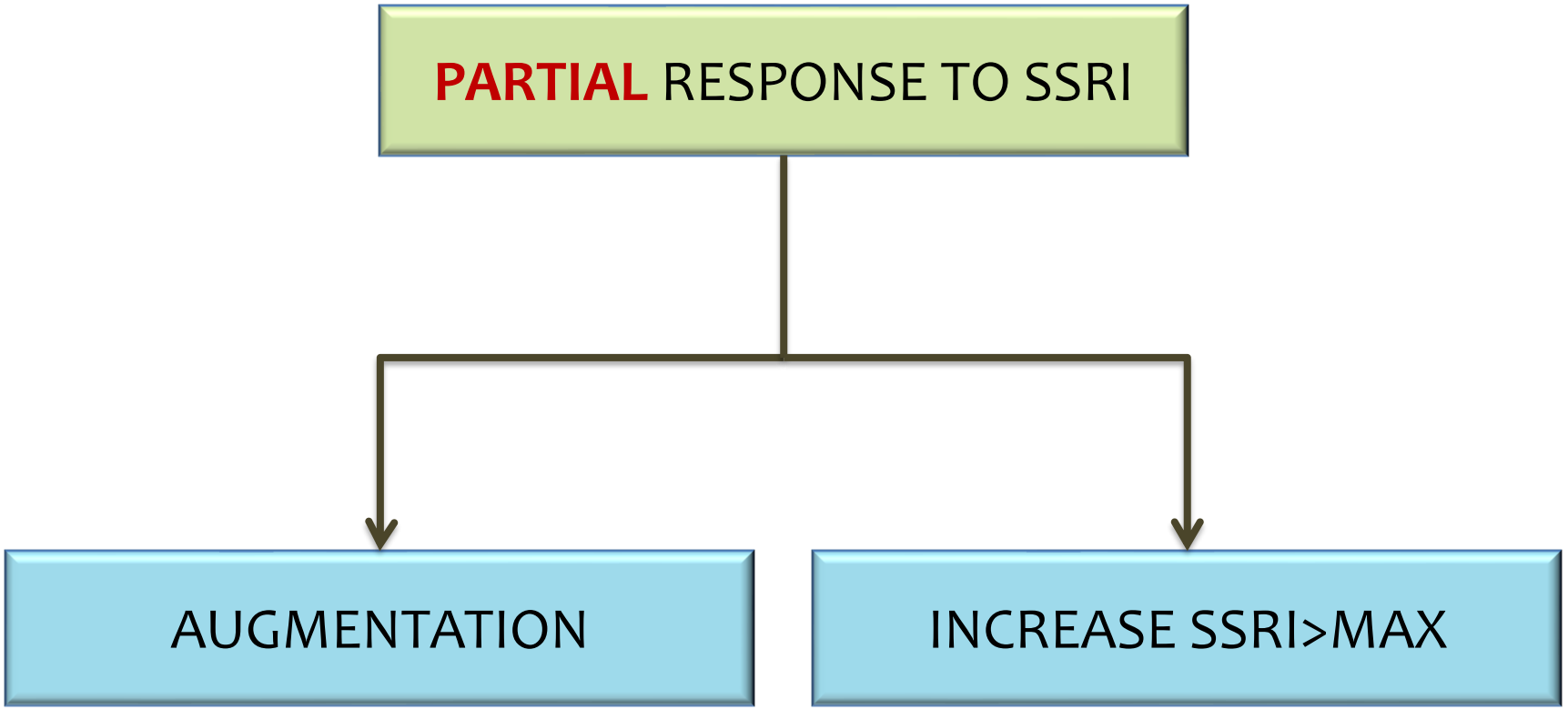
Drug Name	Target Dose	Advantages	Disadvantages
Escitalopram	20 mg/d	well-tolerated	
Sertraline	200 mg/d	well-tolerated	
Fluoxetine	80 mg/d	well-tolerated, long half-life, activating	drug interactions
Citalopram	40 mg/d	well-tolerated	potential ⇧QTc, **Reduced max dose may not be sufficient in OCD**
Paroxetine	60 mg/d		**sedation, weight gain, short half-life**
Fluvoxamine	300 mg/d		**sedation, weight gain**
Clomipramine	250 mg/d		Sedation, constipation, urinary retention, low BP, ⇧QTc seizures, drug interactions, weight gain, **Considered second-line**

SSRI trial in OCD

- **High doses** (max or >max) often required
- **Response delayed** (4-6 wks for initial effect, 10-12 wks for full effect)
- **Trial length: 12 wks** (4-6 wks at the maximum tolerable dose)
- **Rapid titration** recommended
- Duration of treatment
  - **1-2 years recommended**
  - Consider dose reduction after 1-2 years if mostly asymptomatic
  - When ready to taper, taper no more than 10%–25% q1–2mo to prevent relapse

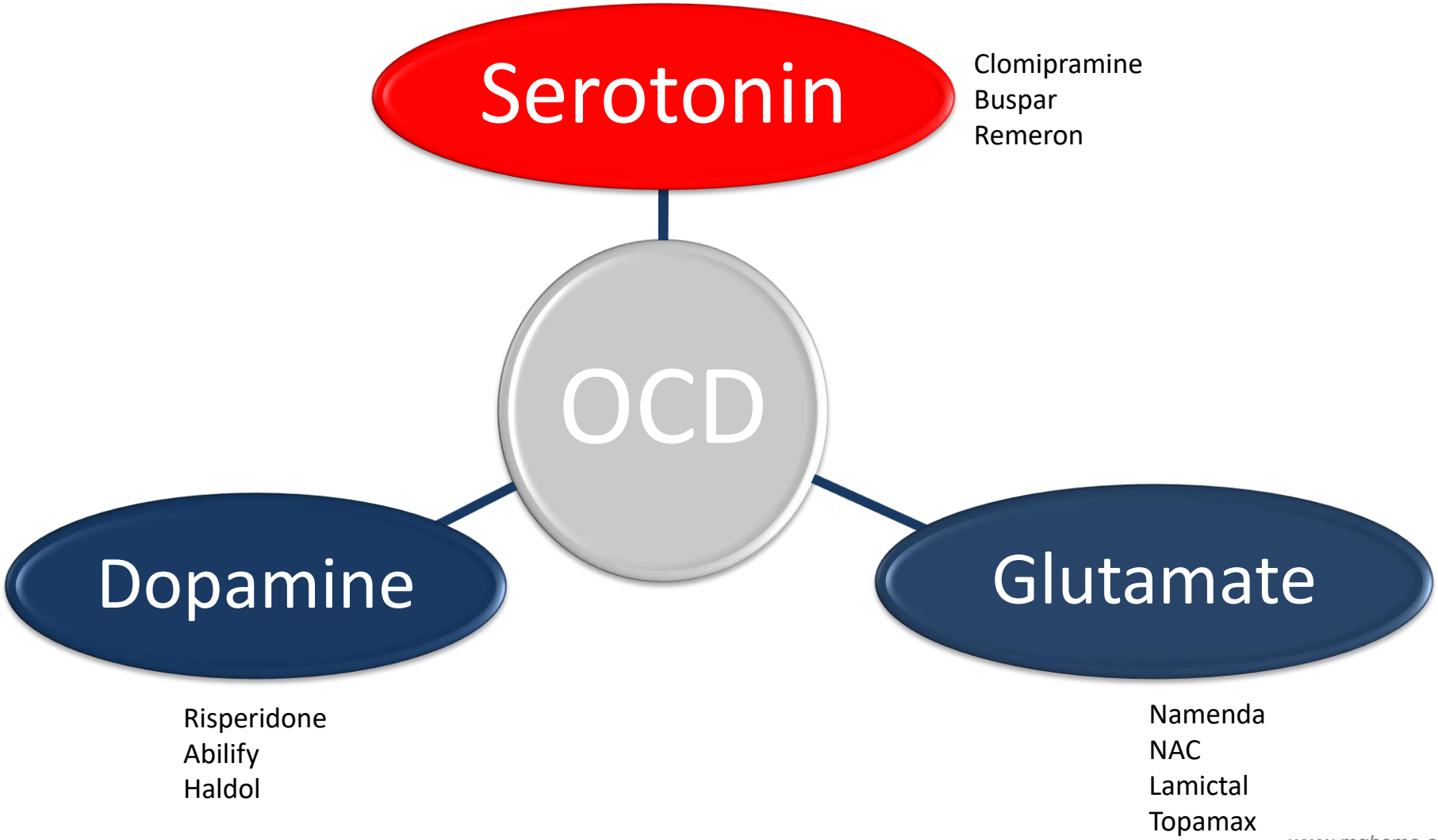
Reviewed in Koran. *Am J Psychiatry.* 2007

Approach to partially effective SSRI



Augmentation and relevant targets

All off-label except clomipramine



Augmenting agents for OCD

- **Risperidone (~1-2 mg/d)**
  - 3 positive RCTs, most often used augmenting agent
  - Other antipsychotics like Aripiprazole and Haloperidone used but less well-studied
    - **Aripiprazole,** 2 positive RCTs, least risk of metabolic syndrome, ~10-15 mg/d
    - **Haloperidone,** 2 positive RCTs, useful in pts with tics, ~2-6 mg/d
  - Quetiapine and olanzapine showing inefficacy in multiple studies so not routinely used
    - Quetiapine, 5 RCTs, mixed results (2/5 positive), ~300 mg/d
    - Olanzapine, 2 RCTs, mixed results (1/2 positive), ~11 mg/d
    - Meta-analysis (multiple):Risperidone >>>placebo while quetiapine and olanzapine are not
- **Memantine (10mg PO BID)**
  - 2 positive RCTs; 5mg PO QHS x7d, then 5mg PO BID x7d, then 10mg PO BID, >6wk trial
- **Clomipramine**
  - Several positive open-label studies and 1 positive RCT, ~55-150mg/d (typically 50-75mg)
  - SSRIs can unpredictably increase clomipramine levels, start low dose (25 mg PO QHS) and monitor QTc before and QTc/clomipramine level while titrating

Reviewed in Arumugham. *Expert Rev Neurother.* 2013; Veale. *BMC Psychiatry.* 2014; Bloch. *Mol Psychiatry.* 2006; Dold. *Int J Neuropsychopharmacol.* 2013; Stewart. *J Clin Psychopharmacol. 2010*; Ghaleiha. *J Psychiatr Res.* 2013; Haghighi. *Psychopharmacology* 2013, Pallanti. *Eur Psychiatry* 1999; Ravizza. *Psychopharmacol Bull* 1996; Diniz. *J Clin Psychopharmacol* 2011.

Additional augmenting agents for OCD

- Other glutamatergic drugs
  - **Lamotrigine**, 1 positive RCT, ~100mg/day
    - May be good option for those with comorbid BPAD
  - **Topiramate,** 2 positive RCTs, ~180mg/day, often intolerable AE
    - May be good option for those with comorbid BPAD, weight gain, HA
  - **N-acetylcysteine (NAC),** 2 RCT, 2000-2400 mg/d TDD, OTC
    - May be good option for those with comorbid skin picking/hair pulling
    - 2 subsequent studies using 3g did not show benefit with augmentation so jury is out
    - Harder to get NAC since 2021, consider https://www.swansonvitamins.com or direct from manufacturer

- Other serotonergic drugs
  - **Mirtazapine,** 15-30mg PO QHS, RCT, no differences in YBOCS at end of study but mirtazapine accelerates response to SSRI
  - **Buspirone**, mixed results
    - Add-on to clomipramine, RCT, ~60mg/d, helpful for only small subset of pts
    - Add-on to fluoxetine, RCT, ineffective; two OLS effective
    - Add-on to fluvoxamine, RCT, ineffective

Bruno. *J Psychopharmacol. 2012;* Mowla. *CNS Spectr*. 2010; Afshar. *J Clin Psychopharmacol.* 2012; Paydary. *J Clin Pharm Ther*. 2016; Costa. *J Clin Psychiatry.* 2017; Sarris. *CNS Drugs*. 2015; Pallanti. *J Clin Psychiatry 2004;* Grady. *Am J Psychiatry*. 1993; Markovitz. *Am J Psychiatry*. 1990; Jenike. *J Clin Psychiatry*. 1991; Pigott. *J Clin Psychopharmacol.* 1992; McDougle. *Am J Psychiatry.* 1993.

A note on anxiolytics

- **Benzodiazepines not proven to be helpful for OCD**
  - Clonazepam ineffective in 2 RCTs
  - Interferes with exposure response prevention therapy
  - Sometimes used when comorbid GAD or panic disorder present

- **Gabapentin**, 900mg TDD, **accelerates response to SSRI** in open-label study

Onder. *Eur Arch Psychiatry Clin Neurosci.* 2008; Hollander. *World J Biol Psychiatry.* 2003; Crockett. *Ann Clin Psychiatry*. 2004

Above max SSRI dosing in OCD

SSRI

Drug	FDA Max Dose	Reported BDD >max dosing	My max dosing	Notes
Escitalopram	20 mg/d	Up to 60mg/d	30 mg/d	Check EKG
Sertraline	200 mg/d	Up to 400mg/d	300mg/d	
Fluoxetine	80 mg/d	Up to 120mg/d	120 mg/d	
Paroxetine	60 mg/d	Up to 100mg/d	80 mg/d	
Fluvoxamine	300 mg/d	Up to 400 mg/d		
Citalopram	40 mg/d	Up to 120mg/d	80 mg/d	**High dosing controversial** given QTc prolongation risk, I consider with EKG, h/o failed medication trials, pt consent
Clomipramine	250 mg/d	Up to 300mg/d		Above max dosing not recommended due to seizure risk

No guidelines on above maximum dosing in OCD exist – doses circled are generally well-tolerated in my practice

Koran. *Am J Psychiatry.* 2007; Ninan. *J Clin Psychiatry.* 2006; Dougherty. *Int Clin Psychopharmacol.* 2009

Managing SSRI Adverse Effects

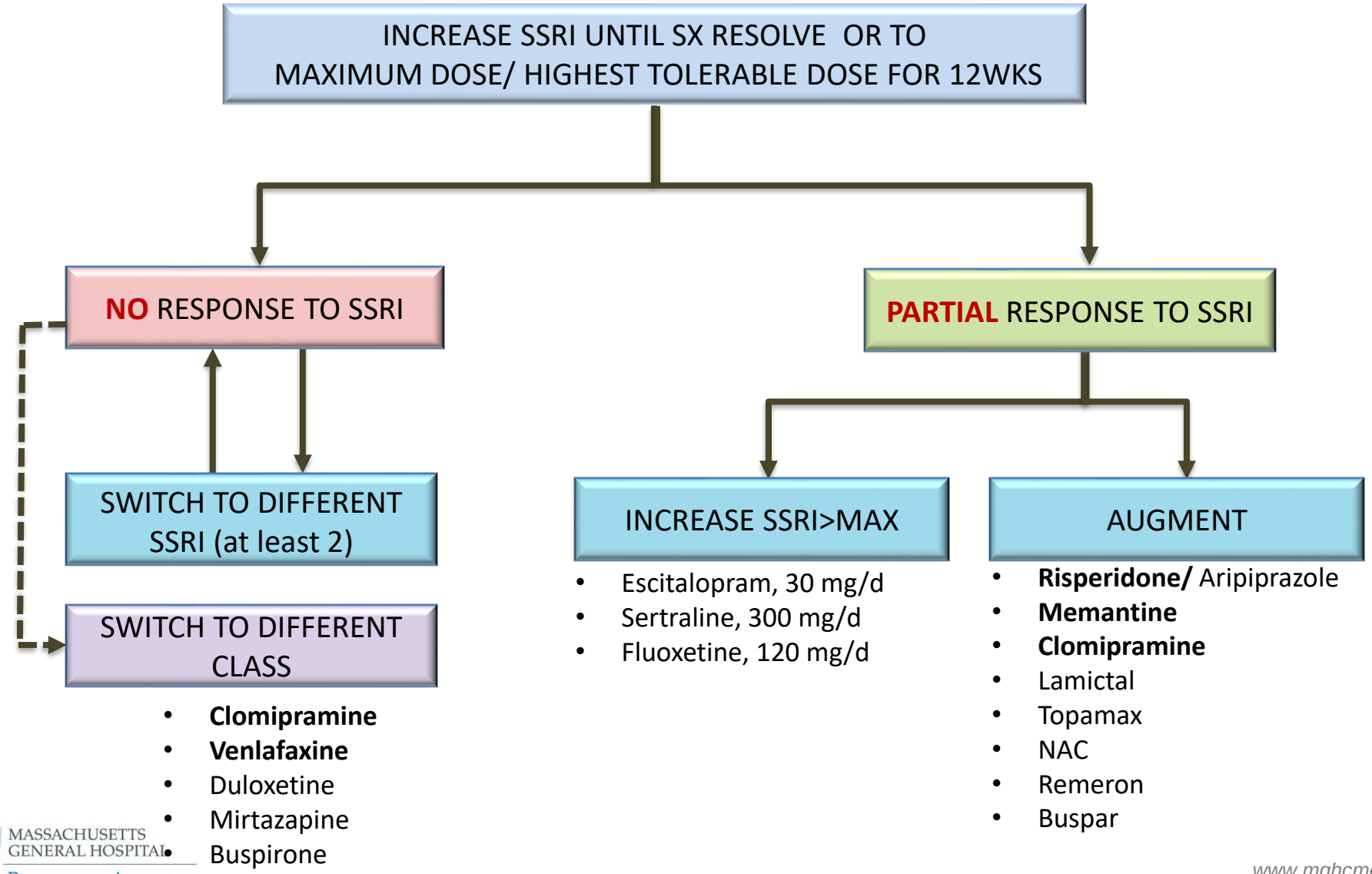
- **Sexual AEs**
- **GI sx**
  - Nausea: taking med w/ food or QHS
  - GERD with initiation: omeprazole 20 mg daily x 14d
- **Hyperhidrosis**
  - Aluminum Chloride antiperspirant (e.g. Drysol)
  - Glycopyrrolate, start 1 mg PO BID, range 2-8 mg/d
  - Benztropine, 0.5-1 mg PO daily
  - Terazosin, 1-4 mg PO QHS
  - Cyproheptadine, start 4 mg PO QHS, up to 4 mg PO BID
  - Mirtazapine, start 15 mg PO QHS

Limited alternatives to SSRIs

- **Clomipramine**, 4 beneficial RCTs, very effective but second-line due to AE
- SNRIs
  - **Venlafaxine**
    - Venlafaxine ~265mg/d as effective as clomipramine in comparator RCT, no placebo
    - Venlafaxine ~300mg/d as effective as paxil in comparator RCT, no placebo
    - No sig effect in 1 small placebo-controlled RCT, but trial too short (8 wks)
    - Limited studies but mostly positive, larger placebo-controlled RCTs needed
    - Used often in practice as second-line to SSRIs
  - **Duloxetine**
    - Beneficial in case series in 3/4 patients, ~120mg/d
    - Beneficial in OLS ~120mg/day
    - Much less well-studied than venlafaxine, but mostly positive, no RCT
- **Buspirone**, 60mg TDD, 1/3 positive RCTs
  - May consider for comorbid GAD (often more effective as an add-on rather than monotherapy)
- **Mirtazapine**, 30-60mg PO QHS, RCT, beneficial
- **NAC has not been studied** as monotherapy for OCD

Rauch. *J Clin Psychopharmacol.* 1996; Sevincok. *Aust N Z J Psychiatry.* 2002; Hollander. *J Clin Psychiatry.* 2003; Albert. *J Clin Psychiatry.* 2002; Denys. *J Clin Psychopharmacol.* 2003; Yaryura-Tobias. *Arch Gen Psychiatry.* 1996; Dell'osso. *J Psychopharmacol.* 2008; Dougherty. *Int J Neuropsychopharmacol.* 2015; Koran. *J Clin Psychiatry.* 2005; *Grady, Am J Psychiatry. 1993;* Pato. *Am J Psychiatry*. 1991

Suggested medication approach to OCD



Experimental medications

- **SRI Augmentation**
  - **Ondansetron**, 4 mg/d - 4mg PO BID , 2 positive RCTs
  - Oral morphine, 30-45mg weekly, positive RCT
  - Pindolol, 2.5mg PO TID, 1/2 positive RCTs
  - **Riluzole,** 50mg PO BID, positive RCT, monitor LFTs/CBC given rare neutropenia and hepatitis (baseline, monthly for first 3 months and then q3m for first year, then periodically), advise pt to report any febrile illness

- **Monotherapy**
  - Tramadol (Ultram), mean 250mg daily, positive open label study
  - **Inositol**, 18mg TDD, positive RCT (helpful alone but not when combined with SSRI)
  - IV clomipramine, positive RCT, not available in the US
  - **MAOIs**- mixed results
    - Multiple CRs showing benefit, particularly with phenelzine
    - Crossover study of clomipramine and MAOI clorgyline, clomipramine helpful but MAOI not as group but for some subjects
    - Crossover study clomipramine and phenelzine, both groups significantly improved, no difference between groups
    - RCT phenelzine/fluoxetine/placebo, fluoxetine group significantly lower than placebo and MAOI group
    - Perhaps helpful for a subset, but who?

Soltani. *Hum Psychopharmacol.* 2010; Heidari. *Int Clin Psychopharmacol*. 2014; Dannon. *Eur Neuropsychopharmacol.* 2000; Fallon. *Arch Gen Psychiatry.* 1998; Pittenger. *J Clin Psychiatry*. 2015; Shapira NA et al. Depress Anxiety 1997; Levine. *Eur Neuropsychopharmacol.* 1997; Fux. *Int J Neuropsychopharmacol.* 1999; Jenike *J Clin Psychiatry. 1983;* Insel. *Arch Gen Psychiatry*. 1983; Allejo . *Br J Psychiatry*. 1992; Jenike. *Am J Psychiatry*. 1997.

And what about…

- Cannabinoids?
- Ketamine?
- Psilocybin?

Cannabinoids

- Limited data
- Only **one RCT** (n=14) to date, **no significant change** in OCD with THC/CBD, NIDA cigarettes used (substantially lower % THC/CBD)
- 70% of participants in **internet study** (n=601) reported that **cannabis improved OCD**
- **Positive case reports**
  - 3 CRs of dronabinol (20-30mg TDD)
  - medicinal cannabis Bedrocan (22% THC/1% CBD)
- Approach to pts
  - may have **some benefit for some**
  - **Review risks**: Drug interactions, driving, hyperemesis, depression, anxiogenesis, psychosis...
  - https://doh.dc.gov/sites/default/files/dc/sites/doh/publication/attachments/Medical%20Cannabis%20Adverse%20Effects%20and%20Drug%20Interactions_0.pdf

Kayser *Depress Anxiety*. 2020; Kayser. *J Obsessive Compuls Rel Disord. 2021;* Kayser *Depress Anxiety*. 2020; Kayser. *Cannabis Cannabinoid Res*. 2019; Dohduhduh (2009). Cannabis leaf [Photo]. From https://commons.wikimedia.org/wiki/File:Potleaf.jpg

Ketamine

- Single ketamine infusion (.5mg/kg)
  - 2012 OLS (n=10), OCD ↓3d (on SSRI)
  - **2013 RCT (n=15), OCD ↓↓7d** (severe OCD, not on SSRI)
  - **2016 OLS (n=10), ketamine** followed by **10 CBT** sessions extends response to **~2 weeks** (severe OCD, not on SSRI)
- Repeated ketamine infusions
  - **Chart review study** (n=14) of inpts with treatment resistant OCD, **3/14 pts w/ robust response**, 11/14 no response
- May have some benefit for a **subset of pts** but unclear for whom and benefit may be relatively **transient**.
- **Ketamine clinics** offering OCD treatment are **premature** as OCD protocols are not known.

Bloch. *Biol Psychiatry.* 2012; Rodriguez. *Neuropsychopharmacology* 2013; Rodriguez. *J Clin Psychiatry.* 2016; Sharma. *Asian J Psychiatry*. 2020; reviewed in Bandeira *Harvard Review of Psychiatry.* 2022

Psilocybin

- **CRs** in 1980s-90s reporting **near resolution of OCD**/BDD following psilocybin use
- **OLS** (n=9) of psilocybin (100-300mg), subjects experienced **acute decrease in YBOCS** (23%-100%)lasting >24h
- **RCT for psilocybin/OCD** (.25mg/kg) **recruiting** at Yale

Moreno. *J Clin Psychiatry*. 2006; Leonard. *Am J Psychiatry*. 1987. Moreno. *Am J Psychiatry*. 1997; Hanes. *J Clin Psychopharmacol*. 1996;

Special Clinical Situations

Late-onset OCD

TABLE 2. Criteria for PANS[12]

1. Abrupt, dramatic onset or recurrence of OCD or restricted eating
2. Comorbid neuropsychiatric symptoms (at least 2), acute onset, severe
   - New onset of and/or severe escalation in anxiety (commonly severe separation anxiety)
   - Sensory amplification to light, sound, smells, or motor abnormalities (deterioration in handwriting, piano finger movements, motoric hyperactivity, tics, etc)
   - Behavioral (developmental) regression
   - Deterioration in school performance
   - Mood disorder: emotional lability, depression, irritability, rage
   - Urinary symptoms (urinary frequency, secondary enuresis)
   - Severe sleep disturbances
3. Symptoms are not better explained by a known disorder (Sydenham chorea, systemic lupus erythematosus, Tourette syndrome)

PANS, pediatric acute-onset neuropsychiatric syndrome; OCD, obsessive-compulsive disorder.

TABLE 1. Criteria for PANDAS[1]

1. Abrupt-onset OCD and/or tic disorder
2. Prepubertal onset
3. Acute onset; episodic course (relapsing-remitting, not waxing and waning)
4. Association with neurological abnormalities (choreiform movements, hyperactivity, handwriting changes)
5. Temporal relationship between symptom exacerbations and group A streptococcal infection

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; OCD, obsessive-compulsive disorder.

- **15%** develop OCD **after age 35**.
- In acute cases, consider **PANS/ PANDAS.** PANS is considered a pediatric disorder, but possible that adults could acquire.
- **PANS is acute-onset OCD or restricted eating** with at least **2+ acute neuropsychiatric sx** thought to be secondary to infection (e.g. mycoplasma, Lyme), metabolic disturbance, or inflammatory reaction.
- **PANDAS** is a subtype of PANS associated with **strep infection**
- Acute onset is not sufficient for dx. Can check labs but **dx is made clinically on basis of criteria.**
- Treatments for PANS may include **antibiotics, NSAIDs, steroids, IVIG** or plasmapheresis as well as standard treatments for OCD.

Thienmann. *Psychiatric Times.* 2017

Patients with OCD and BPAD

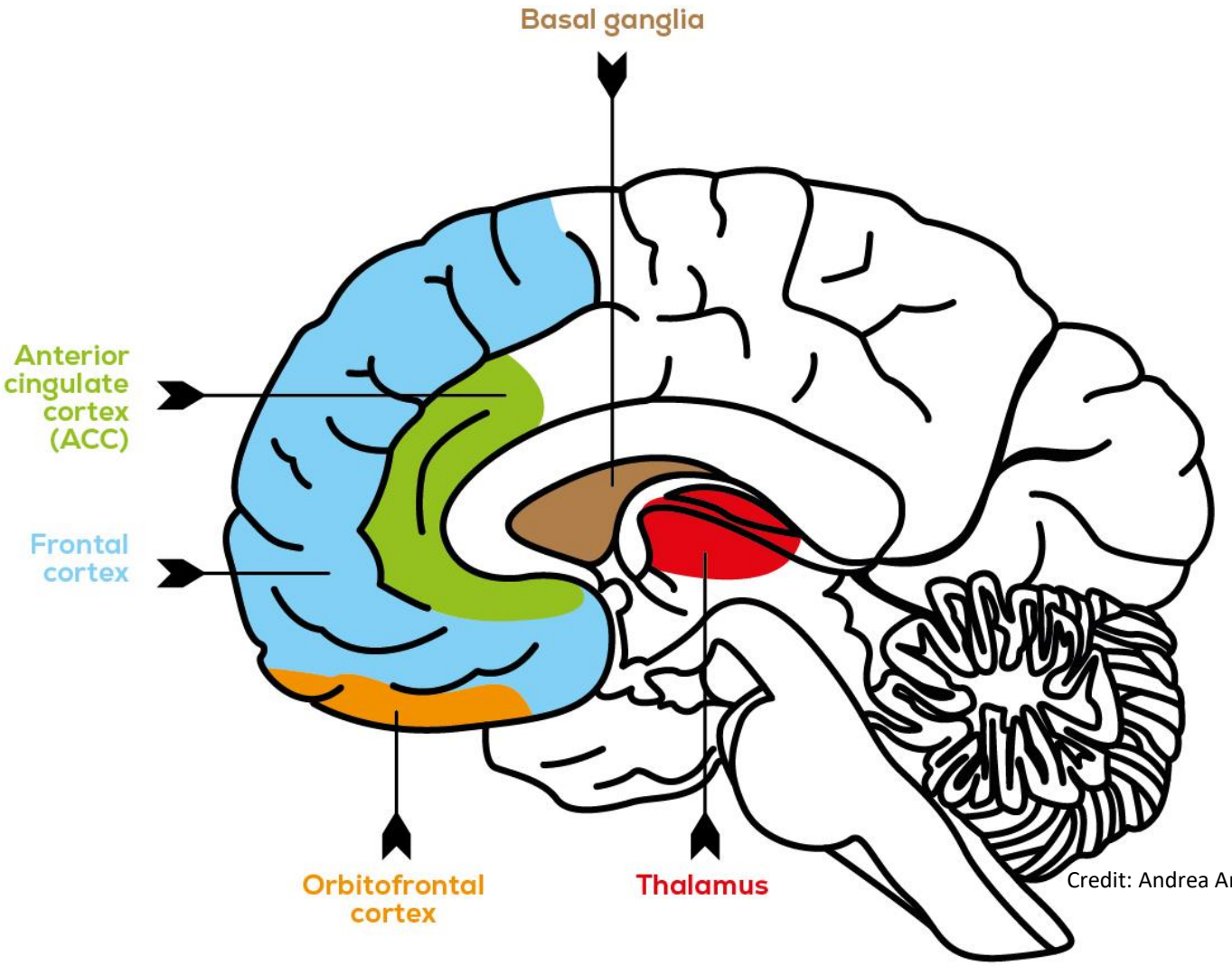
- **11-25% pts** with BPAD have OCD
- SRIs can induce mania
- Not well-studied although a few principles have emerged
  - **Mood stabilization alone may treat OCD sx**
  - Multiple mood stabilizers/antipsychotics may be required for OCD remission
  - SSRIs should only be considered for severe cases and with mood stabilizer
  - **CBT** should be prioritized
  - Think outside the SSRI box
    - **Topiramate**
    - **Memantine**
    - **Lamotrigine**
    - **NAC**
    - **Surgery/ECT**

Reviewed in Kazhungil. *Indian J Psychiatry.* 2016; Perugi. *J Clin Psychiatry.* 2002. Amerio. *J Affect Disord.* 2014. Sahraian. *J Affect Disord.* 2014; Koukopoulos. *J Affect Disord.* 2012; Koukopoulos. *Bipolar Disord.* 2010; Berk. *Biol Psychiatry.* 2008; Magalhães. *Aust N Z J Psychiatry.* 2013; Afshar. *J Clin Psychopharm* . 2012.

Severe OCD

- **Combination** therapy: SSRI + memantine + antipsychotic (e.g. risperidone)
- CBT (again but different)
- Consider **residential** treatment
- **Psychosurgery** (cingulotomy, capsulotomy, DBS)
- **TMS**

Neuroanatomy of OCD

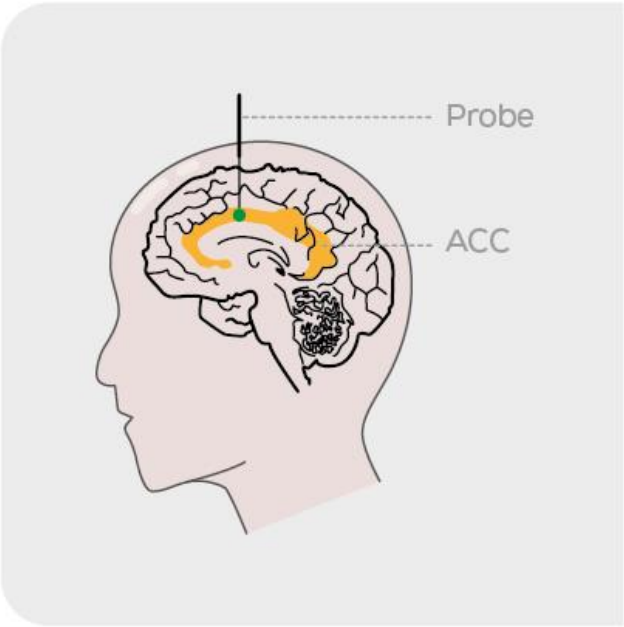


Credit: Andrea Arguindegui

Psychosurgery

Cingulotomy

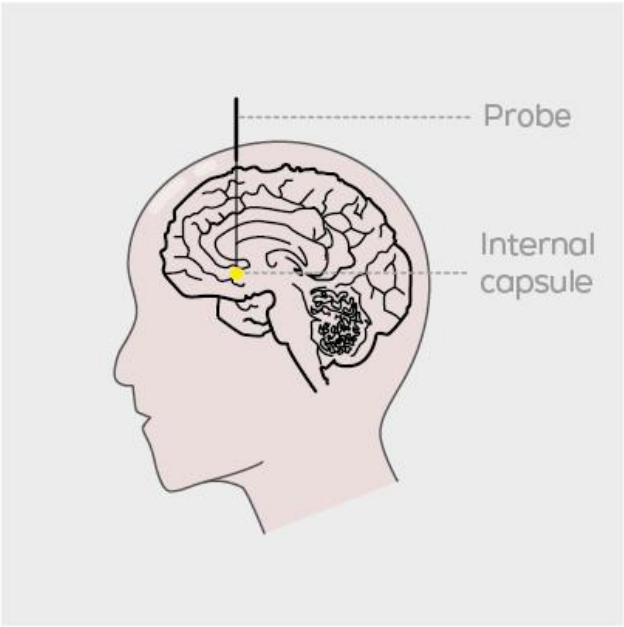
Ablation of area in ACC



Credit: Andrea Arguindegui

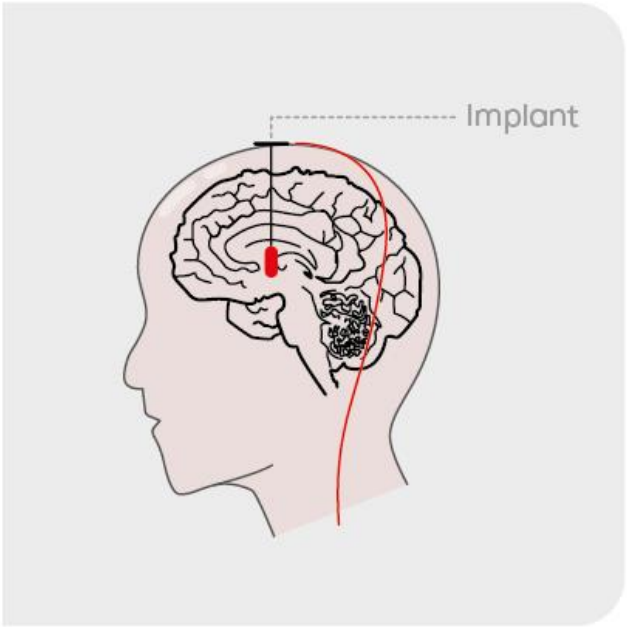
Capsulotomy

Ablation of area in internal capsule



DBS

Electrode delivers current to capsule and surrounding region



FDA-approved for OCD

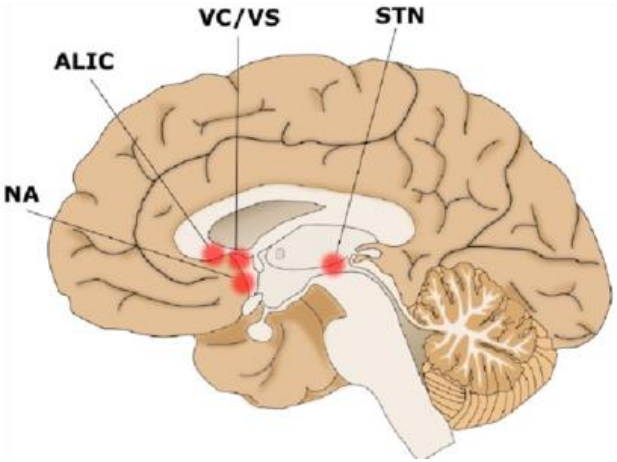
Cingulotomy/Capsulotomy for OCD

- In treatment-resistant pts, nearly **35-47% (cingulotomy) and ~50% (capsulotomy)** show >35% reduction in YBOCS
- Cingulotomy is more common in US
- Surgical AEs include post-op headaches/nausea/urinary retention which resolve in a few days, intracerebral hemorrhage (rare), infection (rare), **seizures (1-9%)**
- **Gamma knife surgery**, non-invasive highly focused radiation to target internal capsule, no incision needed, not available everywhere, minimal AEs
- Not miracle cure, need to do ERP and take meds to maintain effects

Ballantine. *Biol Psychiatry*. 1987; Sheth. *J Neurosurg*. 2013; reviewed in Rasmussen. *Neuropsychopharmacology*. 2022.

DBS for OCD

- Electrodes implanted in the ventral capsule/ventral striatum, nucleus accumbens, or subthalamic nucleus
- Much less well studied than surgery but **reversible, adjustable and has FDA-approval**
- Responder rate 21-75%, depending on placement of electrode (**60% w/ VC/VS**)
- AE: Intracerebral hemorrhage, infection, **mania,** transient agitation, sadness, anxiety, and cognitive AE
- Contraindicated with **BPAD**

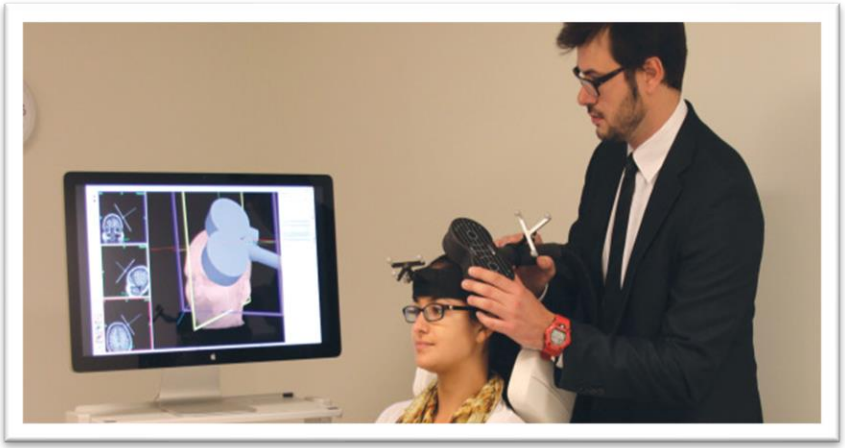


Greenberg. *Mol Psychiatry*. 2010; Illustration on right from Fitzgerald. *Aust N Z J Psychiatry*. 2015 reprinted with permission. Haber. *Biol Psychiatry*. 2020; Reviewed in Bais. *Psychiatr Clin North Am*. 2014.

Criteria for surgery

- **Severe** disabling OCD
- **Three SRI** trials (one of which must be **clomipramine**)
- **SRI trials complete** (high dose, 12 wks)
- Multiple **augmentation** trials (risperidone, memantine, etc.)
- Trial of **SNRI** (venlafaxine, duloxetine)
- Adequate trial of **CBT**
- Typically reviewed by **psychosurgical committee**

TMS for OCD



- **Non-invasive:** coil sends magnetic impulses to stimulate or inhibit specific underlying brain regions
- Different coils:
  - Repetitive TMS (rTMS), targets surface areas of the brain
  - **Deep TMS** (dTMS), targets deeper areas (e.g. anterior cingulate cortex, dmPFC)
- **40% response rate with dTMS in RCT**
- **FDA-approved for OCD 2018**, not well covered by insurance (Brainsway, Magventure)
- Treatments daily for **4-6 weeks**
- Contraindications: h/o **seizures, BPAD** (controversial), metal devices, implants, DBS

Carmi. *Am J Psychiatry*. 2019 Reviewed in Kammen. *Front Neurol*. 2022 and https://iocdf.org/about-ocd/ocd-treatment/tms/

Resources for OCD

- ***Imp of the Mind*** *by Lee Baer* (comprehensive overview for pts, families, and clinicians)
- **APA Practice Guideline for the Treatment Of Patients With Obsessive-compulsive Disorder** by Lorrin Koran et al.
- **International OCD Foundation**, https://iocdf.org/
- **Residential treatment:**
  - **McLean OCDI Institute,** http://www.mcleanhospital.org/programs/ocd-institute-ocdi
  - **Rogers OCD Center,** rogersbh.org/what-we-treat/ocd-anxiety/ocd-and-anxiety-residential-services (helpful for OCD and eating disorders)
  - **Houston OCD Program**, houstonocdprogram.org/residential-support-program/
  - Many others…
- **ACT Workbook for OCD**, https://www.amazon.com/ACT-Workbook-OCD-Mindfulness-Obsessive-Compulsive/dp/168403289X/
- **Virtual CBT for OCD**, NOCD at https://www.treatmyocd.com/
- **PANS/PANDAS,** https://pandasnetwork.org/understanding-pandas/

Koran. *Am J Psychiatry.* 2007 Jul;164

Jenike@comcast.net

Lzakhary@partners.org