# Obsessive-Compulsive Disorder and the Role of Glutamatergic Agents

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# Disclosures

- None

# Misdiagnosis of OCD

- 75% of people with OCD do not receive a diagnosis
- Only 2% of people diagnosed with OCD get Exposure with Response Prevention (E/RP) which is first line treatment
- 72% of patient with OCD- after a mental health assessment- do not get referred for E/RP or any type of CBT at all
- 66% of OCD patients receive SSRIs- the first line medication treatment

Saxena et al 2025

# Treatment Resistant OCD

- Defined as <30% reduction in YBOCS to adequate treatment (high dose SSRI and Exposure with Response Prevention)
- Approximately 40-60% of all patients with OCD
- Strategies to augment high-dose SSRI and E/RP with other medications/methods have been explored
- Glutamatergic agents have been explored recently
  - Have a marked advantage with safety and side effects

# Treatment Resistant OCD

- 12% achieve complete remission
- 25% of patients get no response from initial SSRI. 33% of those will improve with SSRI switch
- 40-60% of OCD patients do not achieve satisfactory improvement
- Responders more depressed than nonresponders

# Potential causes of "Treatment Resistant" OCD

- Misdiagnosis of Symptoms/Disorder
- Inadequate choice of first line medications, or inadequate dosing, duration
- Inadequate psychotherapy (i.e. patient not participating in E/RP)
- Improper use of augmentation strategies

# Poor Prognostic Indicators

- Co-morbid schizotypal personality disorder
- Longer length of illness
- Early age of onset

# Integrated approach to OCD Treatment

- Pharmacotherapy- reduces time spent on obsessions and compulsions, urge to perform compulsions, and frequency of obsessive thoughts
- Exposure with Response Prevention- further reduces the frequency and intensity of obsessions and compulsions

# Integrated Approach to OCD Treatment

- Moderate to severe cases usually require both medications and E/RP
- With mild cases, using E/RP alone can be appropriate

# Medications of Choice for OCD

- SSRI's- first line medication- used at higher doses and longer trials periods than when used for MDD
- SSRI's- second line medication- Stay in class even with treatment resistance
- Clomipramine- third line medication

# SSRI's

- FDA Approved for adults
  - Fluoxetine (Prozac)
  - Sertraline (Zoloft)
  - Paroxetine (Paxil)
  - Fluvoxamine (Luvox)
  - Clomipramine (Anafranil): a TCA

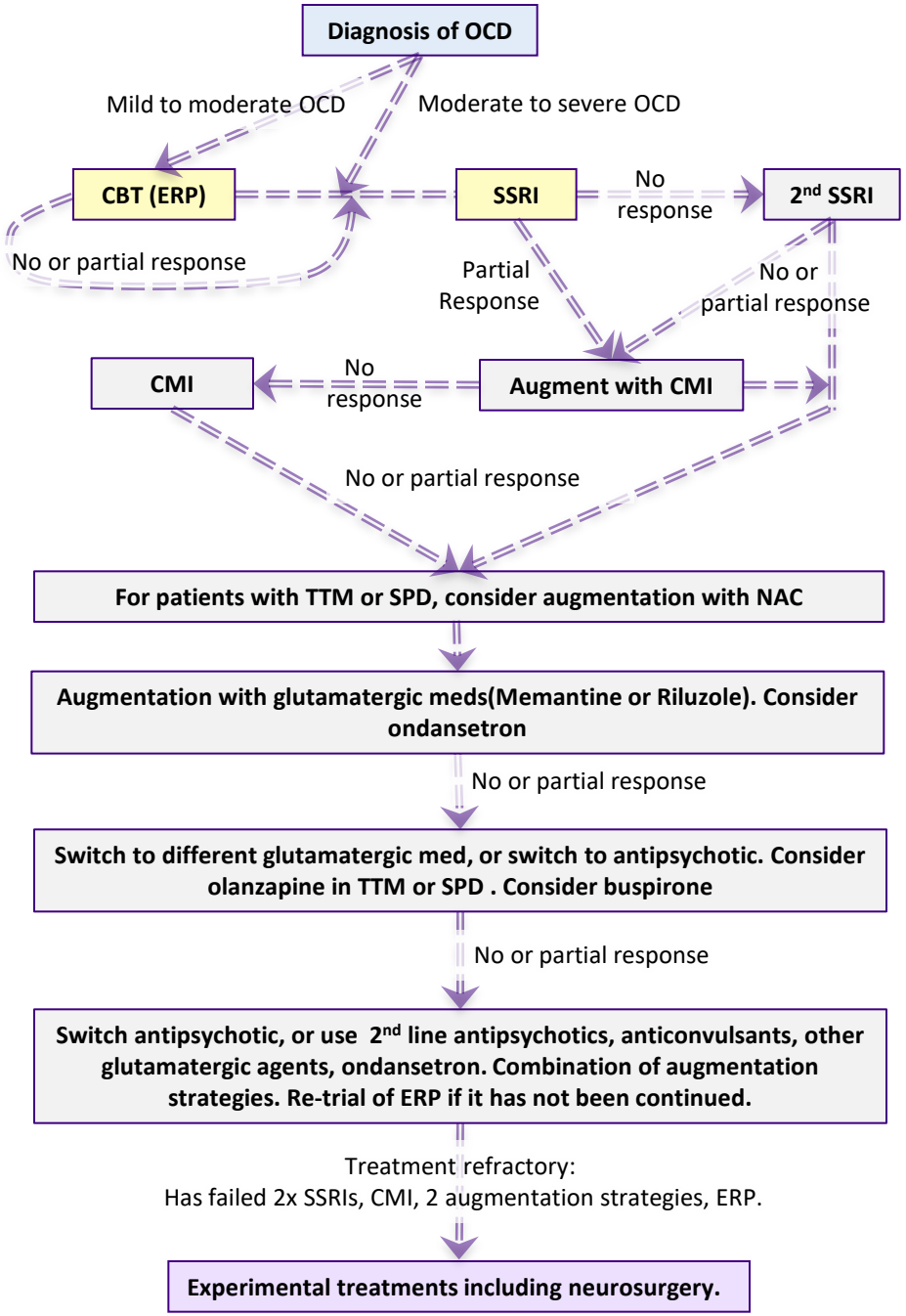
# SSRI's

- Not FDA approved for adults, but still work

Escitalopram (Lexapro)

Citalopram (Celexa)*

*(not typically recommended nowadays due to maximum dosage limitations)


Diagnosis of OCD
Mild to moderate OCD
Moderate to severe OCD
CBT (ERP)
SSRI
No response
2nd SSRI
No or partial response
Partial Response
No or partial response
CMI
No response
Augment with CMI
No or partial response
For patients with TTM or SPD, consider augmentation with NAC
Augmentation with glutamatergic meds(Memantine or Riluzole). Consider ondansetron
No or partial response
Switch to different glutamatergic med, or switch to antipsychotic. Consider olanzapine in TTM or SPD . Consider buspirone
No or partial response
Switch antipsychotic, or use 2nd line antipsychotics, anticonvulsants, other glutamatergic agents, ondansetron. Combination of augmentation strategies. Re-trial of ERP if it has not been continued.
Treatment refractory:
Has failed 2x SSRIs, CMI, 2 augmentation strategies, ERP.
Experimental treatments including neurosurgery.

# Therapeutic Trials for OCD

- Patients should be given a therapeutic trial of SSRI before they are deemed treatment resistant
- Therapeutic trials of SSRIs for OCD are different  than SSRI usage in mood disorders

# Therapeutic Trial for OCD

- SSRI must be used at the maximum dose
- Maximum dose must be maintained for a minimum of 12-16 weeks
- Typically, medication augmentation is not recommended during this time
- Recommended doses may be above FDA maximum guidelines: however, these doses are evidence based and consistent with numerous professional guidelines

# Pharmacologic Treatment

| | Starting (or antidepressant) dose (mg/d) | Maximum (or antiobsessional) dose (mg/d) | Occasional dose (mg/d) |
|---|---|---|---|
| Fluoxetine | 20 | 80 | 120 |
| Sertraline | 50 | 400 | 400 |
| Paroxetine | 20 | 80 | 100 |
| Fluvoxmine | 50 | 400 | 450 |
| Citalopram | 20 | 80* | 120* |
| Escitalopram | 10 | 40 | 60 |
| CMI | 25 | 250 | 250 |

*FDA black box warning on antiobsessional doses

# Potential Causes of Treatment Resistance

- Longer duration of illness
- Schizotypal personality disorder
- Psychotic Disorders
- Autism Spectrum Disorder
- Refusal to do E/RP

# Augmentation

- There is little evidence to guide us on SSRI switch vs augmentation in non-response
- Consider augmentation if the patient gets some improvement with the initial medication (e.g. >10%)
- Consider switching medications if the patient gets little or no improvement with the initial medication (e.g. <10%)

# Augmentation Strategies to Primary SSRI

- Clomipramine
- **Memantine/Riluzole or other glutamatergic medication**
- SGA's (warning: may also worsen OCD)
- Non-SSRI serotonergic agents: buspirone, ondansetron
- 4th line meds: lamotrigine, granisetron, psilocybin, tryptophan, FGAs (comorbid tics)
- Other meds
- For comorbid MDD, use:
  - Buproprion
  - mirtazapine
  - SNRIs

# Glutamatergic Medications

- Glutamate is the primary excitatory CNS neurotransmitter
- Glutamate transporter SLC1A1 has been implicated in OCD
- Animal studies have implicated synaptic proteins SAPAP3
- Evidence from neuroimaging and neurochemical data generally support this

# Memantine

- Non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist
- Approved for Alzheimer's Disease
- 6 of 14 patients improved in a case series
  - Responders: 23.8 to 13.0 Y-BOCS (45.9% decrease)
  - Non-responders: 30 to 28.8 Y-BOCS (3.8% decrease)
- Single blind study of 22 Intensive Residential Treatment (IRT) patients showed improvement
  - 44 patients at OCD-I, 22 received memantine
  - Y-BOCS decreased by 7.2 in memantine group, 4.6 among the others
  - 35.3% of the memantine group were rated as very much improved on CGI compared to 7.1% of control subjects

*Aboujaoude et al 2009; Stewart et al 2010*

# Memantine

- Shown to work in two double blind placebo-controlled trials, one is treatment responsive patients and one in treatment resistant patients
- Should be used at a minimum of 20mg daily, and up to 40mg daily
- May be especially helpful for compulsions
- First line augmentation due to response and low side effect profile
- Meta-analysis from 2026 contains some methodology flaws

# Memantine

- Less side effects than SGAs, and though with less evidence than SGAs, makes a better 1st or 2nd line augmenter
- Shown to be effective for Body Focused Repetitive Behaviors in a single trial. May be used for BFRBs instead of NAC ensuring more consistent formulation

Grant et al 2023

# Riluzole

- Calcium and sodium channel blocker
- Approved in the US for amyotrophic lateral sclerosis (ALS)
- Inhibits synaptic glutamate release and enhances glutamate uptake by astrocytes
- Monthly monitoring of transaminases
- Daily dosing is typically 100mg daily
- Transient elevations in liver enzymes: monitor LFT's once a month for 3 months, and then every 3 months for one year, then periodically

# Riluzole

- Effective in case series and open label trials
- Worked in one RCT, and for a subset of patients for obsessions in another
- Effective in children as single agent (but not as add-on)
- Improves mood and anxiety
- Well tolerated

# Riluzole

- Favorable results in open label trials and case series of adults
- 12 week open label at 100mg daily
- 7 of 13 responders at 100-200mg daily. This was characterized by a >35% reduction in Y-BOCS. No adverse events were noted. (Coric et al 2005)
- A pilot augmentation double blind-randomized controlled trial (DB-RCT) showed a nominal improvement that did not achieve statistical significance

# Riluzole

- 4 of 6 responders at 100mg daily, >39% reduction in Y-BOCS
- No statistical difference in follow-up DB-RCT
  - 60 treatment resistant children enrolled (17 with comorbid autism)
  - 85% of subjects completed trial
  - Riluzole group: Y-BOCS decreased from 27.24 (SD 3.78) to 21.76 (SD 6.28)
  - Placebo group: T-BOCS decreased from 29.13 (SD 3.59) to 22.46 (SD 5.68)
  - Percent responders were 7% in both groups (P = 0.96) on CGI-I

Grant et al 2007; Grant et al 2014

# N-acetylcysteine

- Amino Acid derivative that modulates glutamate neurotransmission
- RCTs have been mixed to negative
- Efficacy has been shown in Body Focused Repetitive Behaviors
- Not recommended for OCD at this time
  - (Oliver et al 2015 was significantly flawed)
- Recommend memantine over NAC for BFRBs simply due to formulation

# D-Cycloserine

- May accelerate extinction learning
- Used to augment E/RP, not primary medication treatment
- Well tolerated (GI distress, dizziness, anxiety)
- In a 2020 study, doses of 100 or 250mg were given at lunch time in the middle of a 4 day long E/RP session. No differences were noted with placebo. (Kvale et al 2020)
- Likely intensive treatment overshadows any drug effect.
- Some studies show initial advantage for DCS that goes away with additional treatment
- Timing and dosing still not standardized
- Not ready for prime time
- Less successful studies in children

# Lamotrigine

- Anticonvulsant with anti- glutamatergic properties
- One DB-RCT showed improvement. Study group (26.83 ±4.0 decreased to 18.31 ±6.6) compared to placebo (28.60 ±3.8 decreased to 23.48 ±5.8) ($P = 0.015$)
- One DB-RCT had 33 completers, with a significant CGI improvement in the active group ($P < 0.0001$)
- Patients with schizoaffective disorder may show even more improvement.
- More studies needed, but may be best in comorbid mood and psychotic disorders

Pittenger et al 2021

# Other Glutamatergic Meds: Ketamine

- Non-competitive NMDA antagonist
- Robust but transient antidepressant effect
- Possible benefit in unmedicated OCD patients, minimal benefit in medicated patients, and triggered new onset SI in 2 patients
- Limited data for esketamine
- Not recommended outside of research settings

# Other glutamatergic meds

- Topiramate- unclear benefits, and side effect to benefit ratio is high. One small (49 patients) RCT showed benefits (32.0% decrease in YBOCS vs 2.4% for placebo), a second showed no statistical improvement at end point. Generally not recommended
- Pregabalin- case series and open label only
- Gabapentin- one negative study. Unfortunately, often used despite no data. Not recommended

# Second Generation Antipsychotics

- 3rd line augmentation only
- Response usually seen in 4-6 weeks
- Should be stopped after 8 weeks if not significantly improved
- Not necessary in patients with schizotypal sxs or ‘delusional’ insight

# Second Generation Antipsychotics

- Patients with tics may have improved response
- No specific characteristics of OCD have been identified that relate to response of SGAs.
- Be aware that SGAs are not a homogeneous group of medications
- Doses are typically less than when used for bipolar disorder or psychosis

# Second Generation Antipsychotics

- May worsen OCD as well as augment
- Reported with clozapine, olanzapine, risperidone, quetiapine
- Less studied in children
- Require biannual or yearly blood sugar, lipid profiles, AIMs test.

# SGAs- in order of recommendation

- Aripiprazole- DB-RCT showed response. Response rates similar to risperidone. Not as much evidence as risperidone, but less side effects. Usual dose: 2-15mg daily
- *Risperidone- most evidence as an augmenter with DB-RCT. Usual dose: 0.5-2mg daily
- *Olanzapine- some DB-RCT data. May also worsen OCD. Usual dose: 2.5-15mg
- *Quetiapine- Less data than the others, both positive and negative. Usual dose: 50-200mg daily
- Other SGAs- little data and not therefore recommended.

* Caution warranted as may also exacerbate OCD symptoms

# Summary

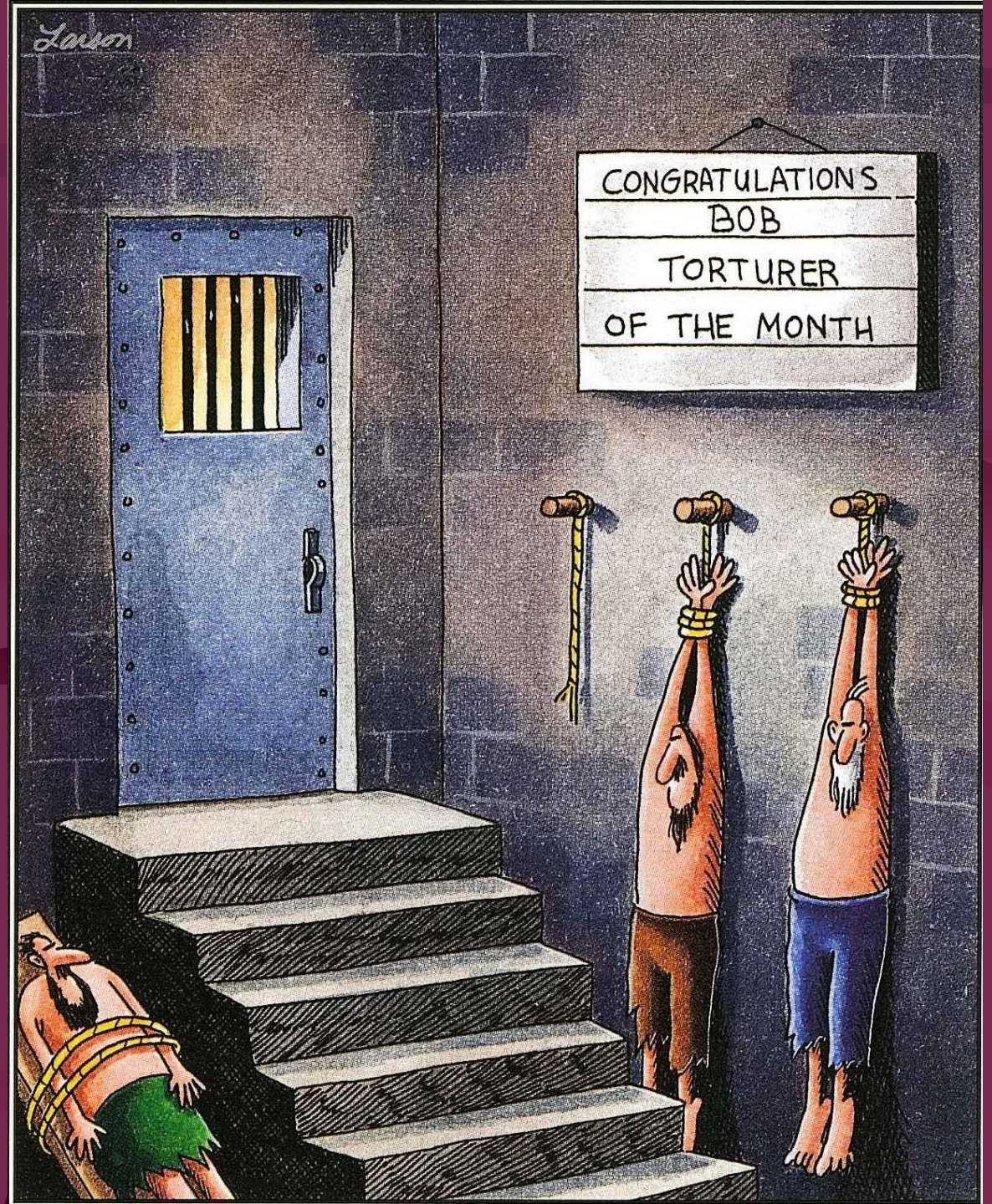
- OCD is one of the most common psychiatric disorders
- Differential diagnosis can be difficult as symptoms are not lways straightforward in presentation
- SSRIs are the pharmacologic treatment of choice

# Summary cont.

- Exposure with Response Prevention is at least as effective as medication therapy
- An integrated approach leads to a better therapeutic outcome than medication alone
- 80% of patients will show at least moderate improvements with an integrated approach

# Summary cont.

- OCD guidelines (expert consensus, APA, etc) state SSRIs are used at doses above FDA guidelines
- Augmentation for SSRIs takes the form of clomipramine, then glutamatergic agents, then SGAs
- $4^{th}$ line meds are rarely used, or only in specialty clinics
- Surgery is reserved for the most severe and irretractable cases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