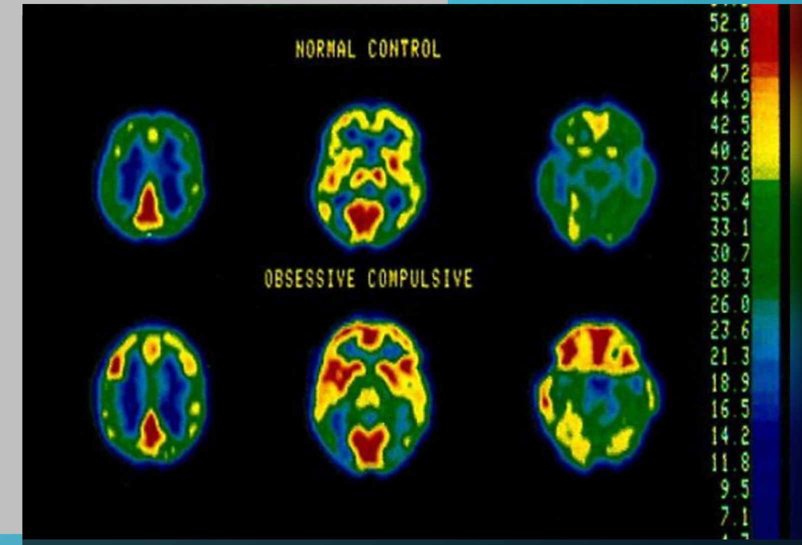
EVIDENCE-BASED PHARMACOTHERAPY FOR OCD AND OCRDS



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LEARNING OBJECTIVES

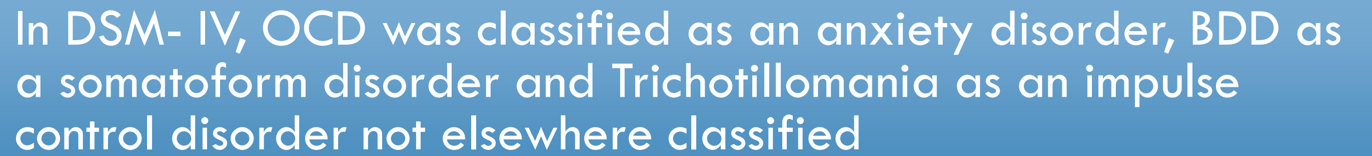
- To reliably diagnose OCD (Obsessive- Compulsive Disorder) and learn about DSM 5 new category of OCRDs (Obsessive Compulsive and Related Disorders)
- To learn the basis for the theories of pathophysiology of OCD
- To learn the evidence-based approach to the pharmacological treatment of OCD
- Briefly discuss alternative/ novel treatments for OCD including non-pharmacological biological treatment options

CONFLICTS OF INTEREST

- Rashesh Dholakia – None
- Rachel Davis - paid ad hoc consulting for Medtronic

OBSESSIVE COMPULSIVE AND RELATED DISORDERS (OCRDS) : A NEW CATEGORY IN DSM- 5

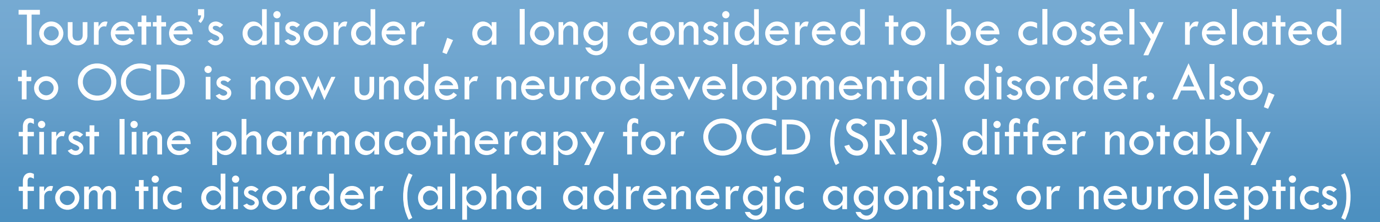
- OCD
- Body Dysmorphic Disorder (BDD)
- Hoarding disorder
- Trichotillomania (hair-pulling disorder)
- Excoriation (skin-picking) disorder
- Substance/medication induced OCD
- OCRD due to another medical condition
- Other specified OCDRD
- Unspecified OCRD



Hoarding disorder and Excoriation (skin-picking) disorder are new to DSM- 5

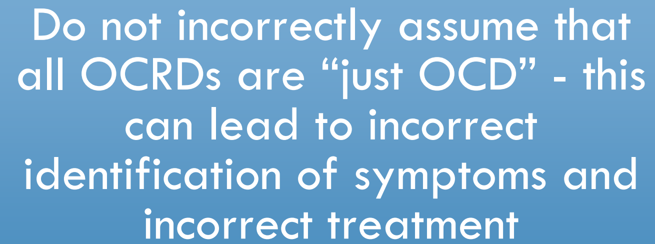
Optimally grouping disorders into categories may usefully guide assessment and treatment

Also, related disorders may be highly comorbid and have increased prevalence in family members



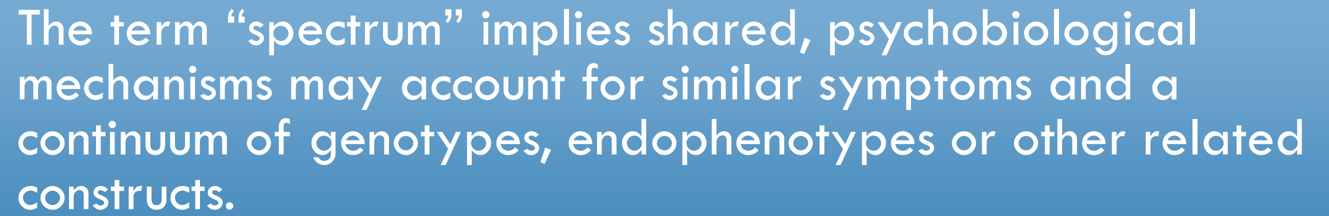
Hypochondriasis (renamed as Illness anxiety disorder) is now under somatic symptom chapter

OCPD is under personality disorder chapter although some similarities with OCD



Although some effective treatments overlap, others meaningfully differ e.g SRIs selectively efficacious for OCD and probably BDD but less clear for Hoarding disorder and Skin Picking disorder

Unlike OCD, hoarding and BDD do not respond well to simple ERP; modified CBT interventions and motivational interviewing usually needed.



Spectrum also implies that related disorders along a spectrum vary continuously in relation to one another in some underlying construct as “impulsivity” or “compulsivity”.

DSM- 5 term for OCRD avoids this assumption

ICD-11 : OBSESSIVE COMPULSIVE OR RELATED DISORDERS

- OCD
- BDD
- Olfactory reference disorder
- Hypochondriasis
- Hoarding disorder
- Body focused repetitive disorder (e.g. hair-pulling, skin-picking, lip-biting)

OCD - DSM-5

A. Presence of obsessions, compulsions, or both

B. Greater than 1 hr per day or cause distress/impairment

C. Not attributable to substance or medical condition

D. Not explained by another mental disorder

Specify:

- Good or fair insight
- Poor insight
- Absent insight
- Tic-related

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: **DSM-5**. Washington, D.C: American Psychiatric Association.

OBSESSIONS

1. Recurrent and persistent thoughts, urges, or images
   - Intrusive and **unwanted**
   - Cause anxiety or distress
2. Individual attempts to ignore, suppress, or neutralize

COMPULSIONS

1. Repetitive behavior or mental act
    - Feels driven to perform in response to an obsession
2. Aimed at preventing or reducing anxiety or distress
    - Excessive or unrealistically connected

OCD

- Lifetime prevalence of 2 - 3%
- Average of 11 years before diagnosis
- Among patients who receive clinical attention, fewer than 40% receive OCD specific therapy, and less than 10% receive evidence-based treatment
- Women 1.6X more likely to experience OCD

- 98% have fair to good insight (not delusional)
- Early Onset (11.81 yrs) vs. Late Onset (26.64 yrs)

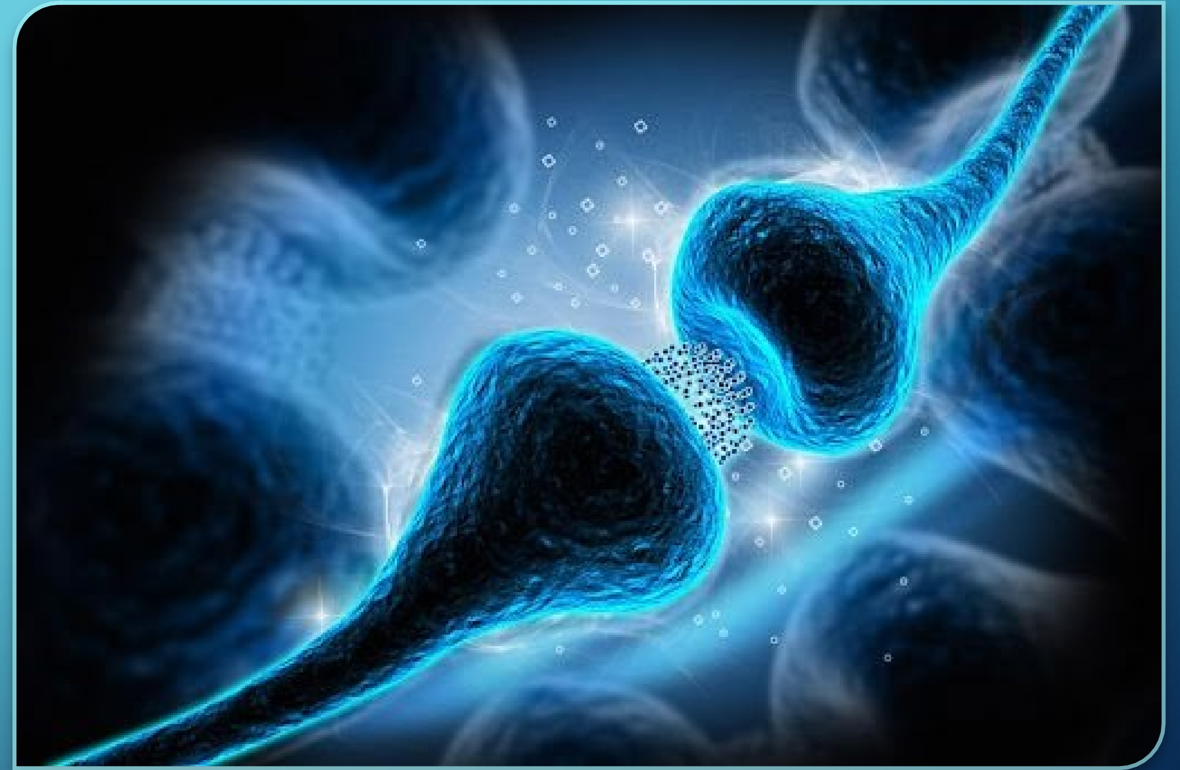
PROGNOSTIC FACTORS

- Scrupulosity, sexual theme obsessions and hoarding have greater symptom persistence
- Poor prognosis predictors
  - earlier onset of symptoms
  - history of inpatient admission
  - comorbid psychiatric conditions (esp. ODD, CD, Bipolar)
  - poor early treatment response

- Cognitive behavioral therapy (ERP) is the most effective evidence-based psychotherapy for OCD
- 40% to 60% of patients endorse residual, impairing symptoms, even after evidence-based treatment

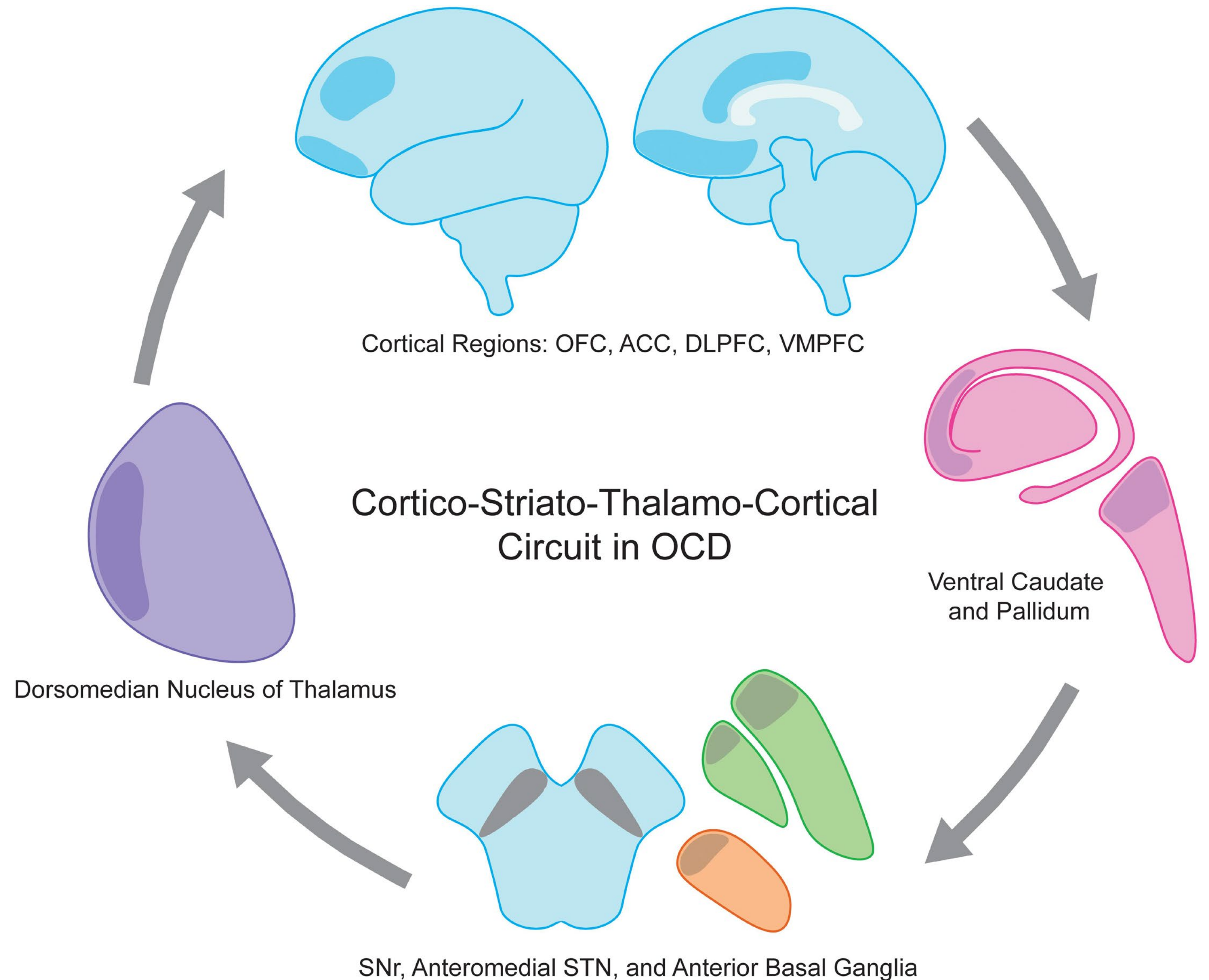
PATHOGENESIS OF OCD

- Psychoanalytic theories
- Serotonin hypothesis
- Glutamatergic hypothesis
- Basal Ganglia – Orbitofrontal Cortex circuit (CSTC circuit)
- Infection-triggered autoimmune process



BRAIN REGIONS IMPLICATED IN OCD

- Prefrontal cortex including ACC and OFC
- Cortico-striatal circuitry



EVIDENCE BASED TREATMENTS FOR OCD

A. Exposure and Response (Ritual) prevention

B. Serotonin uptake inhibitors

C. A + B

MONITORING TREATMENT RESPONSE

Decrease in the Total Y-BOCS score of between 25- 35% relative to baseline

SSRIs have a number needed to treat of 5 (95%CI, 3 to 8) compared with placebo

Remission defined as a total Y-BOCS score <= 10 AND item 1 (time obsessions) not > 1hr AND item 6 (time compulsions) not > 1hr

SRIS IN OCD

- Adequate trial is 10 to 12 weeks long with at least 6 weeks at maximum tolerated dose
- Same or higher doses than used in depression
- Start with selective SRI (SSRI)
- After 2 failed SSRI trials, prescribe clomipramine

PHARMACOTHERAPY – FDA APPROVAL

- ✓ **Clomipramine (age 10 and over)**
- ✓ **Fluvoxamine (age 8 and over)**
- ✓ **Fluoxetine (age 7 and over)**
- ✓ **Sertraline (age 6 and over)**
- ✓ **Paroxetine (adults only)**
- ✓ **citalopram/escitalopram** (no FDA indication)

PHARMACOTHERAPY IN OCD

TABLE 3. Dosing of Serotonin Reuptake Inhibitors (SRIs) in Obsessive-Compulsive Disorder (OCD)

SRI	Starting Dose and Incremental Dose (mg/day)[a]	Usual Target Dose (mg/day)	Usual Maximum Dose (mg/day)	Occasionally Prescribed Maximum Dose (mg/day)[b]
Citalopram ★	20	40–60	80	120
Clomipramine	25	100–250	250	—[c]
Escitalopram	10	20	40	60
Fluoxetine	20	40–60	80	120
Fluvoxamine	50	200	300	450
Paroxetine	20	40–60	60	100
Sertraline[d]	50	200	200	400

[a]Some patients may need to start at half this dose or less to minimize undesired side effects such as nausea or to accommodate anxiety about taking medications.
[b]These doses are sometimes used for rapid metabolizers or for patients with no or mild side effects and inadequate therapeutic response after 8 weeks or more at the usual maximum dose.
[c]Combined plasma levels of clomipramine plus desmethylclomipramine 12 hours after the dose should be kept below 500 ng/mL to minimize risk of seizures and cardiac conduction delay.
[d]Sertraline, alone among the SSRIs, is better absorbed with food.

★ Black box warning

CLOMIPRAMINE

Side effects

- α1-adrenergic antagonism: orthostatic hypotension
- Histamine (H_1) blockade: weight gain and sedation
- Anticholinergic: tachycardia, urinary retention, dry mouth, blurred vision, constipation
- Na channel blockade: seizures and arrhythmias (0.7%)
  - Screening EKG in those with heart disease or >40 y/o

Goal Serum Levels

- 12-hour levels
- Steady state 2-3 weeks (32/69h half-life)
- Clomipramine (CMI): 225-350 ng/mL
- CMI+Norclomipramine (desmethylclomipramine): </= 500ng/mL

http://ocd.stanford.edu/treatment/pharma.html

- There are no data to suggest one SSRI is superior to another – selection should be based on side effect profile
- Early trials showed large effect size for clomipramine, but more recent head-to-head trials with SSRIs show no significant advantage for CMI
- CMI has more side effects than SSRIs (keep Total CMI, DMCI levels <450-500ng/ml and DMCI:CMI ratio < 0.3)
- Nevertheless, no OCD patient should be considered medication resistant without a trial of clomipramine (CMI)

EFFICACY OF SRIS IN OCD

Response is usually graded and incomplete

40 - 60% non-responders – suggest other neurotransmitter system involvement

Among "responders," improvement is rarely complete

TREATMENT REFRACTORY OCD

- Is the diagnosis correct?
- Were trials of CBT adequate?
- Was SSRI dosing and duration adequate? How was adherence?
- Are there comorbidities or significant environmental factors limiting treatment response?
- Apply most stringent criteria before employing experimental or invasive measures

COMBINATION TREATMENT STRATEGIES

- CBT + Meds
- Combining SRIs
- SRI plus other agents
    - serotonergic drugs
    - noradrenergic drugs
    - neuroleptics
    - others

ANTIPSYCHOTICS

- Mixed results
- Those with comorbid tics more likely to respond
- Atypicals may also exacerbate OCD symptoms
  - Clozapine most likely
  - Case reports of Risperdal, olanzapine, and quetiapine

SECOND GENERATION ANTIPSYCHOTICS

Risperidone

In double blind, PCT (mean dose 2.2mg/day) x 6 weeks superior in reducing OCD, anxiety and depression. 50% responders.

2 other smaller studies were +ve , one with fluvoxamine

1 study of SSRI partial or non-responders with adjunctive risperidone (upto 4mg/day) showed no benefit over placebo

Paliperidone

8-week double blind with 34 SSRI resistant – no statistical sig.

Olanzapine

1 small study some benefit

Other study was failed due to not truly SSRI resistant

Quetiapine

Mixed results

Appeared better when combination with specific SRI (Clomipramine, fluoxetine or fluvoxamine) and when SRI dose was lower

Most benefit in pts who are unable to tolerate maximal dose of SRI

Aripiprazole

Two 12 week open label study showed significant improvement with dose upto 10mg showed YBOCS reduction of 30% vs 4% in placebo

Case series in adolescents showed 50% reduction in CY-BOCS

Overall promising across lifespan.

Benzodiazepines

– ineffective

- N-AC – release Glutamate by modulating cysteine- glu antiporter

2 RCTs 3g/day- ineffective

1 trial with Fluvoxamine showed some benefit

- Memantine- low affinity antagonist of extrasynaptic NMDA Glu -R

20mg/day with SRI showed some benefit in 8-12week esp with GAD

- Topiramate – directly inhibits AMPA/kainite Glu-R

3 RCTs showed +ve results , 2 showed no difference

100-400mg/day. Greater benefit with compulsions than Obsessions

- Lamotrigine –reduces glutamate flow through inhibition of certain presynaptic voltage gated Na channels

100-200mg/day in adjunct with paroxetine or clomipramine showed improvement in case reports, retrospective review and 16 week RCT

ALTERNATIVES (OFF-LABEL)

- Ketamine – noncompetitive NMDA –R antagonist

no major studies , mixed result

- Effexor and Cymbalta – mixed results , data weak
- Buspar- largely negative
- Pindolol- nonsignificant trend towards improvement
- Mirtazapine – small trial showed benefit
- Ondansetron- single controlled study suggest benefit
- Riluzole – one study insignificant. Other with Fluvoxamine positive

  Study in children negative and other with n =60 showed no benefit

ALTERNATIVES (OFF-LABEL)

- **Opioids-**
  - Weekly **oral morphine** 20-40mg: N = 23 showed sig. benefit.
  - **Tramadol**: small open label showed improvement
- **Dextroamphetamine** 30mg vs. **Caffeine** 300mg: N = 24, double blind, active control study showed sig. improvement over 5 weeks in both
- **Methylphenidate ER** 36mg: N = 44, RCT, double blind → 59% vs. 5% response
- **Lithium** – case reports positive, small trials negative; most consistently positive with comorbid bipolar disorder
- **IV Clomipramine** – pulse loaded more effective in pilot study, large study did not confirm findings

DIFFERENTIAL DIAGNOSIS

- **OCD vs BDD**

Patients with OCD may have body focused obsessions such as "will I stop breathing if I stop counting my breaths" compared to BDD people are preoccupied by concerns of physical appearance and perceptions of ugliness

- **OCD vs Eating disorder**

Obsessions in OCD may involve food and eating e.g concerns of germs on food and decontamination rituals and wt loss compared to fear of weight gain in anorexia.

- **OCD vs Trichotillomania / skin picking disorder**

Trichotillomania has urge to pull or pick and no accompanying obsession and no ritualistic behavior beyond picking and pulling

- **OCD vs Hoarding disorder**

HD there is preoccupation that is limited to an overattachment to collections and behavior to acts of collecting or accumulating and organizing collections

- **OCD vs ASD**

Narrow consuming interest and patterned behaviors with interpersonal and social deficits

- **OCD vs Tic disorders**

OCD compulsions are usually more elaborate behaviors and carried out to calm anxiety producing obsessions compared to sudden, rapid recurrent, nonrhythmic motor movements or vocalizations and not aimed to neutralize an obsession

- **OCD vs Impulsive behaviors** (Pathologic gambling, Kleptomania, paraphilia, excessive internet use)

Impulsive activity is pleasurable, defined by pleasure seeking and excitement rather than harm avoidance

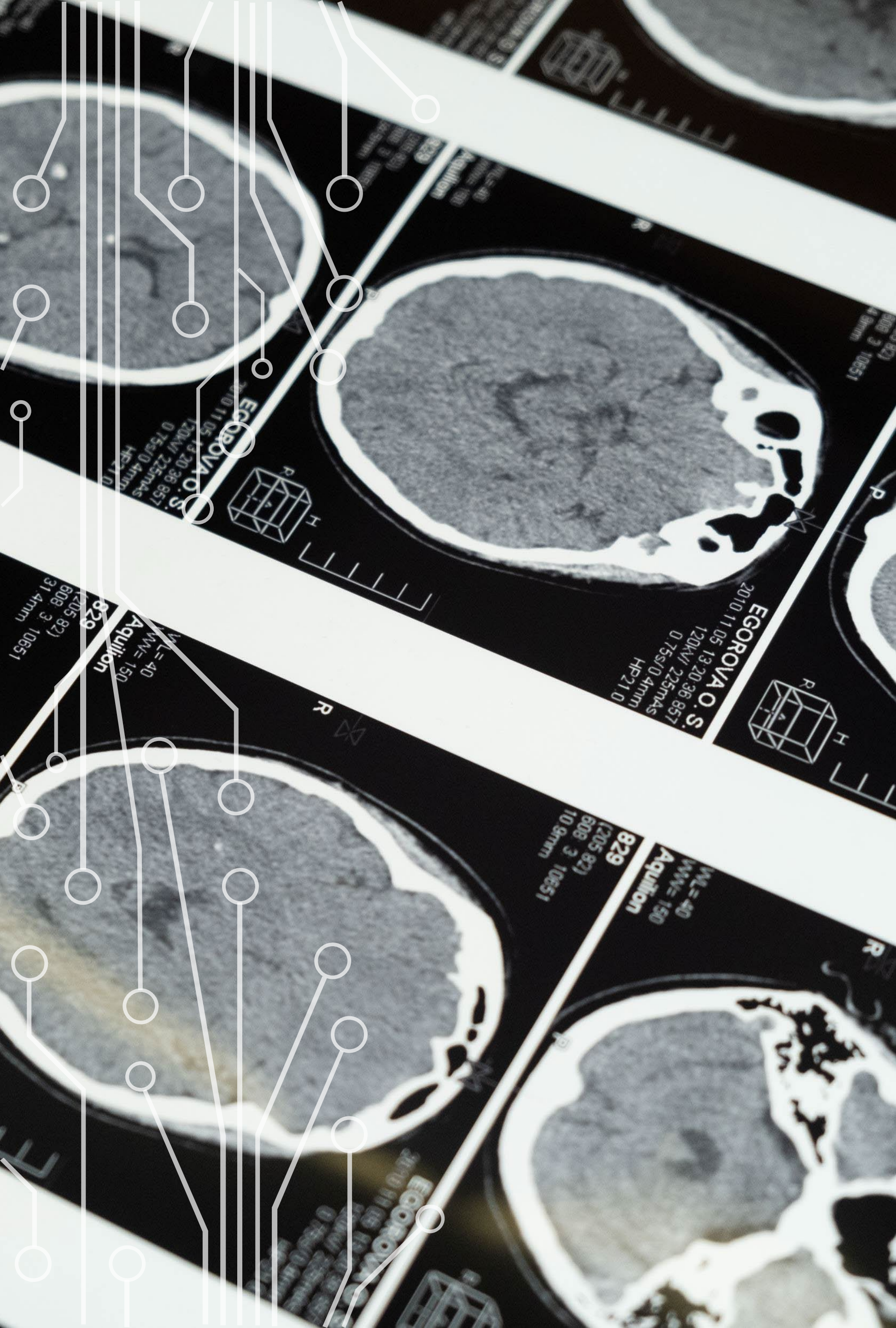
DIFFERENTIAL DIAGNOSIS

- **OCD vs Illness anxiety disorder**

In OCD no presumption of illness or disease. Somatic obsessions are uncertainty of own health functions –HR/ breathing etc.

- **OCD vs OCPD**

OCPD is chronic, rigidity and perfectionism in interests and viewpoints "ego syntonic".



COMORBIDITIES IN OCD

Substance use disorder	27%
Personality disorder	45%
Major depression	35-67%
Bipolar disorder	16%
Eating disorder	13% (11-42%)
Panic disorder	18%
Tic disorder	14%
ADHD	10-30%

OCD WITH TOURETTE'S

- SSRI alone are less effective
- Clomipramine alone
- SSRI and clomipramine
- SSRI or clomipramine & typical or atypical neuroleptic (monitor QTc)
- SSRI or clomipramine & alpha 2 agonist

OCD WITH ADHD

- Treat OCD first
- Stimulants are often needed for ADHD with OCD
- Stimulants may increase primary obsessions and rituals or anxiety
- Consider
  - Clomipramine
  - Atomoxetine
  - Bupropion
  - Clonidine or guanfacine

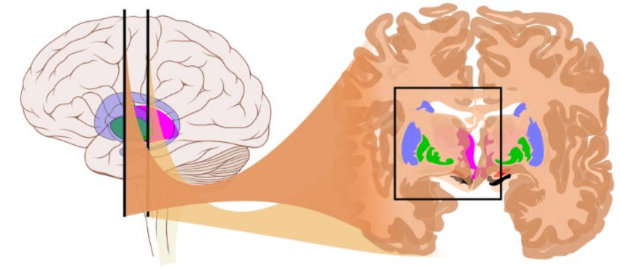
OCD WITH BIPOLAR DISORDER

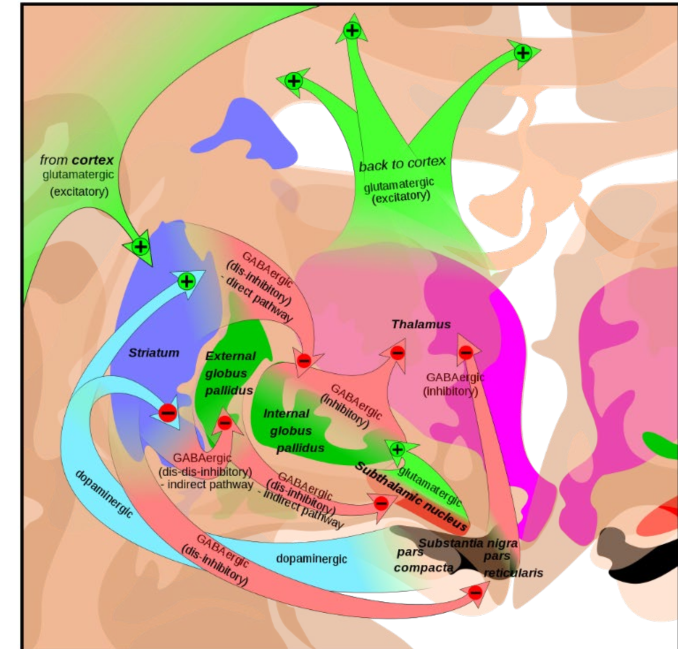
- Difficult to balance
- Treat bipolar disorder first
- Drawbacks of using SRI's to treat OCD: behavioral activation and organic mood changes with hypomania
- Mood stabilizers or atypical neuroleptics may be needed to counteract activating effects of SRI's

SOMATIC THERAPIES

- Transcranial Magnetic Stimulation (rTMS)
  - SMA, mPFC, dmPFC,
  - High frequency (20Hz) deep (Brainsway coil) with positive results
- Ablative surgeries
- Deep Brain Stimulation (DBS)
- ECT
  - **Not** recommended as primary treatment for OCD
  - For co-occurring depression

NEUROCIRCUITRY CORTICO-STRIATAL-THALAMIC-CORTICO (CSTC) PATHWAYS

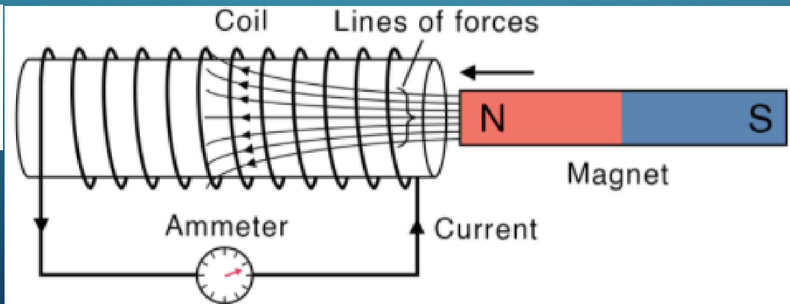




WHAT IS TMS?

- A non-invasive neuromodulation technique
- Uses rapidly alternating magnetic fields to create local electrical currents
  - Faraday's Law

$$\varepsilon = -N\frac{\Delta\Phi}{\Delta t}$$



TMS OCD COILS

- BrainsWay (2018)
- MagVenture (2020)
- Magstim
- Neurostar

OUTCOMES

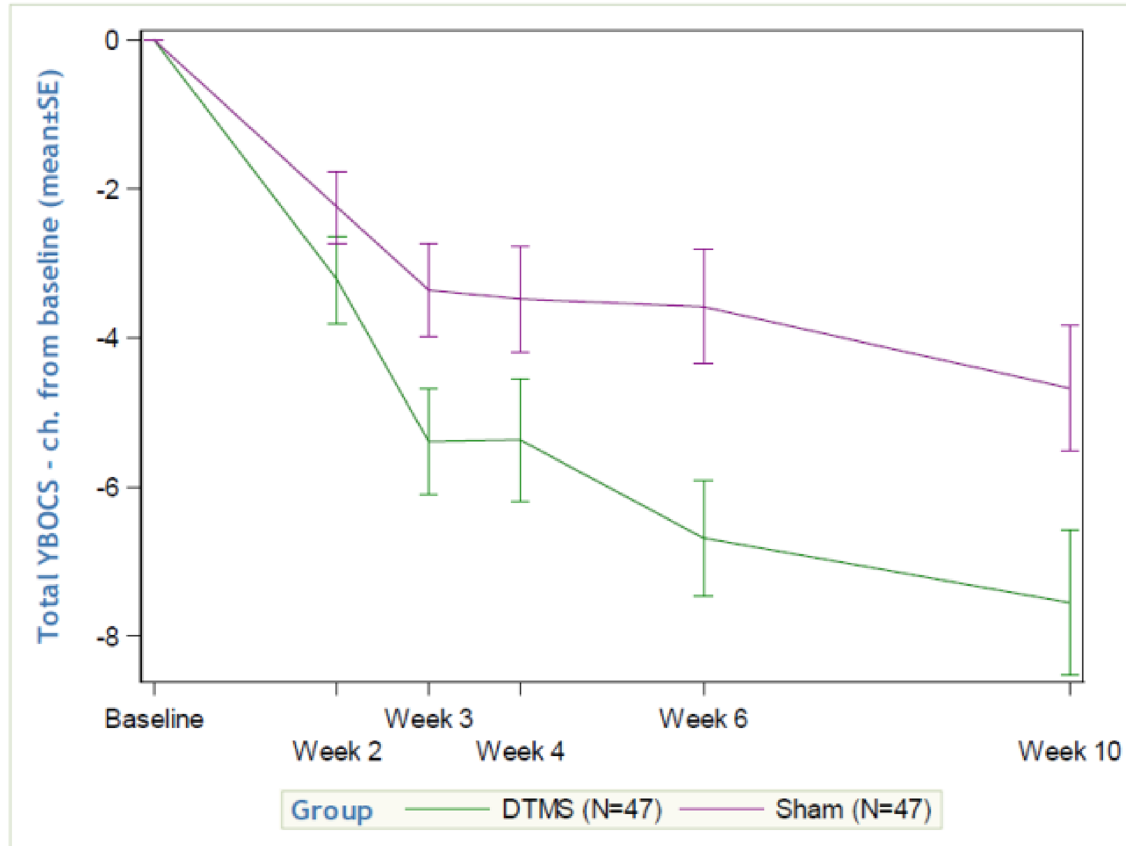


Figure 2: YBOCS Change From Baseline Over Time (mITT)

Change in Y-BOCS at week 6

- Sham: - 3.6
- dTMS: - 6.7

Response rate

- 38.10% response (vs. 11.10% sham)
- 54.76% partial response (vs. 26.67% sham)

Response = 30% reduction

Partial Response = 20% reduction

Brainsway FDA Package Insert 2018.
https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170078.pdf

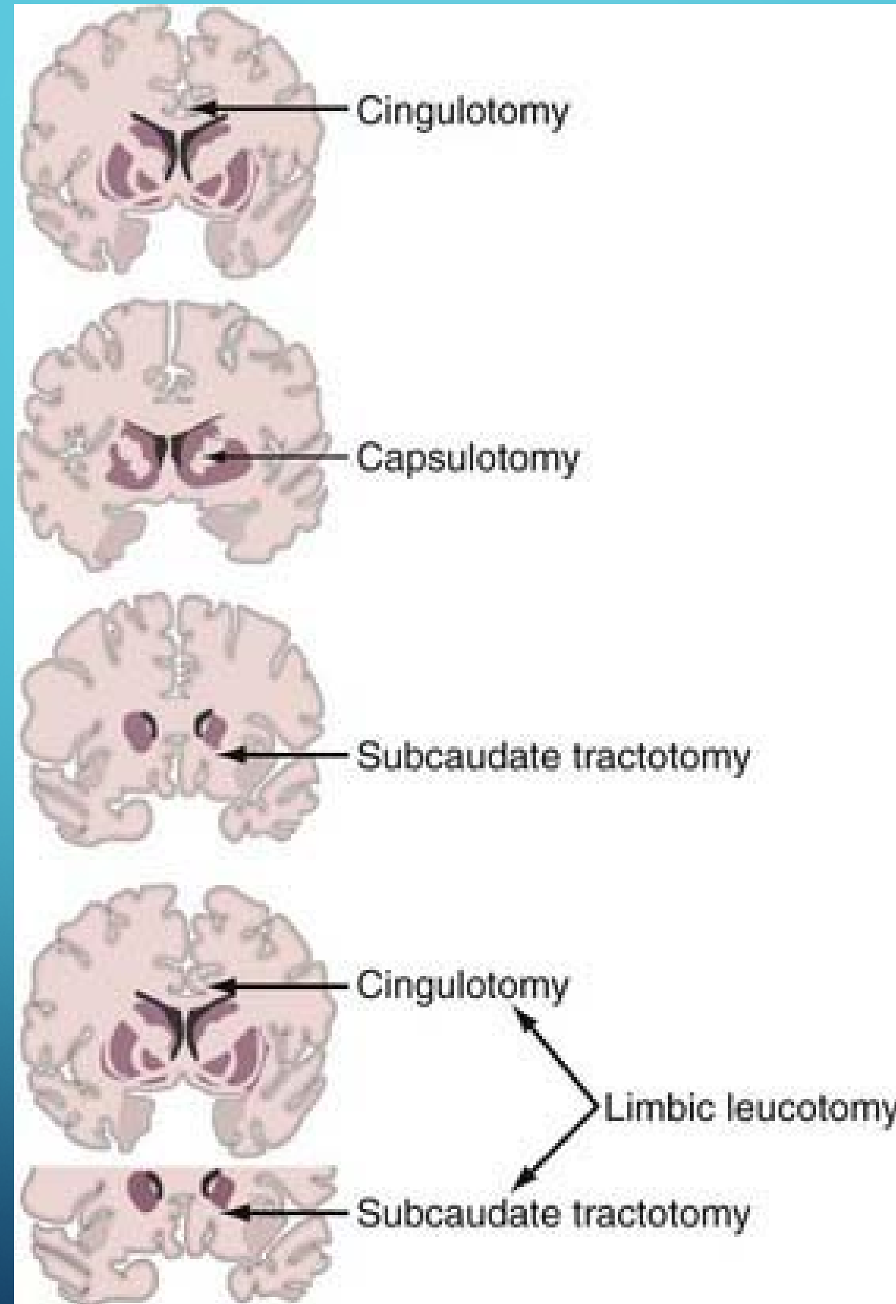
ADVERSE EVENTS

- Headache reported by 37.5% vs 35.3% of sham
- application site pain or discomfort
- jaw pain
- facial pain
- muscle pain, spasm or twitching, and
- neck pain

NEUROSURGERY IN OCD

OCD - Ablative Surgeries

- Success rates of 50-60%
- Performed as early as the 1940's

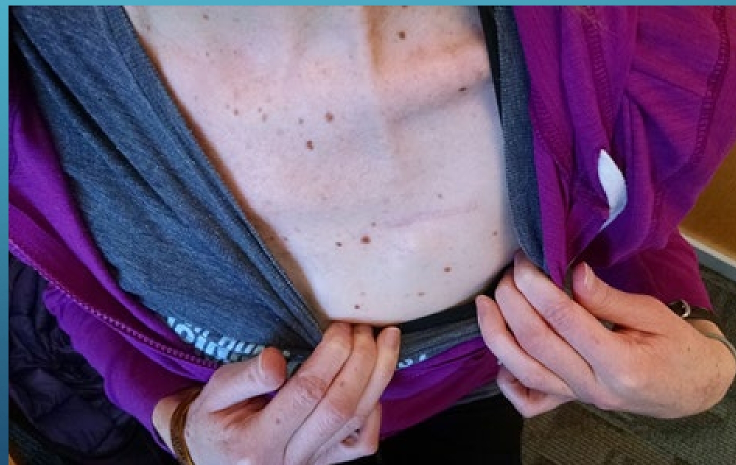


Fins JJ. From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of neuropsychiatric research. *Neurosurg Clin N Am.* 2003;14(2):303-319.

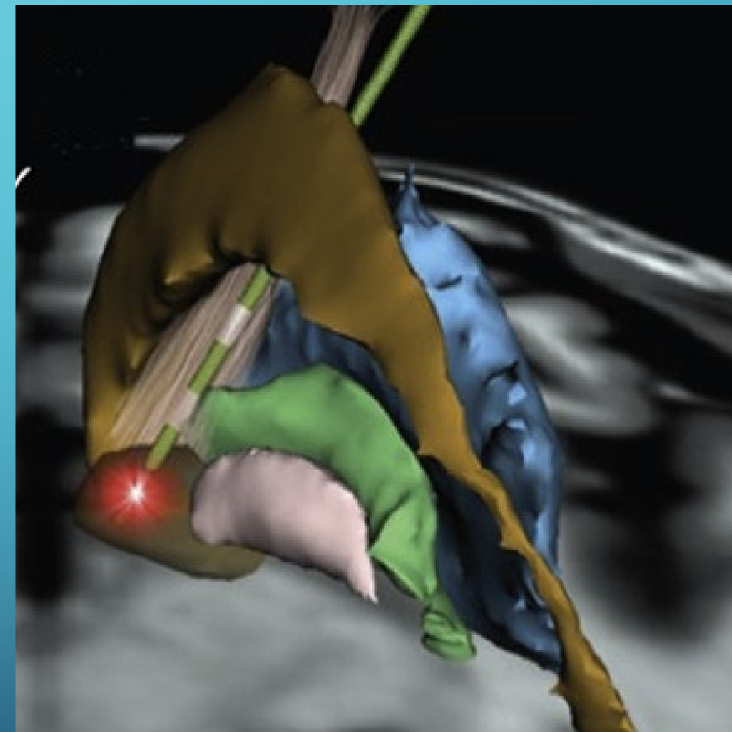
Jenike M. Neurosurgical treatment of obsessive-compulsive disorder. *The British Journal of Psychiatry.* 1998;35(S):79-90.

Image obtained from: http://clinicalgate.com/surgical-treatment-of-major-depression/

WHAT IS DEEP BRAIN STIMULATION?



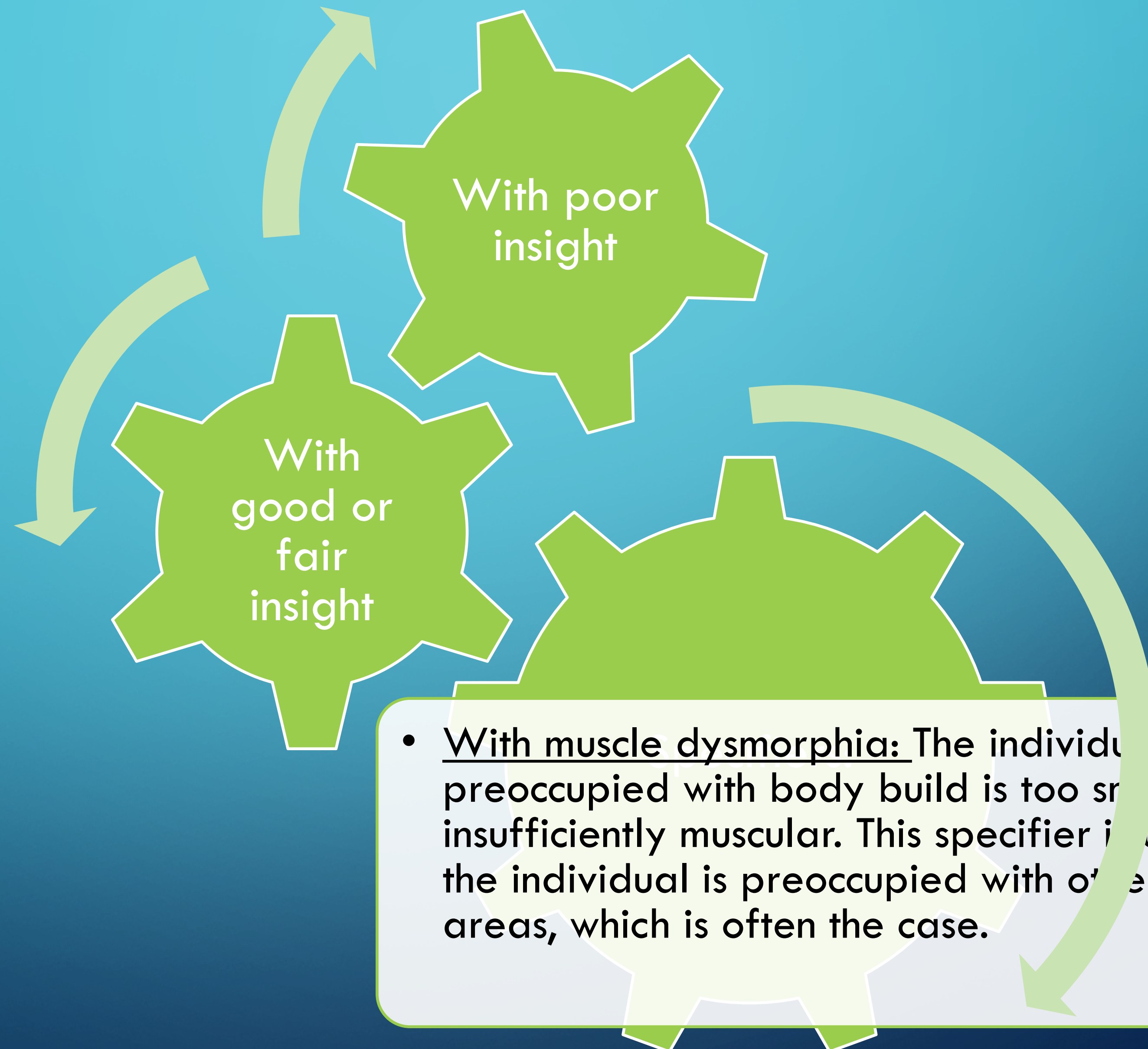
VENTRAL CAPSULE/VENTRAL STRIATUM



OCRDs

BDD (BODY DYSMORPHIC DISORDER)

- Changed from Somatoform disorders to OCD and Related disorders
- Preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others.
- At some point during the course of the disorder, the individual has performed repetitive behaviors (e.g., mirror checking, excessive grooming, skin picking, reassurance seeking) or mental acts (e.g., comparing his or her appearance with that of others) in response to the appearance concerns.



- <u>With muscle dysmorphia:</u> The individual is preoccupied with body build is too small or insufficiently muscular. This specifier is used even if the individual is preoccupied with other body areas, which is often the case.

Often misdiagnosed/ under diagnosed and misunderstood

Overlapping symptoms with Eating disorder, OCD, Psychosis etc.

Common areas of concerns are Face/ skin/ hair/ build/ breasts

Perceived defects related to color/ shape/ size/ symmetry

Repetitive behaviors e.g Excessive mirror checking/ Excessive comparison with the appearance of others / Excessive/elaborate grooming routines/ Wearing clothing/accessories to camouflage the "flawed" body part/ Seeking reassurance /Doctor shopping for cosmetic treatment (e.g. surgical, dermatologic, dental)/ Frequent clothes changing to find a more flattering outfit, or one that hides perceived flaws better/ Taking excessive selfies to check one's appearance

Avoidance of triggering situations – e.g social events, parties, mirrors, bright lighting

No FDA approved meds

SRIs most studied is Escitalopram followed by Fluoxetine

Improvement is gradual with ups and downs

12-16 weeks of course with doses higher than typical in depression

Meds dosing –

- Escitalopram 60mg/day
- Fluoxetine 120mg/day
- Sertraline 400mg/day
- Paroxetine 100mg/day
- Fluoxamine 450mg/day
- Clomipramine 250mg/day

AUGMENTATION AGENTS:

- Buspar
- Atypicals
- Wellbutrin
- SNRIs
- ECT/ TMS ?

HOARDING DISORDER

Persistent difficulty discarding items/ possessions regardless of their value

Accumulation of items lead of congestion/ clutter

Living areas compromised

Specifiers

With excessive acquisition

With good/fair/poor insight/ delusional beliefs

- Differential diagnosis

OCD/ MDD/ Delusions from psychosis/ Neurocognitive deficits/ ASD

- Poor response to CBT as well as pharmacotherapy

- Limited research and no general consensus

- 12-16 week trial of OCD treatment then Anti psychotics/ ADHD meds/ Aricept/ Galantamine

TRICHOTILLOMANIA

- Repetitive behaviors in response to feeling uncomfort-able
- Good feeling/ relief after pulling behaviors
- Common areas ; scalp/ eyelashes/ eyebrows/ beard/ pubic area
- When – watching TV/ reading book/ laying in bed/ sitting at the computer
- Positive as well as negative stressors

Trichotillomania

Trichotillophagia

Rapunzel syndrome

SKIN PICKING DISORDER (EXCORIATION DISORDER)

Recurrent picking at the skin resulting in skin lesions.

Repeated attempts to decrease or stop the excoriation.

Clinically significant distress or impairment in social, occupation, or other important areas of functioning.

Not attributable to the psychological effects of a substance (e.g., cocaine) or another medical condition (e.g., scabies)

Not better explained by another mental disorder (e.g., delusions or tactile hallucinations in a psychotic disorder, attempts to improve a perceived defect or flaw in appearance in body-dysmorphic disorder, stereotypes in stereotypic movement disorder, or intention to harm oneself in non-suicidal self-injury).

TREATMENT OF BFRBS

- Habit Reversal Training (HRT)
- Cognitive therapy
- CBT
- DBT

MEDICATIONS FOR BFRBS

- No FDA approved meds
- No medication helps everyone with skin picking or hair pulling
- Meds for OCD and other anxiety disorders have limited success
- SSRIs
- NAC
- Mood stabilizers / atypical antipsychotics
- Inositol

CONCLUSIONS

OCD is common, highly impairing and remarkably variant

Comorbidity is a rule

40-60% continue to suffer inspite of best evidence based Rx

CBT + ERP is 1st line

CBT + meds can improve QoL, psychosocial functioning and life satisfaction

Meds- higher doses and 12-16 weeks duration

Refractory OCD is common clinical challenge

Integration of phenotypic studies, genetics, imaging e.g Human Connectome project/ ENIGMA

Further research is required

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RESOURCES

- www.IOCDF.org
- www.kids.iocdf.org
- www.bfrb.org
- www.mhanational.org
- www.nimh.nih.gov
- www.AACAP.org