Overview of OCD

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The Problem

- OCD is a common disorder associated with significant disability and chronicity
  - W.H.O.: OCD is one of the world's top ten causes of illness related disability
  - Lifetime prevalence of 2-3%
- Approximately 10-30% of patients are not helped at all or are inadequately helped by current pharmacotherapies.

Patient #1

- 54 year old married woman
- OCD since childhood but not diagnosed until age 43
  - Childhood: get up at night to check homework, erase work and restart
  - Young adult: bumps in road when in car would make her fear she ran someone over
  - Numerous meds & behavior therapy were not helpful (prior to seeing us)

Obsessive-Compulsive Disorder: DSM-IV Criteria

Obsessions

- Recurrent thoughts, images, or impulses that are intrusive and cause marked distress
  - Aggressive, Contamination, Sexual, Religious, Somatic, Symmetry/Order, Hoarding
- Obsessions are not simply excessive worries
- Person tries to suppress or neutralize them
- Obsessions are initially recognized as part of one's mind - not inserted

Obsessive-Compulsive Disorder: DSM-IV Criteria

Compulsions

- Repetitive behaviors (handwashing, ordering, checking) or

  mental acts (praying, counting, repeating words silently) that the person is driven to perform
- Compulsions are aimed at reducing distress or preventing some dreaded consequence

Obsessive-Compulsive Disorder: DSM-IV Criteria

B. Obsessions are recognized at some point as excessive or unreasonable (excludes children).

C. Causes marked distress, is time consuming, or interferes with normal functioning

D. Content is not limited to other Axis I disorders, such as Anorexia, Trichotillomania, Body Dysmorphic Disorder, Hypochondria, Paraphilia, Major Depression

Epidemiology of OCD: Cross-National Collaborative Study (1994)

- U.S. Lifetime prevalence of 2.3 per 100 (ECA)
- Similar prevalence in 7 other countries
- Mean age of onset: 22 - 35
- 12-60% have comorbid major depression and 35-70% had another anxiety disorder
- Female to male ratio of 6:4
- Symptom profiles vary per country. In the U.S., 50% had obsessions only, 34% had compulsions only, and only 16% had both.

Related Features of OCD

- Pathological Uncertainty
  - "How can I be sure?"
- Pathological Sense of Responsibility
  - "Why did I let that happen?"
- Pervasive Avoidance
  - From avoiding public restrooms or shaking hands to avoidance of all contact with the outside world
- Magical Thinking
  - Omnipotence of thought. Merely thinking a thought can cause it to occur

Why propose a corticostriatal model for OCD?

- Neuroimaging Studies
  - Hyperactivity in OFC, Cingulum, Caudate
- Neuropsychologic Studies
  - Subtle fronto-striatal functional deficits
- Neurosurgical approaches target CS tracts
- Other diseases with known striatal pathology have high frequencies of OC features
  - Sydenham's chorea
  - Huntington's disease
  - Tourette's syndrome

Tic-related OCD

- Earlier age of onset (prepubertal)
- Affects males more than females
- Certain OCD symptoms more common:
  - Tic-like compulsions (touch, tap, or rub)
  - Intrusive violent or aggressive thoughts
  - Worries about symmetry and exactness
  - (Contamination, cleaning, checking were independent of pt's tic status)
- Rituals done until "Just right"
- Responds less well to SSRIs….OCD improves with dopamine D2 receptor antagonists

Phenomenology Summary

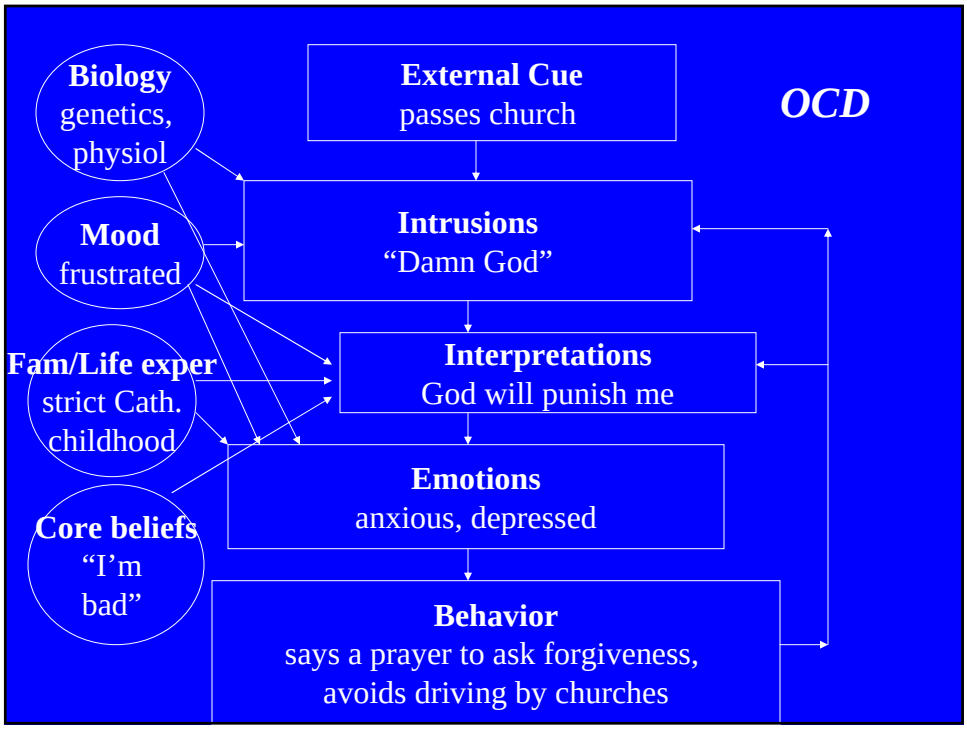
- OCD is a phenomenologically heterogeneous disorder
- Subtypes of OCD may have differing pathophysiology & therapeutic response
- Identification of biologically homogenous subtypes will enhance genetic & neuroimaging studies, early detection & therapeutic intervention

First-Line Treatments for OCD:

- Pharmacotherapy with serotonin reuptake inhibitors (SRIs):
  - clomipramine
  - selective serotonin reuptake inhibitors (SSRIs--fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram)
- Cognitive-Behavioral Therapy consisting of exposure and response (or ritual) prevention (EX/RP)

Cognitive Behavioral Model of OCD

- Common types of interpretations/beliefs that influence the development of OCD (OCCWG, 1997)
  - responsibility for harm
  - overestimation of threat
  - perfectionism
  - intolerance of uncertainty
  - over-importance of thoughts
  - need to control thoughts



What Is behavioral therapy?

- Live confrontations with feared situations or objects ("in-vivo exposure")
- Imaginal confrontations with feared consequences ("imaginal exposure")
- Ritual prevention (i.e., patient refrains from compulsions and avoidance)

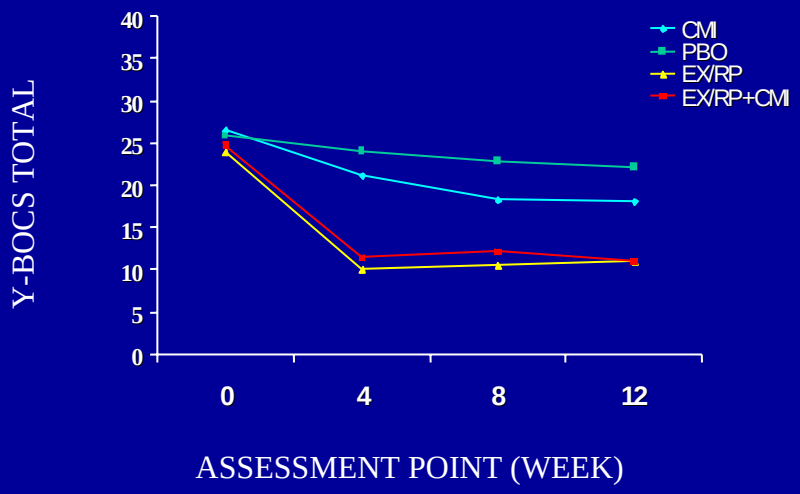
How is behavior therapy done?

- Varies in intensity: 15-25 individual sessions, each lasting 1-2 hours, 1-5 times per week, home visits.
- Initial sessions: review the treatment rationale, constructing a hierarchy of feared stimuli, planning how and when to confront feared stimuli
- EX/RP sessions: therapist-supervised exposures starting with stimuli that generate moderate fear and continuing until the most feared stimuli are faced without ritualizing
- Homework: exposure practice and ritual prevention
  - (Simpson slide)

Explanation for efficacy of BT?

- Habituation. By facing real and imagined fears for a prolonged period without ritualizing, the initial anxiety/discomfort dissipates on its own ("habituation")
  - Breaks the connection between feared stimuli and anxiety
  - Breaks the connection between rituals and anxiety relief
  - Corrects mistaken beliefs (e.g., that harm is likely, that thoughts are the same as actions, that anxiety/discomfort will persist forever, that rituals protect against harm)

Y-BOCS in CMI BT OCD Trial: Treatment completers *(Liebowitz, Foa, Simpson, Kozak)*



Factors Associated with Poor Response to SRIs

- Inadequate duration of trial, inadequate dosing
- Incorrect diagnosis (e.g., OCPD vs OCD)
- Clinical features
  - Hoarders
  - Comorbid tic disorder
  - Comorbid schizotypal features
- Continuous Clinical course (rather than episodic)
- Early Age of Onset
- Poor insight
- Greater severity of neurologic soft signs

Clomipramine

- Clomipramine:
  - Potent 5-HT (CMI) and NE (DCMI) reuptake blockade
  - Average symptom improvement of 36%-46%
  - Ciba-Geigy: dosing up to 300 mg/d
    - much improvement in 60-61% on CMI vs 5-9% on placebo
    - Many AEs, but <10% dropped from studies
    - Improvement starts early (2wks) & increases with time
  - No dose finding studies exist
  - 1980s: CMI > placebo, desipramine, amitriptyline
  - Range in studies: 150-250mg/day, but some studies allow lower dosing of 75-150 mg/d

Dosing Trials of SSRIs:
% Change in Y-BOCS from baseline

- Fluoxetine: 13-wk Fixed Dose Study, n=355 (Tolefson)
  - Y-B: 20 mg (20%), 40 mg (22%), 60 mg (27%), Pbo (3%)
    - A.E.: nausea, dry mouth, tremor
- Sertraline: 12 wk Fixed Dose Study, n=324 (Greist)
  - Y-B: 50 mg (24%),[100 mg (19%)], 200 mg (28%), pbo (15%)
    - A.E.: diarrhea, insomnia, decreased libido, nausea, anorexia
- Fluvoxamine: 10 wk Flexible Dose Study, n=300 (Rasmussen)
  - Y-B: mean dose 249 mg/d (change 20%), pbo (5%)
    - A.E.: insomnia, nausea, somnolence, dry mouth
- Paroxetine: 12 wk Fixed Dose Study, n=263 (Wheadon)
  - Y-B: [20 mg (19%)], 40 mg (25%), 60 mg (29%), pbo (13%)
- Citalopram: 12 wk Fixed Dose Study, n=401 (Montgomery 2001)
  - **Y-B:** 20 mg (34%), 40 mg (34%), 60 mg (40%) or pbo (22%)

Meta-Analyses of CMI vs SSRIs

- Effect size> for CMI than for SSRIs
  - EF CMI> fluoxetine (Jenike 1990)
  - EF CMI>sertraline and fluvoxamine (Davis 1991)
  - EF CMI>fluoxetine, sertraline, fluvoxamine (Greist 1995)
    - SSRIs comparable to one another:
      - Proportion of pts improved (43%-44%)
      - Percentage decrease in Y-BOCS (20-27%)
    - Patients treated with CMI had significantly better results
      - Proportion of pts improved (60%)
      - Percentage decrease in Y-BOCS (39%)
- Critique of Meta-analyses:
  - Cohort effect: pts treated with CMI had not had prior SSRI exposure

Double-blind Comparisons of CMI vs SRIs

- Fluvoxamine similar to CMI (Freeman 1994, Koran 1996)
  - F: Flex dose, n=66, similar in AE also
  - K: Flex dose, n=79, fl:100-300mg v cmi: 100-250 mg
- Fluoxetine similar to CMI (Lopez-Ibor 1996)
  - Fixed dose, n=55, 8 wk, fl: 40 mg v cmi:150 mg
- Sertraline similar to CMI (Bisserbe 1997)
  - Flex , n=86, 16 wks, mean ser: 129mg, cmi: 90mg/d
- Paroxetine similar to CMI and better than placebo (Zohar 1996)
  - Flex dose, n=399, 12 wks. Range: Paroxetine 10-60, CMI 25-250
  - Mean dose: Parox 37.5 mg/d, CMI 113 mg/d
  - CMI associated with more AE than placebo and than paroxetine

Augmentation Strategies

- Many agents helpful in case reports or small series, but few have either been studied at all or shown to be effective when subjected to a randomized, placebo-controlled design.
  - Trytophan, d-fenfluramine, gabapentin, donepezil, clonazepam, pindolol, lithium, buspirone, inositol, bromocriptine, oxytocin, morphine, naltrexone
- Multiple studies support use of adjunctive typical or atypical neuroleptics

Controlled trials of conjoint SRI-neuroleptic Treatment in refractory OCD

- Haloperidol (~6mg) + Fluvoxamine (McDougle, 1994) (RPCT)
  - 34 pts with partial or no response to 8 wks of Fluv were given 4 weeks of either Pbo or haloperidol adjunctively.
  - 11 of 17 (65%) given H responded vs 0 of 17 given Pbo
  - 8 of 8 pts with comorbid tic disorders responded (with a 47% decrease in YBOCS) compared to 3 of 9 pts without tic disorder.
- Risperidone + SSRI (McDougle 2000) (RPCT)
  - Effective among pts with and without tics
  - 50% given Risperidone + SRI responded vs 0% given Pbo + SRI
  - Y-BOCS improved 31% over baseline in Risperidone group
- Olanzapine + SSRI (Bystritsky)
  - Effective with a 20% reduction in Y-BOCS
- No placebo-controlled trials yet of quetiapine, ziprasidone or aripiprazole, although numerous case reports and small series report favorable results for the use of quetiapine as an augmenter.

Reports on Atypical Antipsychotics for adjunctive SRI therapy for OCD

Table 1. Decrease in Yale-Brown Obsessive Compulsive Scale (YBOCS) Scores in Trials in Which Atypical Antipsychotics Were Added to Serotonin Reuptake Inhibitors[a]

Study	Drug	Type of Trial	Patients (N)	Decrease in YBOCS Score, %		
				Mean	Median	SD
McDougle et al[2]	Risperidone	Open	3	54	56	10
Saxena et al[4]	Risperidone	Open	21	NA[a]	NA[a]	NA[a]
Stein et al[5]	Risperidone	Open	8	22	10	29
Pfanner et al[6]	Risperidone	Open	20	30	32	9
McDougle et al[7]	Risperidone	Double-blind	20	31	30	27
Weiss et al[8]	Olanzapine	Open	10	40	42	25
Koran et al[9]	Olanzapine	Open	10	16	9	22
Bogetto et al[10]	Olanzapine	Open	23	30	NA[a]	NA[a]
Francobandiera[11]	Olanzapine	Open	9	37	42	25
Bystritsky[12]	Olanzapine	Double-blind	13	20	NA[a]	NA[a]

[a]Individual YBOCS scores were not available.

Bilateral Neurosurgery

- Anterior Cingulotomy: success rate of 56%
  - Interrupts fibers in the cingulate bundle
- Subcaudate tractotomy: success rate of 50%
  - Lesions in rostral part of orbitofrontal cortex ventral to head of the caudate
- Limbic Leukotomy: success rate of 61%
  - Lesions in cingulate & orbitomedial frontal areas which contain a segment of the fronto-caudate-thalamic tract
- Anterior Capsulotomy: success rate of ~50-67%
  - Lesions in the anterior limb of the internal capsule
  - Fibers of fronto-striatal-pallidal-thalamic-frontal loops are believed to pass through anterior limb of the internal capsule.

Corticostriatal Circuitry & Corticostriatal Hypothesis of OCD

- Striatum: caudate, putamen, nucleus accumbens (a.k.a. ventral striatum). Functions to modulate motor, cognitive, and affective processes.
- "Direct" and "Indirect" Corticostriatal Collaterals
  - Direct: direct projections from striatum to globus pallidus interna (substance P) with net excitatory effect on thalamus, overdriving the corticothalamic branch
  - Indirect: indirect projections from striatum to globus pallidus externa (enkephalin) to GP interna with net inhibitory effect on thalamus.
  - A dominant direct collateral may lead to a reverberating corticothalamic "worry circuit"

Deep Brain Stimulation for OCD

- Case reports suggest effectiveness
- Lead follows anterior limb of internal capsule (similar to capsulotomy). Pulse generator is implanted in abdomen or chest.
- Reversible…improvement may occur rapidly
- Risks (due to tissue displacement and damage to vasculature): seizure (1-3%), hemorrhage (1-5%), infection (2-25%)
- Mechanisms of action unclear: inhibits transmission via depolarization blockade or neural jamming

DBS for 3 Pts with Treatment Refractory OCD Gabriels et al, Acta Psychiatric Scand 2003

- Quadripolar electrode implants in anterior limb of int capsule bilaterally
- Stimulation parameters optimized over 2 weeks based on mood/anxiety reduction…then continuous bilat stim.
- Outcome 1 year later: personality, OCD, & frontal lobe tests.

Treatment Summary

- Treatment stategies:
  - SSRIs or clomipramine
  - Behavioral therapy
  - Combo of Drug and behavioral therapy
  - Then if patient is not responding well
    - Reassess diagnosis
    - Neuroleptic augmentation
    - Address comorbid conditions
    - Consider anticonvulsant trial
    - Consider neurosurgery or deep brain stimulation
  - Efficacy of Yoga? Of Transcranial Magnetic Stimulation?