Obsessive Compulsive Disorder (OCD)

Wayne K. Goodman, MD

Learning Objectives

- To reliably diagnose OCD and differentiate it from other anxiety disorders
- To learn the basis for the theories of pathophysiology of OCD
- To learn the evidence for a rationale approach to the treatment of OCD

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Outline

- **Nosology, Phenomenology & Differential Diagnosis**
- **Demographics, Prevalence and Course**
- **Putative Subtypes**
- **Pathophysiology**
  - Serotonin and neurochemical hypotheses
  - Neuroanatomical circuits
  - Pathogen-triggered autoimmune-mediated theory

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Outline (cont'd) of Treatment

- **Behavioral therapy**
- **Pharmacotherapy basics**
  - Preferential efficacy of SRIs
  - Measuring change
- **Approaches to treatment-resistant OCD**
  - Augmentation strategies (e.g., adding antipsychotics)
  - Novel biological interventions (e.g., deep brain stimulation)

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Question #1

Which may be a manifestation of OCD?

a. distorted belief of being fat and counting calorie intake not to exceed 1000 per day

b. can't get ex-girlfriend out of his mind and feels compelled to know her whereabouts

c. recognizes irrationality of need to check envelopes to ensure 5-year old daughter is not inside

d. compulsively eats everything in front of him and feels guilty afterwards

Question #2

The serotonin hypothesis of OCD is

a. supported by PET imaging studies

b. no longer consistent with treatment studies

c. based primarily on preferential response of SRIs

d. confirmed by post-mortem data

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Question #3

The brain regions implicated in OCD are

a. orbito-frontal cortex and basal ganglia

b. amygdala and cerebellum

c. hippocampus and locus ceruleus

d. unknown

Question #4

Evidenced based treatments for OCD include

a. SSRIs and buspirone

b. SSRIs, SNRIs and alprazolam

c. SSRIs, clomipramine and CBT

d. SSRIs and ECT

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Question #5

Use of antipsychotics in OCD is

a. inappropriate because these patients are not psychotic

b. confined to augmentation of SRIs in refractory cases

c. an option as either monotherapy or adjunctive treatment

d. only effective for suppressing tics

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Obsessive Compulsive Disorder (OCD)

- Classified as anxiety disorder in DSM-IV.
- Recurrent unwanted and distressing thoughts (obsessions) and/or repetitive irresistible behaviors (compulsions).
- Majority have both obsessions and compulsions.
- Insight present: acknowledged as senseless or excessive at some point during illness.
- Compulsions usually reduce anxiety but are not pleasurable.
- Symptoms produce subjective distress, are time-consuming (>1hr/day), or interfere with function.

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Obsessions

- Recurrent and disturbing thoughts, impulses, or images
- Experienced as intrusive (ego-dystonic)
- Not just excessive worries about real-life events such as in GAD

Obsessions

- Attempts are made to ignore, suppress or neutralize the thoughts with some other thought or action (a compulsion)
- Person knows it's his/her own thoughts

Common Obsessions

- **Typical concerns include:**
  - **contamination**
  - **aggression**
  - **safety/harm**
  - **sex**
  - **religion (scrupulosity)**
  - **somatic fears**
  - **need for symmetry or exactness**

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Compulsions Defined

- **Repetitive behaviors or mental acts the person feels driven to perform either**
  - In response to an obsession, OR
  - According to rigid rules
- **Designed to prevent or reduce distress or to prevent some dreaded event from occurring**
- **The acts are clearly excessive or senseless**

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Common Compulsions

- **Typical behaviors include:**
  - **cleaning/washing**
  - **checking**
  - **ordering/arranging**
  - **counting**
  - **repeating**
  - **hoarding/collecting**

Differentiating Tics From Compulsions

- **Tics**
  - **Involuntary, sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization**
  - **Experienced as irresistible, but can be suppressed to some degree**
- **Compulsions**
  - **Repetitive and seemingly purposeful behaviors that the person feels driven to perform, usually, but not always, in response to an obsession**

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Differentiating Tics From Compulsions

- Complex motor tics
  - Facial gestures, grooming behaviors, jumping, touching, stamping, and smelling an object
- Tic-like compulsions
  - Touching, tapping, rubbing, stereotyped repeating of routine activities , and “evening-up” behaviors

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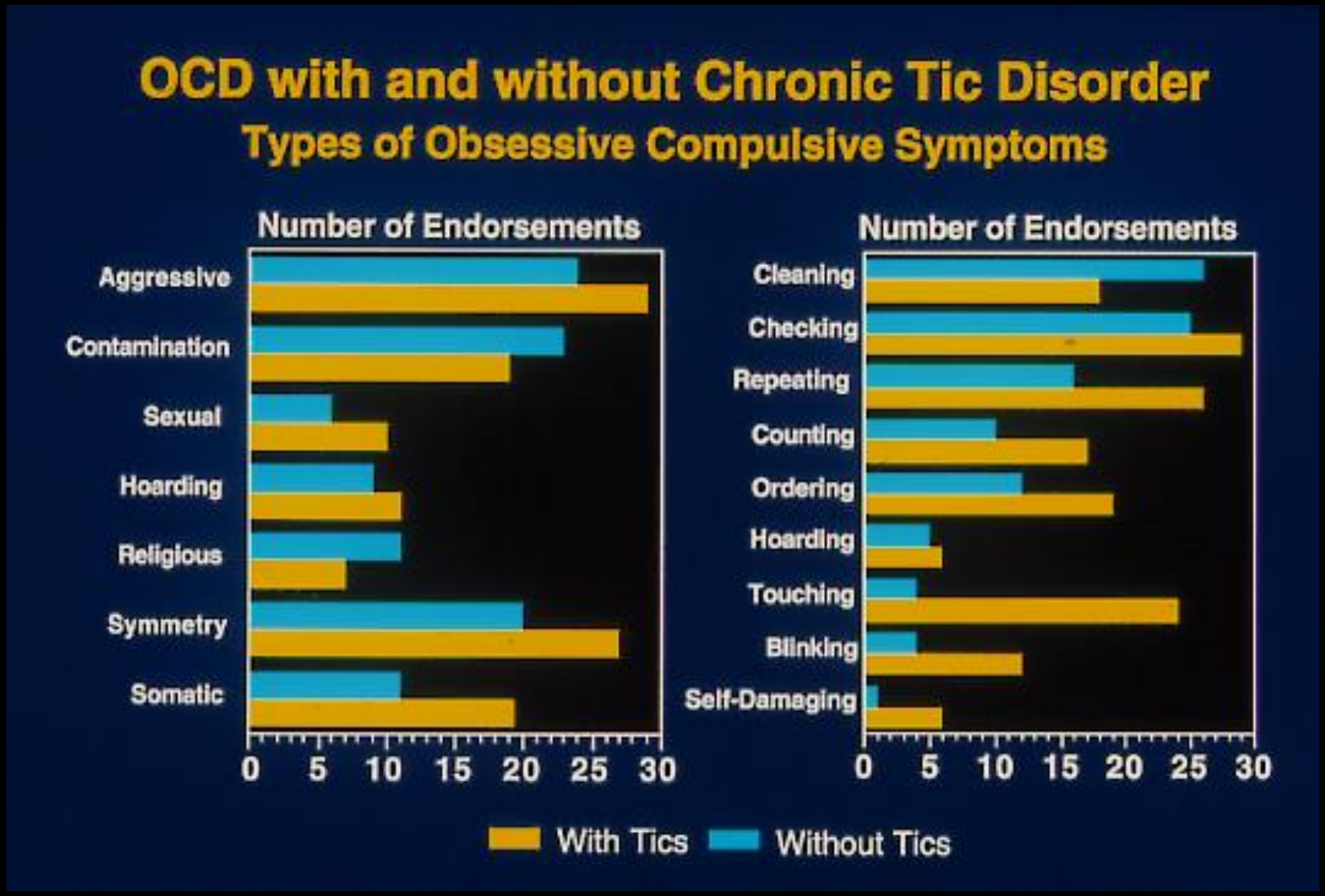

Holzer, Goodman, McDougle, 1994; Cath et al., 2001.

Symptom Continuum

OBSESSIONS

Fears
Anxiety
Harm Avoidance

Intrusive Ideas

Tension
reduction
"just right"
Risk-taking

Sensory Triggers
Unwanted Impulses
Tics

COMPULSIONS

Identifying OCD

- Patients reluctant to disclose their unwanted thoughts and odd behaviors
- Think of OCD in patients presenting with depression or anxiety
- OCD Screening Question
  - Sometimes people will be bothered by unwanted or repetitive thoughts or sudden, strong urges to check, wash, or count things. Does anything like that ever happen to you?

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OCD: Prevalence & Course

- Lifetime prevalence = 2 - 3%
- Childhood Onset > 50%
- Chronic, sometimes disabling
- Men and women equally affected.

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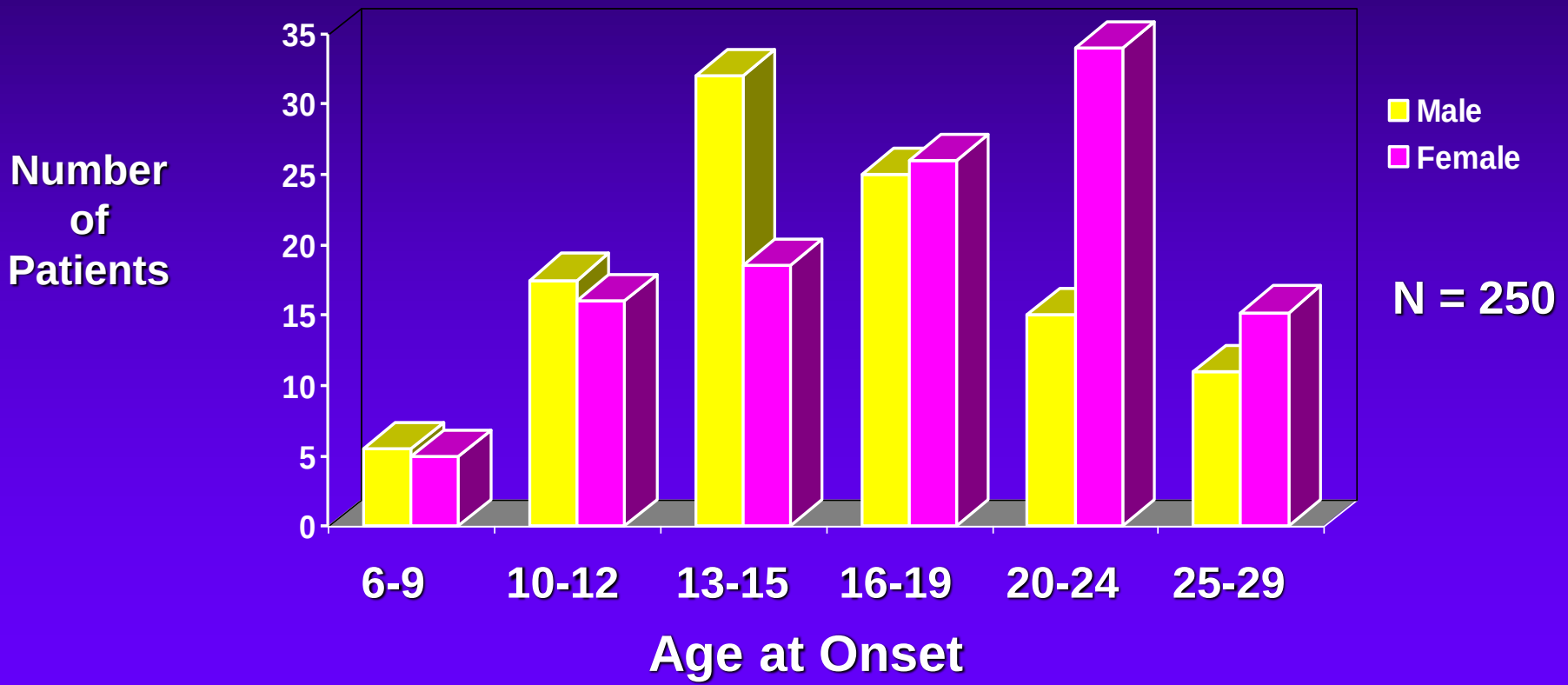
Brown Obsessive Compulsive Study: Age at Onset of OCD



Rasmussen et al. *J Clin Psychiatry* 51(suppl 8):20, 1990

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Summary: Recognition & Course

- OCD is common, typically chronic and can be disabling
- Some cases in childhood follow an episodic course
- Patients may camouflage their symptoms out of embarrassment
- Probe for OCD in patients presenting with depression or another anxiety disorder

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Comparison of Childhood- vs. Adult-Onset OCD

- About 50% of OCD has onset 18 years or younger
- Higher incidence of co-morbid tics
- Higher rate of first degree relatives with tic disorder or OCD (i.e., childhood onset more likely to be familial)
- “Insight” not required to make diagnosis in children

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Heterogeneity of OCD

- **Putative Subtypes**
  - Symptom Typology (e.g., hoarding)
  - Comorbidity (e.g., Tourette's Syndrome)
  - Childhood Onset/Familial
  - PANDAS*
  - Traumatic (Acquired) – suspect in onset after age 60 years (e.g., basal ganglia stroke)

*Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep

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Clinical Dimensions That May Represent Different Subtypes of OCD

- Fear of Harm
- Aggressive or Other Unacceptable Urges
- Incompleteness/”Just So”/Exactness
- Disgust
- Hoarding/Collecting
- Tic-like Phenomena

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Summary: Subtypes of OCD

- Childhood onset OCD is more likely to be associated with tics and to be familial
- Hoarding and Pathological Slowness clinical subtypes may be more resistant to treatment
- OCD patients with tics are more likely to present with OC symptoms involving symmetry, exactness, touching and evening up and other "tic-like" behaviors

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Pathogenesis of OCD

- Psychoanalytic theories
- Learning theory models
- Serotonin hypothesis
- Glutamatergic hypothesis
- Basal Ganglia – Orbitofrontal Cortex circuit
- Infection-triggered autoimmune process

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Approaches to Investigating 5HT Function in OCD

- **Inferences from treatment response data**
  - Pharmacological dissection
  - Augmentation trials
- **Challenge studies using specific 5HT probes (e.g., tryptophan depletion)**
- **Biomarkers in periphery, CNS or brain (post-mortem)**
- **Functional imaging (e.g., PET)**
- **Animal models**
- **Genetic studies**

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Summary: Serotonin Hypothesis

- The serotonin hypothesis is based on the preferential efficacy of potent blockers of serotonin reuptake in OCD
- However, direct support for a role of serotonin in the pathophysiology (e.g., biomarkers in pharmacological challenge studies) of OCD is lacking
- Functional imaging studies (both fMRI and PET) show fairly consistent evidence for increased brain activity in orbit-frontal cortex and caudate nucleus of patients with OCD
- Furthermore, these abnormalities normalize during successful treatment of OC symptoms whether with SRIs or CBT

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Evidence for Glutamatergic Involvement in OCD

- Glutamine is excitatory neurotransmitter in cortico-striato-thalamo-cortical circuit
- Increased caudate glutamate by MRS (Rosenberg et al, JAACAP 2000)
- Elevated CSF glutamate (Chakrabarty et al, Neuropsychopharm 2005)
- Riluzole augmentation (Coric et al, Biol Psych 2005)

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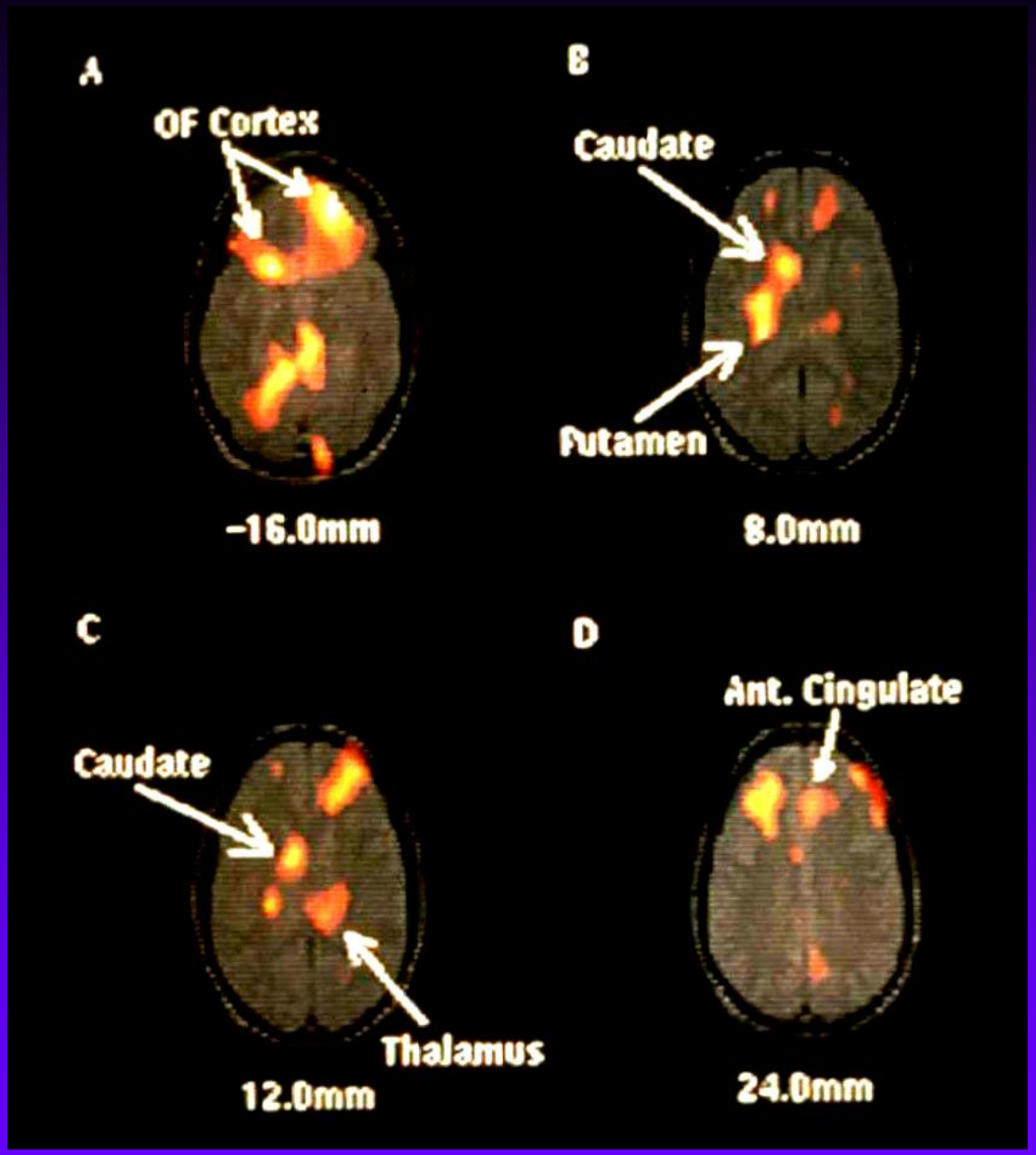

Rauch et al 1994

Evidence for Basal Ganglia Involvement in OCD

- Functional Neuroimaging
- Accidents of Nature
- Relationship to Tourette's Syndrome
- Results of Neurosurgery
- Neuroethology Perspective

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Brain Regions Implicated in OCD

- **Frontal Lobes (esp. orbito-frontal cortex)**
- **Basal ganglia (esp. caudate & globus pallidus)**

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PET and fMRI Studies of OCD and Other Anxiety States: Symptom Provocation Paradigms

			Regions Activated		
Study	Dx	Modality	Caudate	A/LOFC	Paralimbic
Rauch 1994	OCD	PET	Yes	Yes	Yes
McGuire 1994	OCD	PET	Yes	Yes	Yes
Breiter 1996	OCD	fMRI	Yes	Yes	Yes
Rauch 1995	Simple Phobia	PET	No	No	Yes
Rauch 1996	PTSD	PET	No	No	Yes
Benkelfat 1995	Normal	PET	No	No	Yes

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PANDAS

- **Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus**

- **Dramatic childhood onset of OCD/tics**
- **Other neurological signs (eg, “choreiform” movements)**
- **Evidence of strep infection associated with onset or exacerbation of symptoms**
- **Episodic or Sawtooth course**

Relationship Between OCD and Sydenham's Chorea

- Swedo et al proposed Sydenham chorea (SC) as a medical model for childhood-onset OCD
- SC is a late manifestation of rheumatic fever (RF)
- RF is a complication of untreated group A β-hemolytic strepococcal (GAS) infection
- GAS infection triggers antineuronal antibodies that cross-react with an epitope on basal ganglia neurons

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Possible PANDAS Treatments

- Plasmapheresis
- IV immunoglobulin
- Prednisone
- Penicillin Prophylaxis

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Clinical Implications of PANDAS

- Consider Sydenham's variant of OCD in child with acute onset adventitous movements, hypotonia, and behavioral changes
- Obtain history and serology for recent strep pharyngitis.
- Look for cardiac and other major manifestations of RF
- Treatments under study include antimicrobials or immunomodulatory interventions

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Treatment of OCD

- Previously considered treatment resistant
- Insight-oriented therapy rarely helps core symptoms
- Effective treatments:
  - Behavior therapy
    (ie, exposure/response prevention)
  - Potent serotonin reuptake inhibitors

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Behavior Therapy for OCD

- Doesn’t concern itself with origins of illness
- Attempts to change thinking and behavior using practical techniques
- Technique used in OCD is called Exposure and Response (Ritual) Prevention (ERP)

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Behavior Therapy for OCD
Reasons for Treatment Failure:

- Inadequate Trial (e.g., noncompliance, < 20hrs exposure)
- Severe depression
- Conviction that fear is realistic
- Mainly obsessions/few rituals

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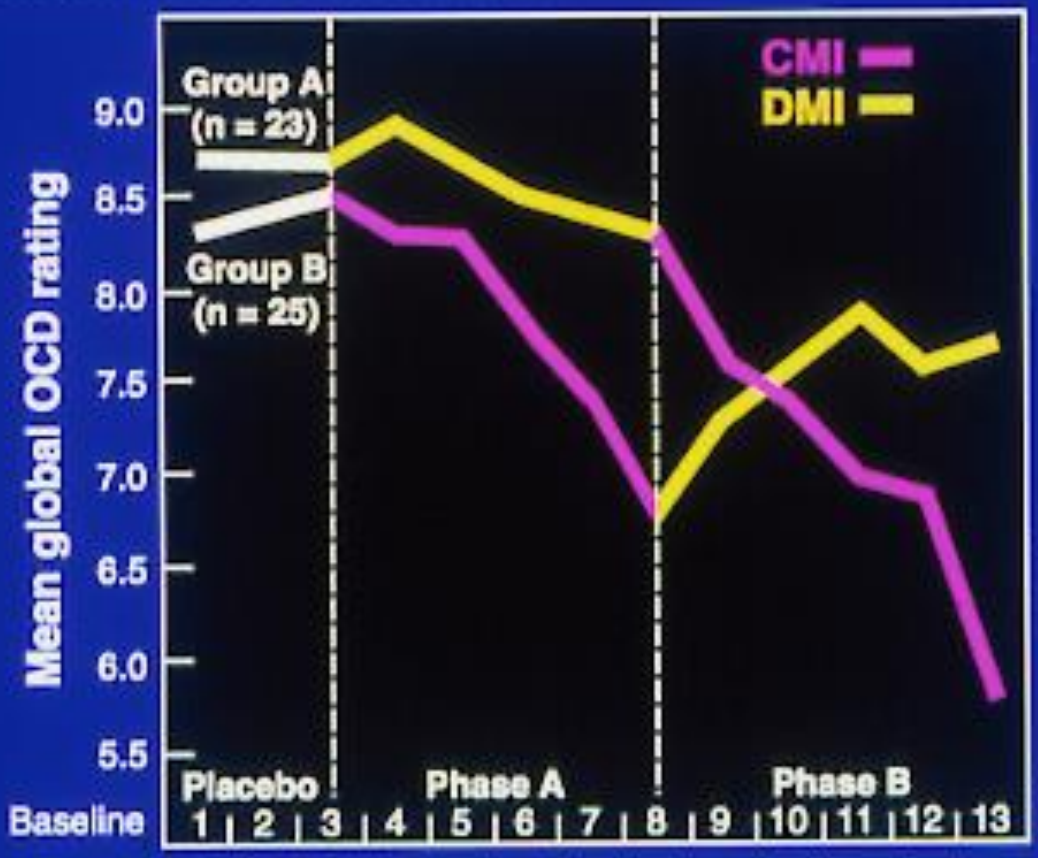
Efficacy of SRIs in OCD

- **Anti-OC efficacy established with:**
  - **clomipramine**
  - **fluvoxamine**
  - **fluoxetine**
  - **sertraline**
  - **paroxetine**
  - **citalopram/escitalopram** (no FDA indication)
- **SRIs preferentially effective compared to other antidepressants (e.g., desipramine)**

Results of a Double-Blind, Crossover Trial of Clomipramine (CMI) vs Desipramine (DMI)

Children and Adolescents



Source: Adapted from Leonard HL, et al. *Arch Gen Psychiatry.* 1989.

Study phase and study week

Efficacy of SRIs in OCD

- Response is usually graded and incomplete
  - 40 - 50% non-responders
  - Among “responders”, improvement is rarely complete

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SRIs in OCD

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

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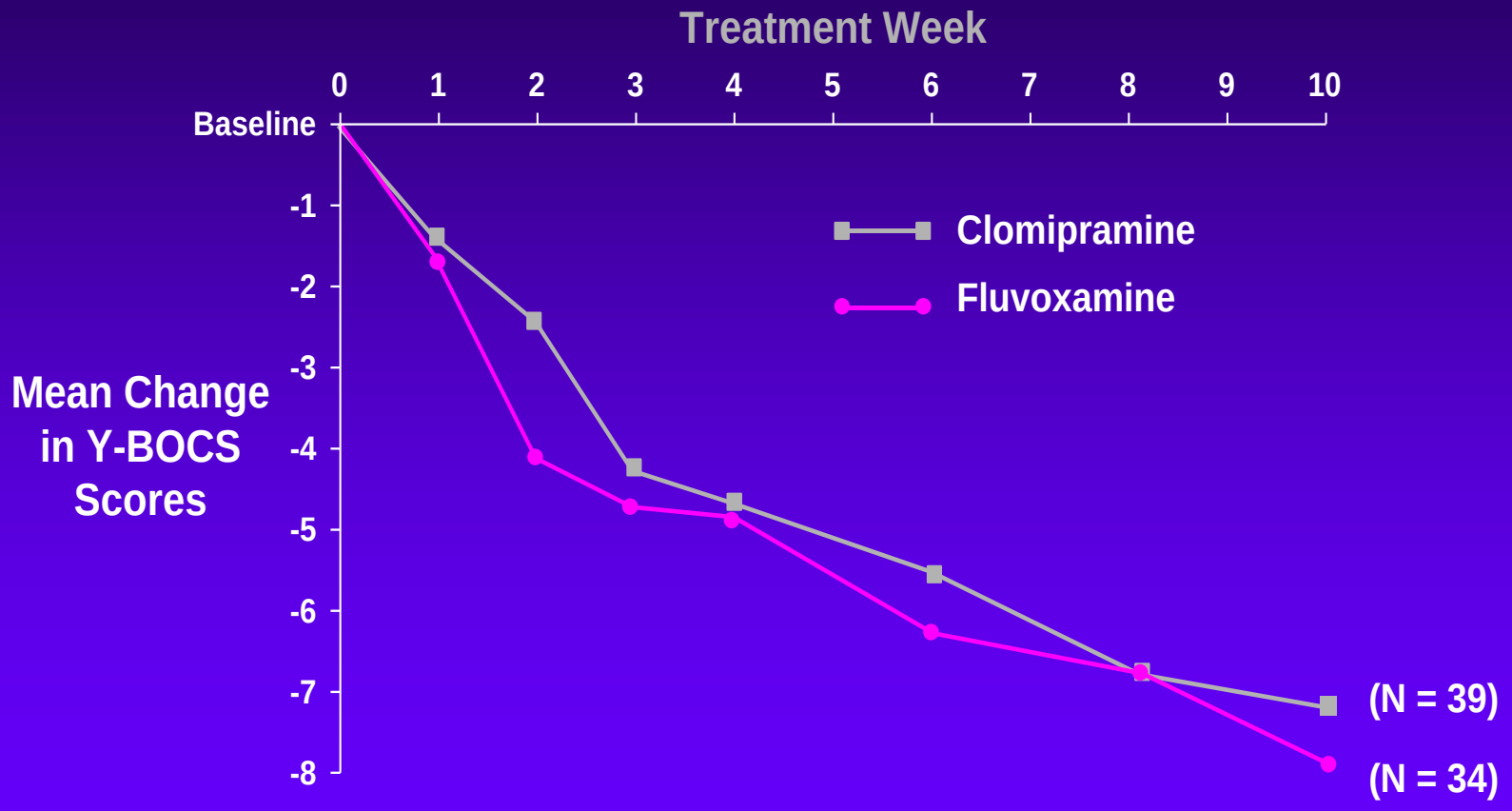
Fluvoxamine vs. Clomipramine (U.S. Trial)



Koran et al, *J Clin Psychopharmacol* 16:121, 1996

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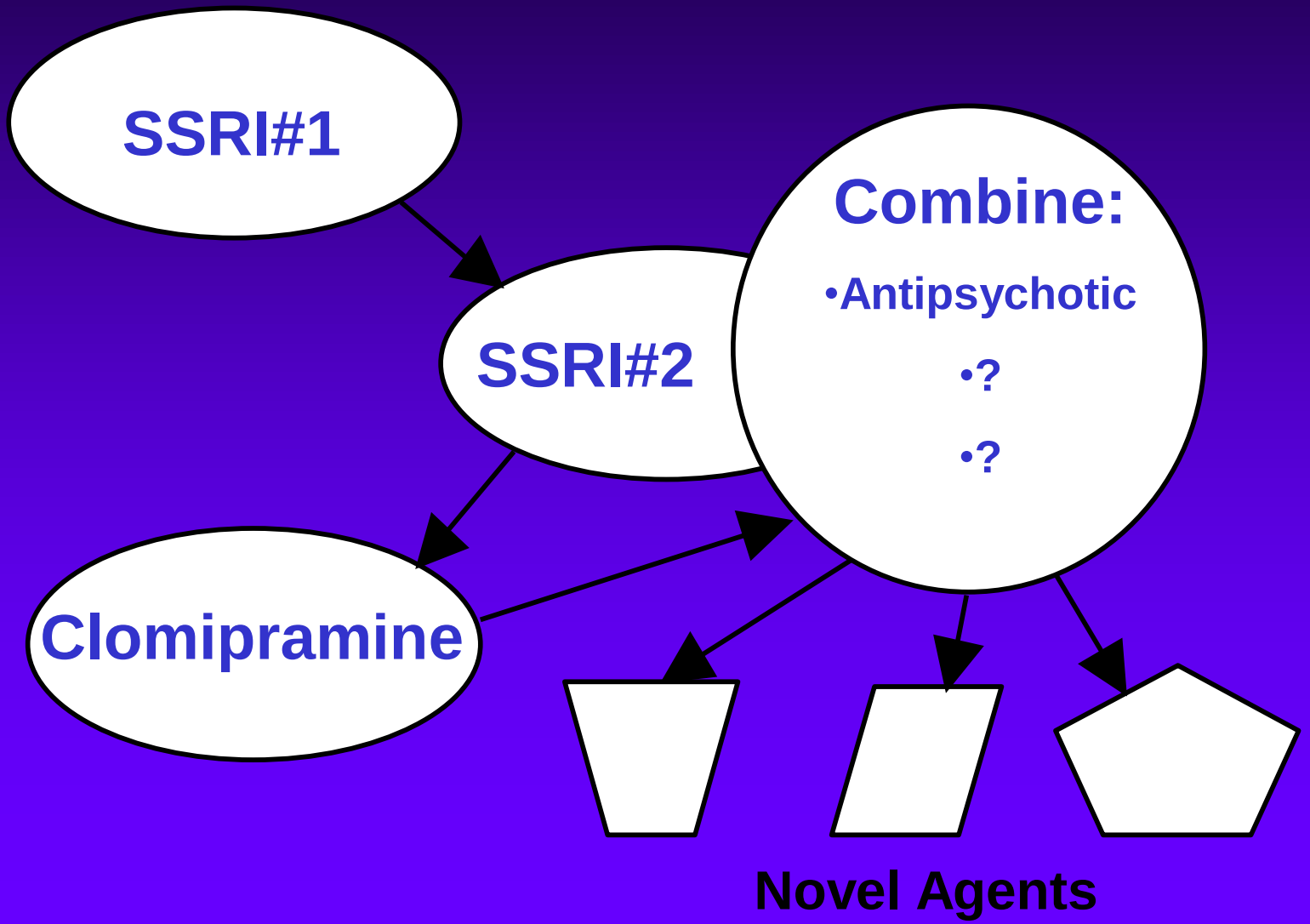
Initial Sequence of Trials



Treatment-Resistant OCD

- **Evaluate adequacy of trials**
  - Duration
  - Dose
  - Adherence
- **Differentiate intolerance from lack of efficacy**
- **Different levels of treatment resistance**
- **Apply most stringent criteria before employing experimental or invasive measures**

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Defining Endpoints

- **Response**
  - Change from baseline in acute trial
- **Remission**
  - Magnitude of symptom severity is low
  - No universally accepted definition in OCD

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Y-BOCS Scores and Clinical Change

- Responder defined by 25% or greater change in Y-BOCS from baseline.
- Some studies have used more stringent criterion of 35%.
- Change of 25% and endpoint Y-BOCS ≤ 10, is in range of being remitted.

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Defining Remission in OCD

- Total Y-BOCS ≤ 10
- AND item 1 (time obsessions) not > 1
- AND item 6 (time compulsions) not > 1
- Subthreshold for DSM-IV diagnosis based on time < 1 hour per day.

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Y-BOCS

Overview

- **Intended as a specific measure of OCD symptom severity in diagnosed patients.**
- **Score independent of type or number of obsessions or compulsions.**
- **Divided into two parts:**
  - Symptom Checklist
  - 10 Severity Questions
- **Emphasizes process over content**

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Y-BOCS Scores and Clinical Severity

Score	*Global*
0-7	Subclinical
8-15	Mild
16-23	Moderate
24-31	Severe
32-40	Extreme

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Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

- Language simplified (e.g., "habits" instead of "compulsions")
- Symptom checklist modified (e.g., checking backpack for school books)
- Consistent use of informants
- Reliability and validity confirmed by Scahill et al (JAACAP, 36: 844, 1997)

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Summary: Mainstays of Treatment

- The two well-established evidence-based treatments for OCD are serotonin reuptake inhibitors and a form of CBT
- For the most part, the literature shows a higher rate of response with CBT
- However, a number of patients do not adhere to CBT and assess to qualified therapists is limited

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Summary: Treatment of OCD vs. Depression

- In general, antidepressant doses necessary for optimal control of OCD are higher than those used in depression
- SSRIs are generally less effective in OCD than they are in depression or panic disorder
- Even “responders” to SSRI treatment usually have residual OC symptoms
- However, SSRIs are preferentially effective in OCD: meaning that other classes of antidepressants (e.g., the NE uptake inhibitor desipramine) are effective in depression yet ineffective in OCD
- Another difference between treatment of OCD and depression is that ECT, the gold standard for depression, is ineffective in OCD

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Summary: SSRIs and Clomipramine

- Initiate treatment with an SSRI for 10 -12 weeks at an adequate dose
- 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
- Nevertheless, no OCD patient should be considered medication resistant without a trial of clomipramine (CMI)

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Combination Treatments
Strategies

- Combining SRIs
- SRI plus other agents
  - serotonergic drugs
  - noradrenergic drugs
  - neuroleptics
  - others
- SRI plus behavior therapy

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Summary: Combining CBT and SRIs

- Conventional wisdom suggests that a combination of CBT and SRI is the best treatment for OCD
- Surprisingly, some studies do not show an advantage of combined therapy over monotherapy alone
- CBT appears to have the largest effect size but its usefulness is limited by non-adherence and availability of trained therapists.

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Combining SRIs

- SSRI - SSRI combination
  - rationale unclear
- Clomipramine (CMI) plus SSRI:
  - to minimize or capitalize on side effect of CMI
  - to enhance efficacy (assumes “something special” about CMI)

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Combination Treatments
Adding serotonergic drugs

- L-tryptophan: safety issues; limited trials
- Fenfluramine: safety issues; no db trials
- Buspirone: 3 negative db, pc trials
- Lithium:
  - negative db, pc trials
  - may help comorbid depression
- Pindolol: does not appear effective in OCD unless combined with L-tryptophan

db, double-blind; pc, placebo-controlled

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Neuroleptics in OCD

- Increasing number of positive reports
- Search for clinical predictors of response
  - "Schizo"-obsessives
  - "Delusional" OCD
  - "Tic-spectrum" OCD

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Adding Neuroleptics to SRIs in OCD

- Earlier studies suggested that conventional neuroleptics preferentially benefit patients with comorbid tic disorders
- More recent studies with atypical antipsychotics suggest broader spectrum of action
- Atypical neuroleptics have been associated with induction of OC symptoms in schizophrenic patients.

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Tourette's Syndrome

- **DSM-IV criteria:**
  - **Both multiple motor and one or more vocal tics**
  - **Occur many times a day nearly everyday for more than 1 year (no tic-free period of >3 consecutive months)**
  - **Marked distress or significant impairment**
  - **Onset before age 18 years**

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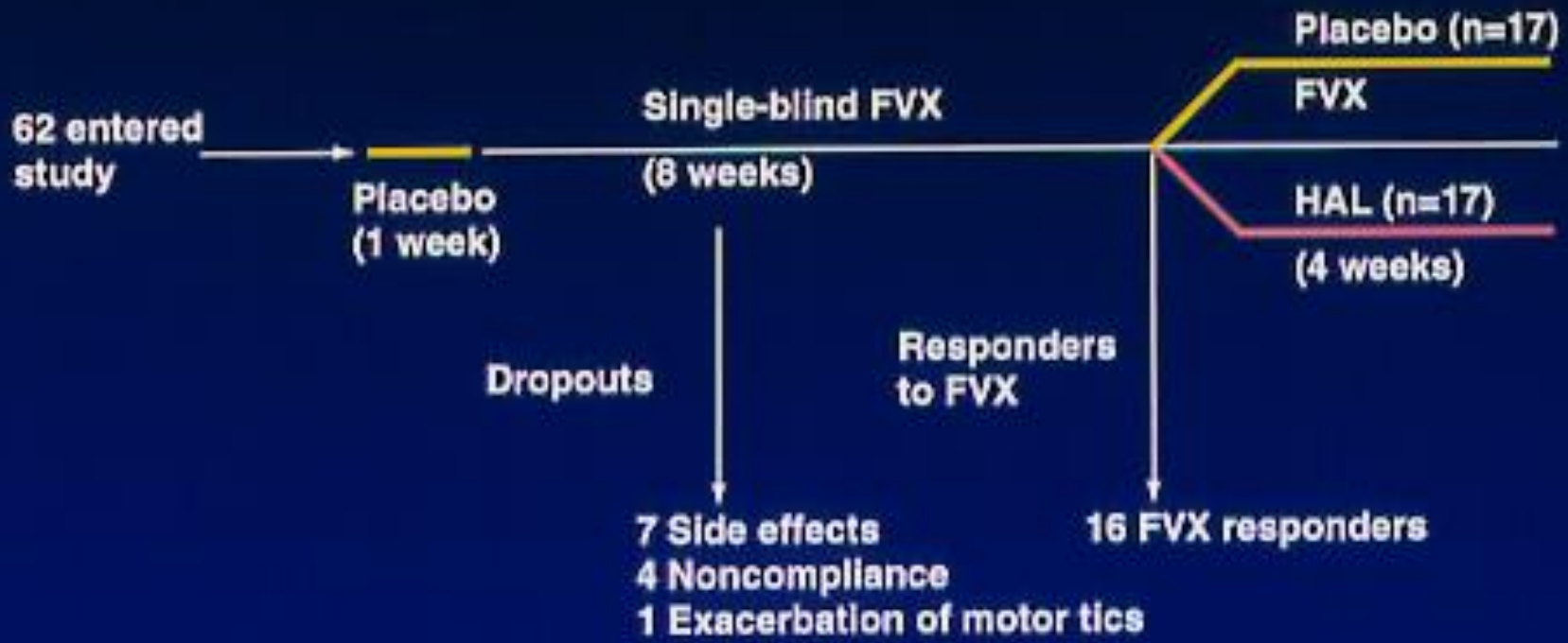
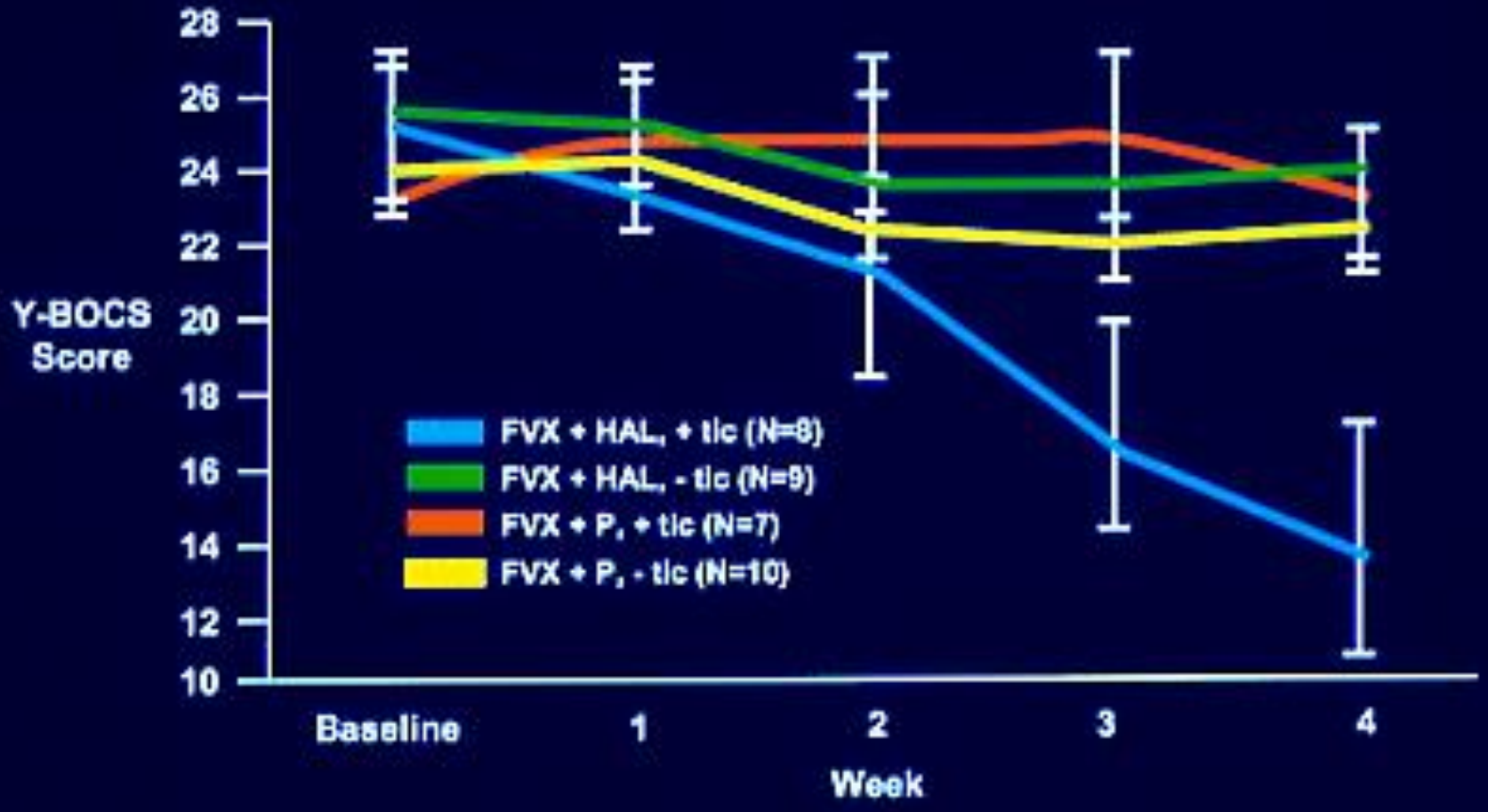
Overall Design and Patient Flow for Fluvoxamine (FVX) - Haloperidol (HAL) Study (N=34)



McDougle CJ, et al. *Arch Gen Psychiatry.* 1994;51:302-308.

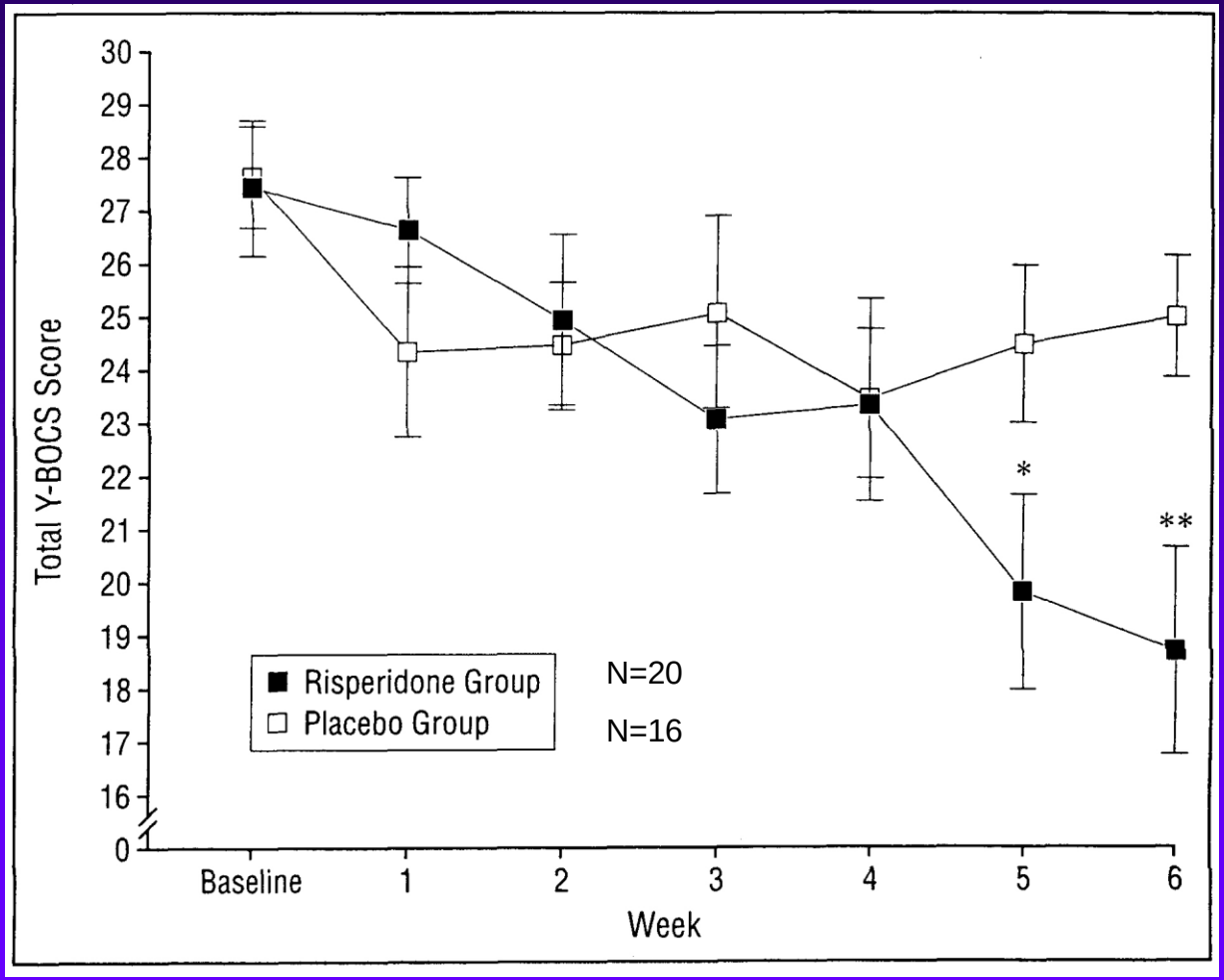
Response Of OC Symptoms (±Tic): FVX + HAL VS FVX + P



SRI + Risperidone in OCD

McDougle et al, 2000

36 SRI non-responders entered 6-week double-blind, placebo-controlled trial



Novel Drug Treatments
Worthy of Further Study

- Tramadol
- IV clomipramine or citalopram
- Inositol
- Rizulole
- Plasmapheresis (for PANDAS)
- Antimicrobial treatments (for PANDAS)

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Summary: Augmentation

- Consider augmentation in partial responders to SSRIs
- Adjunctive antipsychotics (especially risperidone) has the most support
- Although the evidence from controlled trials for the efficacy of other augmentation approaches (e.g., buspirone) is negative or limited, individual patients may benefit – there is always something else worth trying

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Non-Pharmacological Biological Treatments

- Electroconvulsive therapy (ECT)
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Vagus Nerve Stimulation (VNS)
- Neurosurgery
  - Ablative
  - Stimulatory (DBS)

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ECT

- No large scale controlled trials in OCD
- Sporadic positive case reports
- May be considered in comorbid severe depression or for suicidality
- Unlikely to benefit OCD
- Contrasts with efficacy in depression where it is gold standard

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rTMS
(repetitive transcranial magnetic stimulation)

- Pulsatile high-intensity electromagnetic field induces focal electrical currents in the underlying cerebral cortex
- Cortical activity can be stimulated or disrupted
- Greenburg et al studied rTMS in 12 OCD pts
- Compulsive urges decreased for 8 hrs after right prefrontal rTMS
- Small risk of seizures

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Neurosurgery in OCD

- Evidence that some patients are helped
- Difficult to compare procedures (e.g., cingulotomy vs. anterior capsulotomy)
- Modern stereotactic techniques produce less morbidity
- Last resort in patients with debilitating and refractory illness

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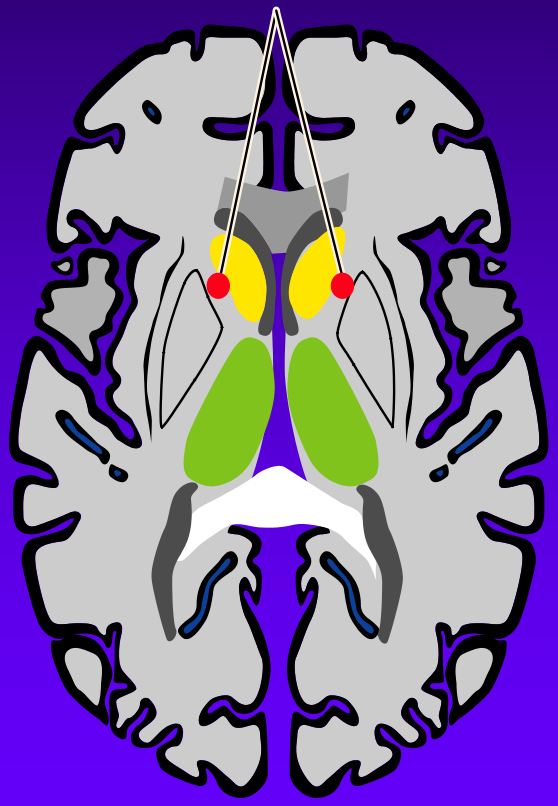
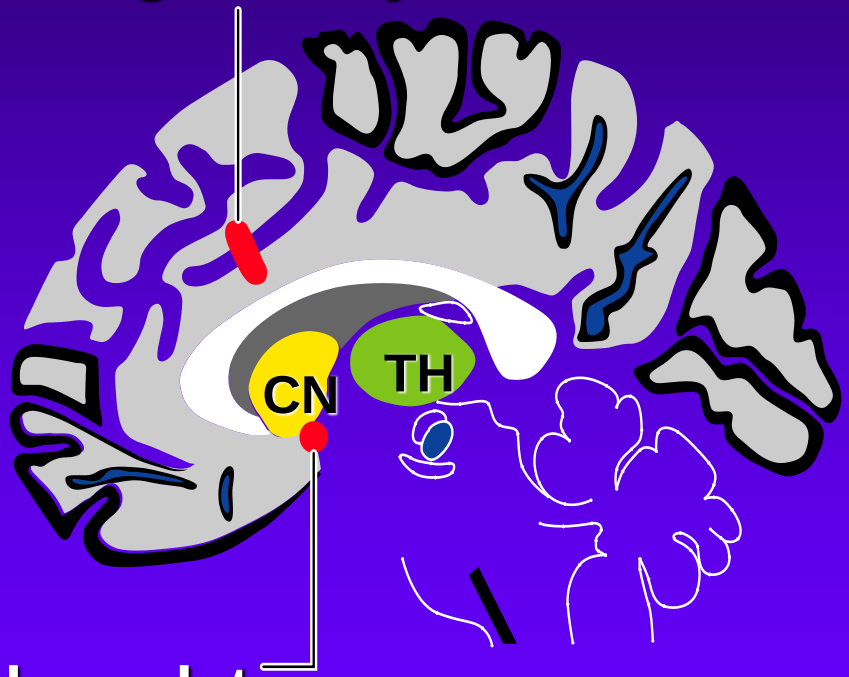
Neurosurgery in OCD

Anterior Capsulotomy



Anterior Cingulotomy



Subcaudate Tractotomy

TH = Thalamus

CN = Caudate Nucleus

Neurosurgery in OCD

- **Surgical technique**
  - Introduce instrument through cranium that destroys tissue (e.g., thermolytic)
  - Radiotherapy destroys target only (e.g., Gamma Knife or LINAC)
- **Potential for serious side effects**
- **Irreversible**

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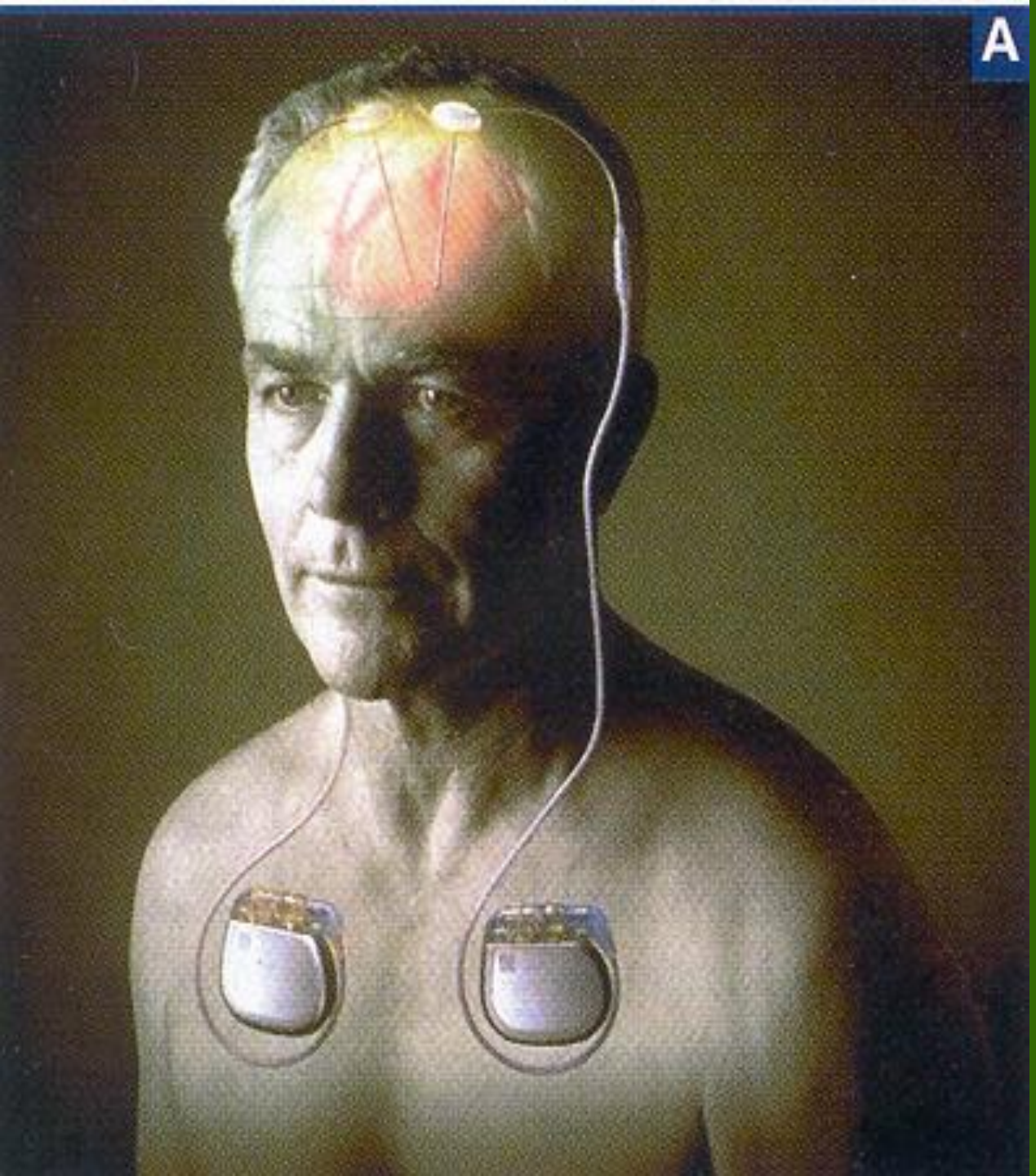

Deep Brain Stimulation

(DBS)

Comparison of Neurosurgical Approaches

	Ablative	DBS
Destructive	Yes	No
Reversible	No	Yes*
Adjustable	No	Yes
Invasive	Yes	Yes
Serious A/Es	Yes	Yes

**with caveats*

Clinical Uses of DBS

- Approved for essential tremor
- Expanded use in Parkinson's Disease (PD) and other movement disorders
- Replacing pallidotomy for PD
- Risk of hemmorhage is about 2-3% during implantation
- Risk of infection is about 4%

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DBS in OCD

Nuttin et al, Lancet 354, 1999

- **Bilateral stimulation of anterior limbs of internal capsule in severe, chronic OCD**
- **3 of 4 cases showed improvement**
- **Follow up in 3 cases showed:**
  - ON/OFF blinded testing confirmed superiority of stimulation condition
  - Lasting improvement for 6 to 12 months

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Rationale for Neurosurgery in OCD

- **Gravity of the illness**
  - Chronicity
  - Impairment
  - Treatment resistance
  - Paucity of effective treatments
- **Published case series suggesting efficacy and absence of cognitive/personality changes after ablative surgery in intractable OCD**
- **Capacity for informed consent: retention of insight and reasoning; absence of psychosis**

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Rationale for Neurosurgery in OCD (*cont*.)

- **Conceptualize OCD as reverberating circuit involving basal ganglia-thalamo-cortical loops that manifest as primitive fears and ritualistic behaviors outside of conscious control: interrupting that circuit might reduce symptoms.**

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DBS in OCD: Summary

- Last resort for stringently selected patients
- As alternative to ablative surgery, not to expand role of surgery
- Need for independent, multidisciplinary team to confirm appropriateness of candidate and monitoring of safety and outcome
- Like ablative surgery, use of DBS already spreading
- Further systematic evaluation required

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After DBS

- To date (early 2008) world-wide experience (N~25) shows a 60% response rate with bilateral stimulation of anterior limb of internal capsule at long-term follow up*
- Some of these responders were able to reduce their medications
- And they seemed to be using the tools they learned in CBT more effectively.
- For non-responders to DBS, the device can be deactivated or explanted and novel medication trials can be considered.

*Greenberg BD et al., Molecular Psychiatry 2008

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Question #1

Which may be a manifestation of OCD?

a. distorted belief of being fat and counting calorie intake not to exceed 1000 per day

b. can't get ex-girlfriend out of his mind and feels compelled to know her whereabouts

c. recognizes irrationality of need to check envelopes to ensure 5-year old daughter is not inside

d. compulsively eats everything in front of him and feels guilty afterwards

Question #2

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c. based primarily on preferential response of SRIs

d. confirmed by post-mortem data

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b. amygdala and cerebellum

c. hippocampus and locus ceruleus

d. unknown

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b. confined to augmentation of SRIs in refractory cases

c. an option as either monotherapy or adjunctive treatment

d. only effective for suppressing tics

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Answers to Pre & Post Lecture Exams

1. C
2. C
3. A
4. C
5. B