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Treatment of Tic Disorders and Other Repetitive Behaviors

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Disclosure: John T. Walkup, MD January 2019

	Consultant	Advisory Board	Speaker's Bureau	Royalties
Tourette Syndrome Assoc.		X (current)	X (current)	
Oxford Press Guilford Press Wolters Kluwer				X (current)

Discussion of Off Label Use of Medication

- Discussion of all medications should be considered "off label" unless specifically noted otherwise

- All clinical material has been adapted to protect confidentiality

Tic Disorders

- Tourette's Disorder
- Persistent (chronic) motor or vocal tic disorder
  - Motor specifier
  - Vocal specifier
- Provisional tic disorder
- Etc.

Historical Context

- Childhood chorea (Sydenham's chorea)
- Charcot and Freud, and Tourette
- Psychology
- Neurology
- Neuropsychiatric
  - Neurological
  - Genetics and environment
  - Behavioral and functional

Sorting Out
Clinically Complex Cases

What do complex cases look like?

TS Plus = TS + ADHD + OCD +

Condition X

Complex Clinical Presentations

- **Tics Plus** and **separation anxiety disorder**
- **Tics Plus** and **other anxiety disorders**
- **Tics Plus** and ASDs
- **Tics Plus** and disruptive behavioral disorders
- **Tics Plus** and major depression
- **Tics Plus** and bipolar disorder
- **Tics Plus** and substance abuse
- **Tics Plus** and personality disorders

Tic Disorder Treatment

- Antipsychotic efficacy studies
  - Haloperidol, pimozide, ziprasidone, risperidone, aripiprazole, ecopipam
- Alpha agonists – clonidine and guanfacine
- Other somatic treatments
  - ECT
  - Repetitive transcranial magnetic stimulation
  - Deep brain stimulation
- Behavioral treatment
  - Numerous very small studies focusing on habit reversal training
  - Large scale trials in children and adults

Tic Suppression Interventions Small, Medium and Large

- Small – Commonly used
  - Clonidine
  - Guanfacine
- Medium – Not commonly used
  - TCAs
  - Benzodiazepines

Tic Suppression - Large

- Old antipsychotics
  - Fluphenazine (Prolixin®)
  - Pimozide (Orap®)
  - Haloperidol (Haldol®)
- New Antipsychotics
  - Risperidone (Risperdal®)
  - Aripiprazole (Abilify®)
  - Ecopipam
  - Ziprasidone (Geodon®)
  - Tetrabenazine/Deutetrabenazine
  - Quetiapine (Seroquel®)
  - Olanzapine (Zyprexa®)
  - Clozapine (Clozaril®)
  - others

Antipsychotics - European Style

- Sulpiride
- Tiapride

Tic Suppression - Larger Botulinum Toxin

- Single muscle
- Long acting
- Reversible

Tic Suppression - Larger

- Electroconvulsive treatment
  - Self-injurious behavior
- Repetitive Transcranial Magnetic Stimulation (rTMS)

Tic Suppression - Largest Behavioral Neurosurgery

- Ablative surgery
  - Complex cases
  - Results for tics are mixed
- Deep brain simulation
  - News worthy cases
  - One small open trial
  - Tourette Registry

Tourette DBS Registry

- N= 185; 72% males
- Age = 29 years; range 13-58
- 31 institutions; 10 countries
- Implantation sites
  - centromedial thalamic region – 93/163 (57.1%)
  - anterior globus pallidus internus - 41/163 (25.2%)
  - posterior globus pallidus internus - 25/163 (15.3%)
  - anterior limb of the internal capsule - 4/163 (2.5%)
- Adverse Events
  - 35% had something - 2 bleeds; 4 infections
  - Stimulation events - dysarthria 10 (6.3%) and paresthesia 13 C8.2%)

Martinez-Ramirez D et al., Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome: The International Tourette Syndrome Deep Brain Stimulation Public Database and Registry. JAMA Neurol. 2018 Mar 1;75(3):353-359.

Tic Suppression - Complementary and Alternative Interventions

- Nicotine - agonist
- Mecamylamine – nicotine antagonist
- Opiates/cannabinoids
  - Naloxone
  - Marijuana reports
  - Cannabinols
- Hormones
  - Mild efficacy of flutaminde, antiandrogen compound
- Omega-3
- Health supplements
- Others

Slide courtesy of K Kompoletti

Tic Supression – Wow!!!!

- Marijuana

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PANDAS/PANS

Pediatric
Autoimmune
Neuropsychiatric
Disorders
Associated with
Strep

PANDAS or PANS

- Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep

- Pediatric Acute Neuropsychiatric Symptoms
  - Autoimmune mediated
  - Can be devastating
    - Loss of sensorium
    - Seizures

PANDAS

- Acute onset of tics or anxiety symptoms and abrupt changes in tic or anxiety severity
- Evidence of strep infection
- Childhood onset
- Other symptoms
  - Neurological findings
  - Handwriting problems

PANDAS

- Not validated disorder
- Epi-like studies suggest rare if at all
- Treatment outpaced our knowledge of the disorder
- Most treatments should be done as a part of a research trial

PANDAS, PANS Controversy

- This study provides no evidence for a temporal association between GABHS infections and tic/OC symptom exacerbations in children who meet the published PANDAS diagnostic criteria. (Leckman et al., 2010)
- Overall, the available **evidence does not convincingly support the concept that PANDAS are a well-defined, isolated clinical entity** subdued by definite pathophysiological mechanisms; larger, prospective studies are necessary to reshape the nosography and disease mechanisms of post-streptococcal acute neuropsychiatric disorders other than SC. Research is also under way to shed further light on a possible relationship between streptococcal infections, other biological and psychosocial stressors, and the complex pathobiology of chronic tic disorders. (Marcerollo and Martino 2013)

PANDAS, PANS Controversy

- The diagnostic criteria for PANDAS can be used by clinicians to accurately identify patients with common clinical features and shared etiology of symptoms. Although difficulties in documenting an association between GAS infection and symptom onset/exacerbations may preclude a diagnosis of PANDAS in some children with acute-onset OCD, they do appear to meet criteria for pediatric acute-onset neuropsychiatric syndrome (PANS). (Swedo et al 2015)
- Cunningham MW et al studies

Thienemann M, Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part I-Psychiatric and Behavioral Interventions. J Child Adolesc Psychopharmacol. 2017 Sep;27(7):566-573. doi: 10.1089/cap.2016.0145. Epub 2017 Jul 19.

- **While underlying infectious and inflammatory processes in PANS and PANDAS patients are treated, psychiatric and behavioral symptoms need simultaneous treatment to decrease suffering and improve adherence to therapeutic intervention**. Psychological, behavioral, and psychopharmacologic interventions tailored to each child's presentation can provide symptom improvement and improve functioning during both the acute and chronic stages of illness. In general, typical evidence-based interventions are appropriate for the varied symptoms of PANS and PANDAS. Individual differences in expected response to psychotropic medication may require marked reduction of initial treatment dose. Antimicrobials and immunomodulatory therapies may be indicated, as discussed in Parts 2 and 3 of this guideline series.

PANS "Therapies"

- Complex evaluation (false positives)
- Antibiotics acutely and chronically
- Steroids
- Intravenous immunoglobulin ($10K)
- Plasmapheresis ($6K)
- Other immuno treatments

Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders.

- Methods
  - 12 month baseline year
  - 12 month randomized, double blind (no placebo) controlled trial
  - PCN vs. Azithromycin
- Outcomes
  - Strep Infections
  - Neuropsych exacerbations
- Conclusions
  - Penicillin and azithromycin prophylaxis were found to be effective (sic) in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup.

Snider LA, et al., Biological Psychiatry April 2005.

PANDAS

- Suspected cases
  - Throat culture
  - If positive – treat
    - Consider treating for extended period – 20 days vs. 10 (Murphy, personal communication)
  - A one time titer is meaningless
  - Probably no role in non-research settings for other immunologically-based treatments

Summary

- Many treatment options for people with Tourette syndrome
- Many biological treatment approaches
  - Tics
  - Co-occurring conditions

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Non Pharmacological Strategies for Tics: What Does it all Mean?

Tics and the Environment

- Tic worsening
  - Excitement and stress
  - Fatigue
  - Attending to tics
  - Free to tic
- Tic improvement
  - Calm focused activities
  - Deep relaxation
  - Inhibiting environments
- Adults' experience with behavioral strategies

Behavior Therapy for Children With Tourette Disorder

A Randomized Controlled Trial

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Context Tourette disorder is a chronic and typically impairing childhood-onset neurologic condition. Antipsychotic medications, the first-line treatments for moderate to severe tics, are often associated with adverse effects. Behavioral interventions, although promising, have not been evaluated in large-scale controlled trials.

Objective To determine the efficacy of a comprehensive behavioral intervention for reducing tic severity in children and adolescents.

Design, Setting, and Participants Randomized, observer-blind, controlled trial of 126 children recruited from December 2004 through May 2007 and aged 9 through 17 years, with impairing Tourette or chronic tic disorder as a primary diagnosis, randomly assigned to 8 sessions during 10 weeks of behavior therapy (n=61) or a control treatment consisting of supportive therapy and education (n=65). Responders received 3 monthly booster treatment sessions and were reassessed at 3 and 6 months following treatment.

Intervention Comprehensive behavioral intervention.

Main Outcome Measures Yale Global Tic Severity Scale (range 0-50, score >15 indicating clinically significant tics) and Clinical Global Impressions–Improvement Scale (range 1 [very much improved] to 8 [very much worse]).

Results Behavioral intervention led to a significantly greater decrease on the Yale Global Tic Severity Scale (24.7 [95% confidence interval {CI}, 23.1-26.3] to 17.1 [95% CI, 15.1-19.1]) from baseline to end point compared with the control treatment (24.6 [95% CI, 23.2-26.0] to 21.1 [95% CI, 19.2-23.0]) ($P<.001$; difference between groups, 4.1; 95% CI, 2.0-6.2) (effect size=0.68). Significantly more children receiving behavioral intervention compared with those in the control group were rated as being very much improved or much improved on the Clinical Global Impressions–Improvement scale (52.5% vs 18.5%, respectively; $P<.001$; number needed to treat=3). Attrition was low (12/126, or 9.5%); tic worsening was reported by 4% of children (5/126). Treatment gains were durable, with 87% of available responders to behavior therapy exhibiting continued benefit 6 months following treatment.

Conclusion A comprehensive behavioral intervention, compared with supportive therapy and education, resulted in greater improvement in symptom severity among children with Tourette and chronic tic disorder.

Trial Registration clinicaltrials.gov Identifier: NCT00218777

JAMA. 2010;303(19):1929-1937 www.jama.com

TOURETTE DISORDER IS A CHRONIC neurologic disorder characterized by motor and vocal tics. Prevalence estimates in school-aged children range from 1 to 10 per 1000, with a rate of 6 per 1000 replicated in several countries.[1,2] Tics are usually brief, rapid movements (eg, blinking, facial grimacing) or vocalizations (eg, throat clearing, grunting) but can include more complex movements and vocalizations. Tics begin in childhood; severity peaks in early adolescence and often declines in young adulthood.[3] Epidemiologic and clinical data indicate that Tourette disorder can be associated with considerable impairment[2] and social isolation[4] in school-aged children. Tics are commonly preceded by premonitory

ORIGINAL ARTICLE

Randomized Trial of Behavior Therapy for Adults With Tourette Syndrome

Sabine Wilhelm, PhD; Alan L. Peterson, PhD; John Piacentini, PhD; Douglas W. Woods, PhD; Thilo Deckersbach, PhD; Denis G. Sukhodolsky, PhD; Susanna Chang, PhD; Haibei Liu, MPH; James Dziura, PhD; John T. Walkup, MD; Lawrence Scahill, MSN, PhD

Context: Tics in Tourette syndrome begin in childhood, peak in early adolescence, and often decrease by early adulthood. However, some adult patients continue to have impairing tics. Medications for tics are often effective but can cause adverse effects. Behavior therapy may offer an alternative but has not been examined in a large-scale controlled trial in adults.

Objective: To test the efficacy of a comprehensive behavioral intervention for tics in adults with Tourette syndrome of at least moderate severity.

Design: A randomized controlled trial with posttreatment evaluations at 3 and 6 months for positive responders.

Setting: Three outpatient research clinics.

Patients: Patients (N = 122; 78 males; age range, 16-69 years) with Tourette syndrome or chronic tic disorder were recruited between December 27, 2005, and May 21, 2009.

Interventions: Patients received 8 sessions of comprehensive behavioral intervention for tics or 8 sessions of supportive treatment for 10 weeks. Patients with a positive response were given 3 monthly booster sessions.

Main Outcome Measures: Total tic score on the Yale Global Tic Severity Scale and the Clinical Global Impression–Improvement scale rated by a clinician masked to treatment assignment.

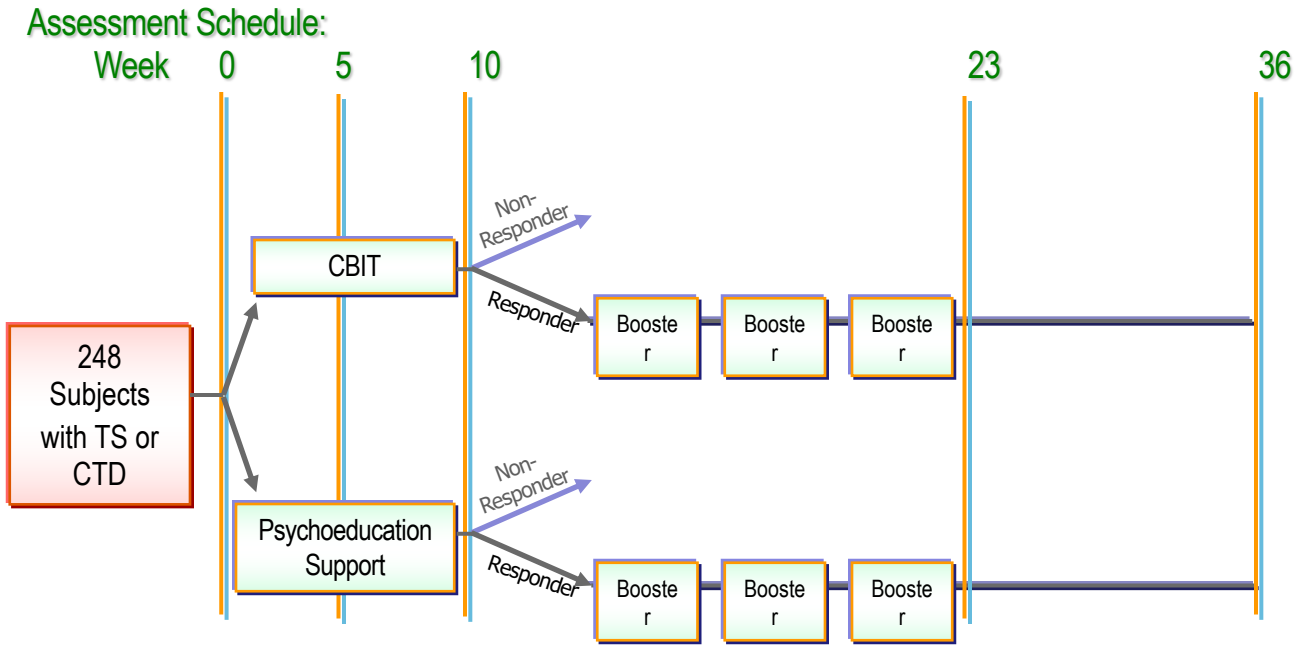
Results: Behavior therapy was associated with a significantly greater mean (SD) decrease on the Yale Global Tic Severity Scale (24.0 [6.47] to 17.8 [7.32]) from baseline to end point compared with the control treatment (21.8 [6.59] to 19.3 [7.40]) ($P < .001$; effect size = 0.57). Twenty-four of 63 patients (38.1%) were rated as much improved or very much improved on the Clinical Global Impression–Improvement scale compared with 4 of 63 (6.4%) in the control group ($P < .001$). Attrition was 13.9%, with no difference across groups. Patients receiving behavior therapy who were available for assessment at 6 months after treatment showed continued benefit.

Conclusion: Comprehensive behavior therapy is a safe and effective intervention for adults with Tourette syndrome.

Trial Registration: clinicaltrials.gov Identifier: NCT00231985

Arch Gen Psychiatry. 2012;69(8):795-803

CBITS Study Design

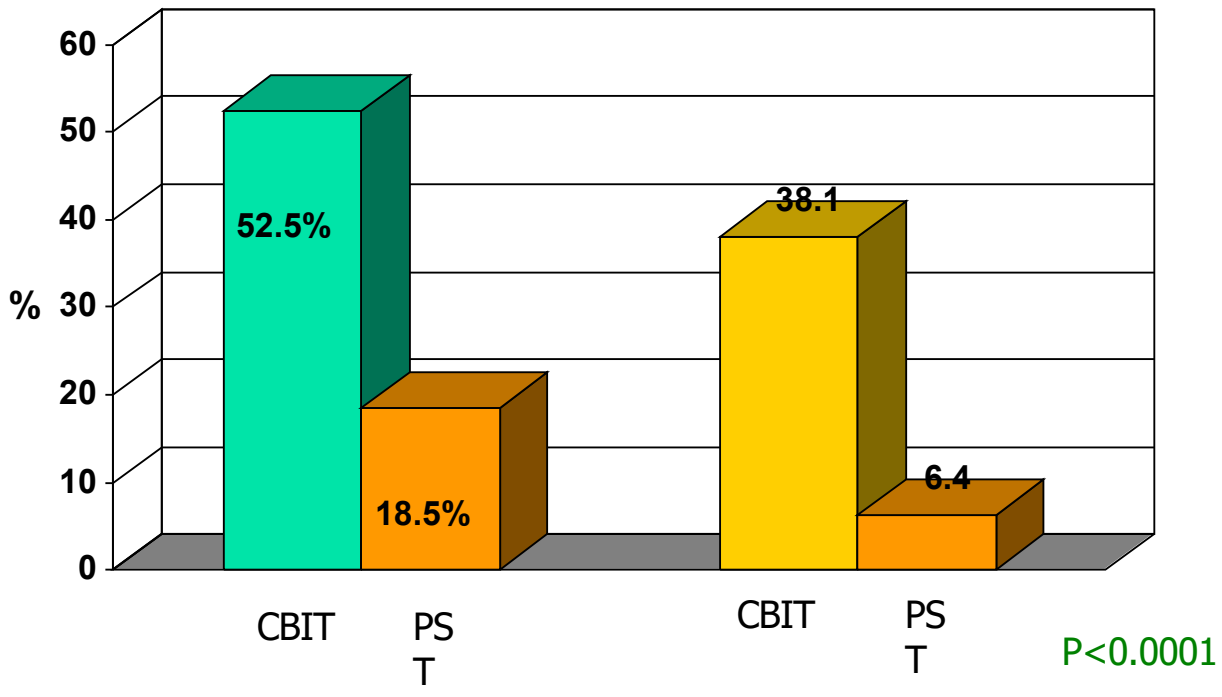


Pre -Treatment – Pt#001

Post -Treatment – Pt#001

Responder Status at Week 10

(CGI-Improvement = 1 or 2)



P<0.0001

Change In Advice

- **Old - intuitive**
- Ignore tics
- Can't be controlled
- Don't punish
- Behavioral treatments don't work
- Don't try to suppress
- Suppression worsens tics
- Suppression worsens premonitory urges
- New tics develop when you suppress
- He/she holds them all day then releases

- **New - counterintuitive**
- Become more aware
- Learn to manage
- Reward successful management
- Use behavioral strategies
- Tics don't get worse with behavioral treatment
- Premonitory urge will fade away
- New tics don't develop when you use behavioral strategies
- He is focused activities all day

New Treatment Paradigms

- Readiness for reducing tic severity
  - Comorbidity management
  - Family and child intervention for "CBIT Lifestyle"
- CBIT
- CBIT + Meds
- Meds + CBIT
- Meds + CBIT to CBIT only
- Training nurses in Neurology clinics
- Training OT for broad dissemination
- CBIT + Parent training for children under 9 yrs

Summary

- New effective treatments bring excitement and hope
  - Behavioral strategies
  - Neurosurgery
- If you think about it, it makes sense
- Lots more to learn to realize the full promise of new treatments for tic severity
- Tics and BFRBs have a lot in common,
  - Behavioral treatments should be first line
  - Co-occurring distress syndromes are very common and their treatment is key to optimal outcomes

OCD and Related Disorders

- OCD
- Body dysmorphic disorder
- Trichotillomania (hair pulling disorder)
- Hoarding disorder
- Excoriation (skin-picking) disorder
- Substance or medication induced
- Due to another medical condition
- Other OCRD
- Unspecified OCRD

Basic Approaches to Body Focused Repetitive Behavior

- Behavioral treatments are core
- Pharmacotherapy has limited benefit for repetitive behaviors, yet every med has been helpful for someone
- An Approach
  - Repetitive Behavior – use behavioral approaches
  - +/- pharmacological target - stabilize

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Obsessive Compulsive Disorder

Introduction

- OCD
- The OCD Spectrum
- Repetitive thoughts and behaviors
- Subtyping
- The Basics
- Treatment
  - Basic
  - Refractory

OCD in DSM 5

- OCD removed from the anxiety section of the DSM
- Replaced the word "impulse" with the word "urge" to capture the nature of obsessions more accurately.
- Replaced the word "inappropriate" with the word "unwanted"
- Removed criteria that obsessions and compulsions are unreasonable or excessive.

OCD

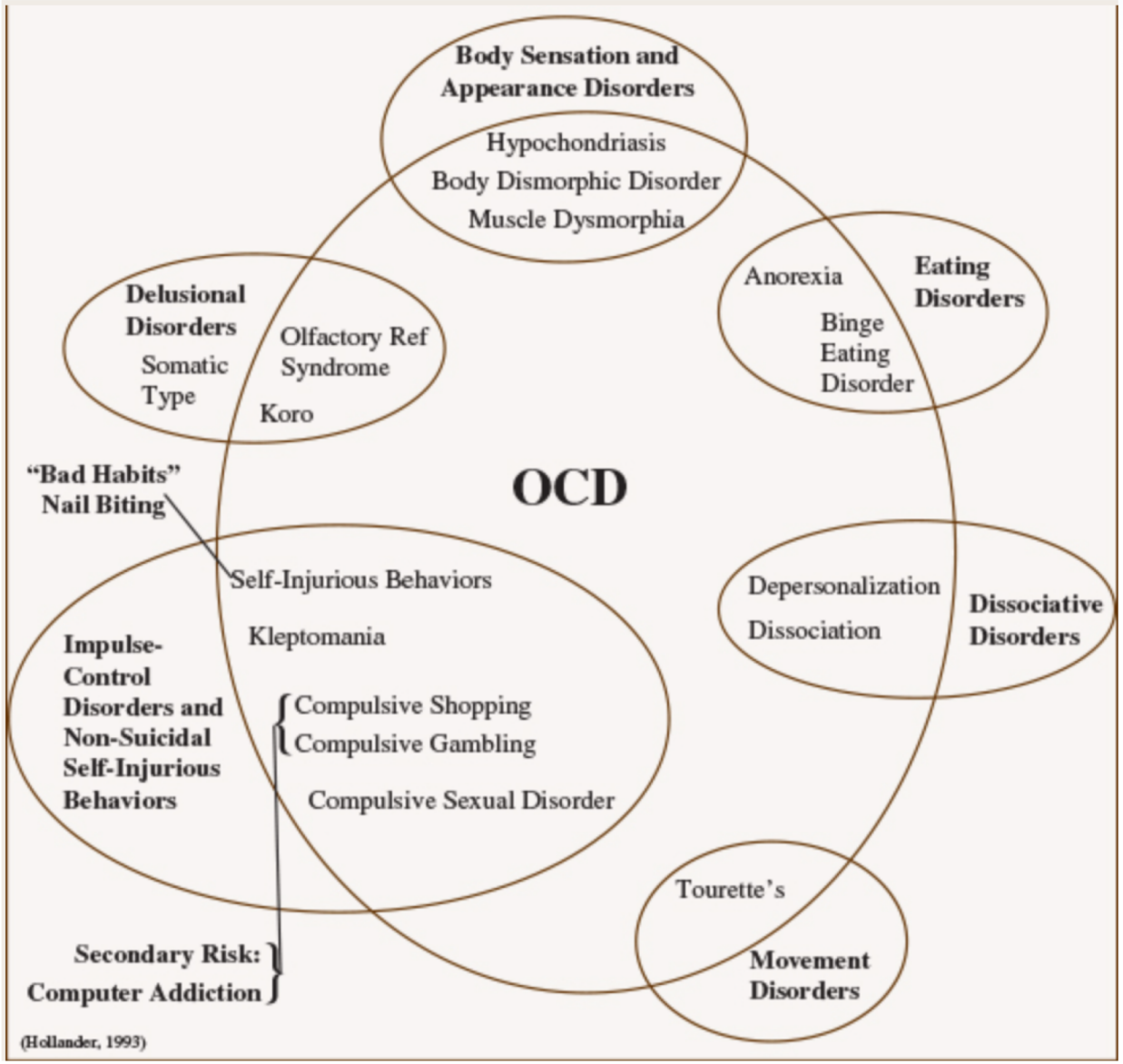
- Repetitive thoughts and behaviors that cause distress
  - Obsessions
    - Intrusive and unwanted, recurrent and persistent thoughts, urges, or images.
    - The person attempts to suppress, ignore or neutralize
  - Compulsions
    - Ritualistic behaviors or mental acts
    - The goal of the compulsion is to reduce anxiety or distress
    - The compulsions are senseless and excessive

Spectrumization

- Treatment Driven – epochs of care
- Accumulation of conditions that might be treated similarly
  - Similarity of phenotype
  - Potentially responsive to the same treatment
  - Maybe neurobiological similarities
  - Syncretic thinking
- Dismantling of the Spectrum

Obsessive Compulsive & Related Disorders

- Obsessive-Compulsive Disorder
- Body Dysmorphic Disorder
- Hoarding Disorder
- Trichotillomania (Hair-Pulling Disorder)
- Excoriation (Skin-Picking) Disorder
- Substance/Medication-Induced Obsessive-Compulsive and Related Disorder
- Obsessive-Compulsive and Related Disorder Due to Another Medical Condition
- Other Specified Obsessive-Compulsive and Related Disorder
- Unspecified Obsessive-Compulsive and Related Disorder


Body Sensation and Appearance Disorders
Hypochondriasis
Body Dismorphic Disorder
Muscle Dysmorphia
Delusional Disorders
Somatic Type
Olfactory Ref Syndrome
Koro
Anorexia
Eating Disorders
Binge Eating Disorder
"Bad Habits"
Nail Biting
OCD
Self-Injurious Behaviors
Kleptomania
Depersonalization
Dissociation
Dissociative Disorders
Impulse-Control Disorders and Non-Suicidal Self-Injurious Behaviors
Compulsive Shopping
Compulsive Gambling
Compulsive Sexual Disorder
Tourette's
Movement Disorders
Secondary Risk:
Computer Addiction
(Hollander, 1993)

Dismantling the Spectrum

- Hoarding
- Tic-related OCD
- Other behaviors more related to tics than to OCD
  - Trichotillomania
- Mislabeling of the repetitive thoughts and behaviors

Repetitive Behaviors

- Compulsions
- Tics
- Stereotypies
- Perseverative behaviors
- Addictive behaviors
- Habits

Repetitive Thoughts

- Obsessions
- Premonitory sensations or urges
- Ruminations
- Delusions
- Perseverative thoughts
- Cravings
- Over-valued ideas
- Flash-backs

Subtypes of OCD

- Pure Obsessions
- Contamination
  - Least likely associated with other Axis I disorders
- Symmetry/Order
  - Breeds true
- Hoarding
  - Breeds true
  - Poorer treatment response.

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Treatment of OCD

Serotonin Reuptake Inhibitors - Food and Drug Administration (FDA) Approvals

- Clomipramine: FDA approved to age 10 OCD.
- Fluvoxamine: FDA approved to age 8 OCD.
- Sertraline: FDA approved to age 6 OCD.
- Paroxetine: Effective for OCD and social phobia (SoP).
- Fluoxetine: Effective for OCD, major depressive disorder (MDD) to age 7.
- Citalopram: No controlled trials in children.
- Escitalopram: FDA approved > age 12 for depression.
- Venlafaxine: Effective for SoP but $\pm$ GAD
- Duloxetine: FDA approved GAD 7 years of age and over.

Cognitive Behavioral Therapy

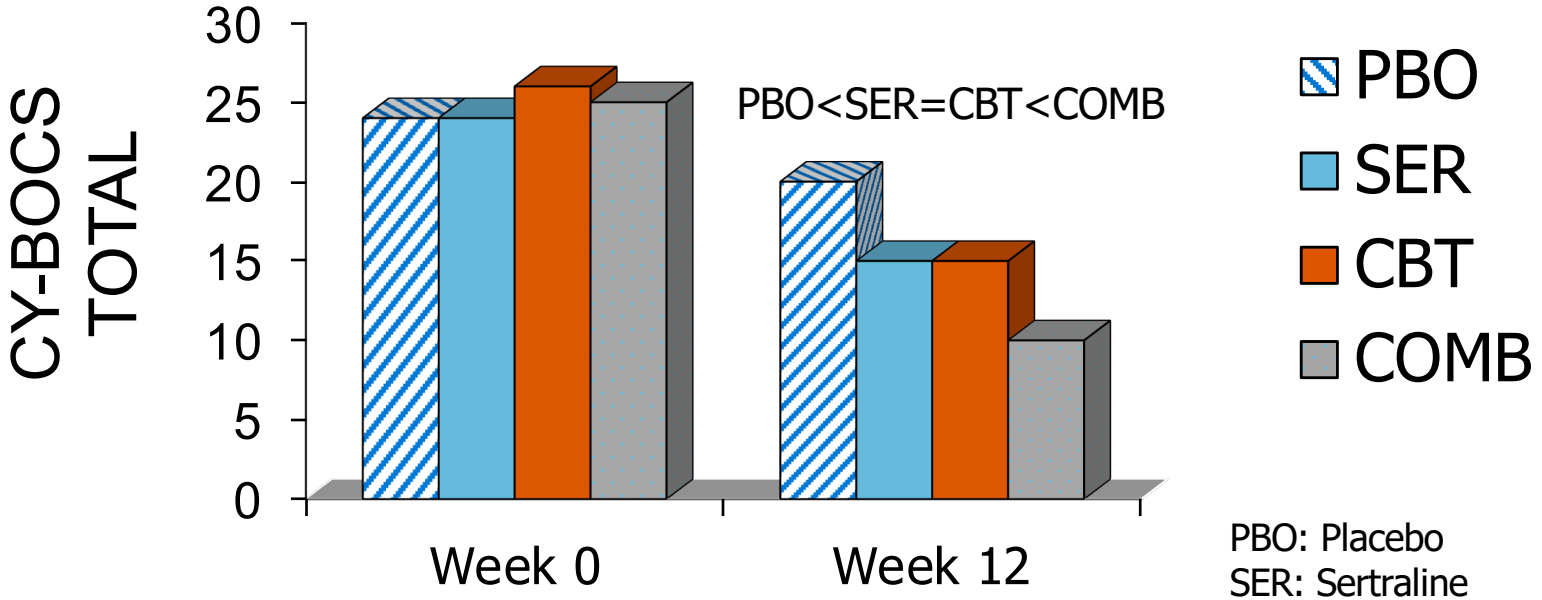
- Psychoeducation about OCD
- Fear hierarchy
- Exposure and resp0nse prevention
  - In office
  - Out of office

Pediatric OCD Treatment Study (POTS)

- n=112
- Ages 7-17 years
- 3 sites, 12 weeks
- Cognitive behavioral therapy (CBT), sertraline (SER), combination (COMB), and placebo (PBO)

Pediatric OCD Treatment Study. 2004.

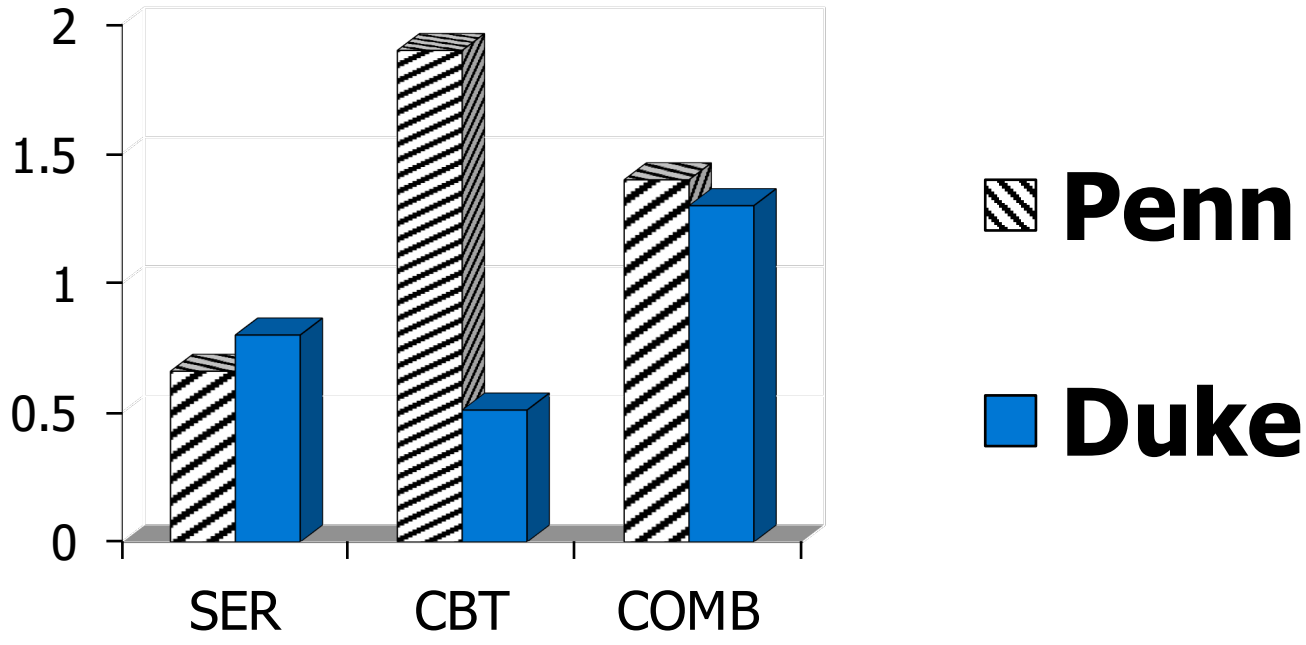
Children's Yale-Brown Obsessive-Compulsive Scale intention-to-treat (CY-BOCS ITT) Outcomes



PBO: Placebo
SER: Sertraline
CBT: Cognitive behavioral therapy
COMB: Combination

Pediatric OCD Study Team. *JAMA*. 2004.

Site x Treatment Interaction



Pediatric OCD Study Team. *JAMA*. 2004.

Augmentation vs. Adjunctive

- Augmentation
  - e.g. Li addition to antidepressants
    - Serotonergically sensitize the brain, then "turbocharge" with addition of another 5-HT med
    - Lithium will not work alone
    - Lithium does not work when started first
- Adjunctive treatment
  - e.g SSRI + BZD

Medication Augmentation Strategies

- Clomipramine
- Clonazepam
- Neuroleptics
- IV Clomipramine
- Buspirone
- Add second SSRI
- Lithium
- Stimulants
- Psychotherapy augmentation – d-cycloserine

March J, et al. Expert consensus guidelines: treatment of obsessive-compulsive disorder. *J Clin Psychiatry.* 1997;58(1-72).

Summary

- New effective treatments bring excitement and hope
  - Behavioral strategies
  - Neurosurgery
- If you think about it, it makes sense
- Lots more to learn to realize the full promise of new treatments for tic severity
- OCD – the right diagnosis is critical to good treatment outcomes