



Obsessive-Compulsive Disorder and PANDAS

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Disclosures

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

Syneos Health	Research support: On IRB for ecopipam trial for individuals with TS at MGH
Tourette Association of America (TAA)	Medical Advisory Board

Take-aways

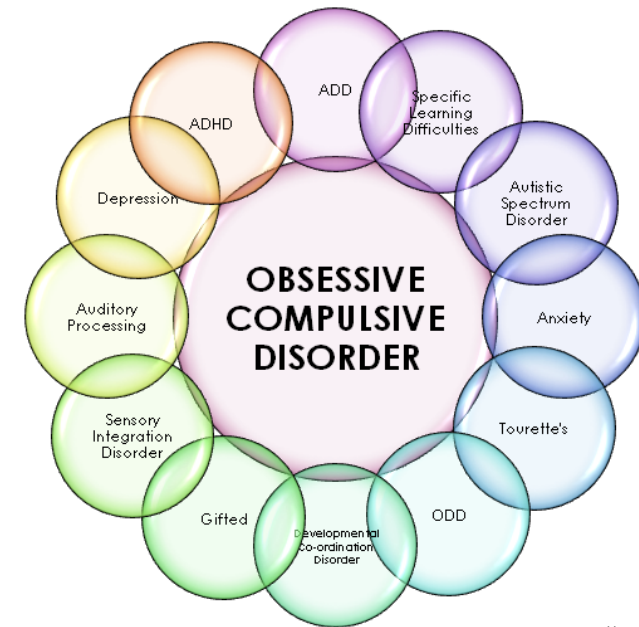
- Childhood-onset OCD responds best to a combination of medication (SSRIs) and behavioral therapy (exposure response prevention)
- PANDAS (pediatric autoimmune neuropsychiatric disorder associated with strep) and PANS – (pediatric acute-onset neuropsychiatric syndrome) currently have very limited evidence—based treatment approaches
- When treating PANDAS/PANS, one should start with typical evidence-based symptom-targeting treatments
 - Can add additional anti-inflammatory approach

Obsessive-Compulsive Disorder (OCD)

- Diagnostic Criteria
 - Obsessions and/or compulsions
 - *Obsessions*: Unwanted, intrusive, fixed or repetitive ideas, thoughts, images or impulses
 - *Compulsions*: Behaviors one “must do” to get rid of the unwanted feelings caused by the obsession
 - At least **one hour** a day, and/or
 - Need to cause **distress** and/or **impairment** in daily functioning
 - Insight? (“I know this doesn’t make sense... but I can’t help it!”)
 - **Tic-related?**

OCD characteristics

- 2-3% prevalence in children/adolescents
- Onset between **8-12 (early-onset)** or late teens/early adulthood
- >50% have at least 1 co-occurring condition
 - Other obsessive-compulsive related disorders
 - Hair-pulling/skin picking disorder
 - Anxiety disorders
 - Tic disorders
 - ADHD
 - Depression/mood disorders
- Course:
 - Wax and wanes
 - Frequently chronic



<http://www.lanc.org.uk/wp-content/>

OCD Subgroups

Four subtypes:

- Symmetry
 - Includes: symmetry, ordering, counting, repeating, re-writing
- Forbidden thoughts
 - Includes: aggressive, sexual, religious, somatic, checking
 - Taboo thoughts
 - Doubt and checking
- Cleaning/contamination
- Hoarding*

Possible feeling states preceding compulsions... not just anxiety!

- Fear
 - e.g. stop something bad from happening
- Disgust
- “Not just right”

Pediatric OCD Treatment Study (POTS)

- Combination therapy (CBT and medication) is most effective for moderate-severe OCD (aiming for CY-BOCS<11)
 - Combined: 53.6%
 - CBT: 39.3%
 - Sertraline: 21.4%
 - Placebo: 3.6%
- POTS II: For children/adolescents who are partial responders to SRIs
 - Weekly CBT with antidepressant (69% improvement)
 - Instructions on CBT and antidepressant (34% improvement)
 - Antidepressant alone (30%)

Garcia et al, JAACAP, 2010: Pediatric OCD Treatment Study (POTS)

OCD Treatment

- Behavioral Therapy:
 - Cognitive Behavioral Therapy (CBT) and Exposure Response Prevention (ERP)
- Medication
 - SSRIs – fluoxetine, sertraline, *fluvoxamine, clomipramine
 - 30-40% reduction in symptoms (6 points on CY-BOCS), clinical effects begin within weeks, plateau at 10 weeks
 - 2/3 of changes in first 2-3 weeks
- Moderators:
 - Tics, Hoarding, Low Insight, Increased Accommodation, autism spectrum disorder (formally pervasive developmental disorder (PDD))
- ~70% of children experience treatment response with first-line treatments

Medications used in Treatment of OCD: Empirical Support and Dosing Guidelines

Medication	Empirical Support		Starting Dose (mg)	Usual Dose Range (mg/day)
	Child	Adult		
Clomipramine*	A	A	25-50	100-250
Fluoxetine*	A	A	5-20	10-60
Sertraline*	A	A	25-50	50-250
Fluvoxamine*	A	A	25-50	50-350
Paroxetine	B	A	5-10	10-60
Citalopram	B	A	5-10	20-60
Escitalopram**	B	A	5-10	10-20

*FDA-approved for OCD

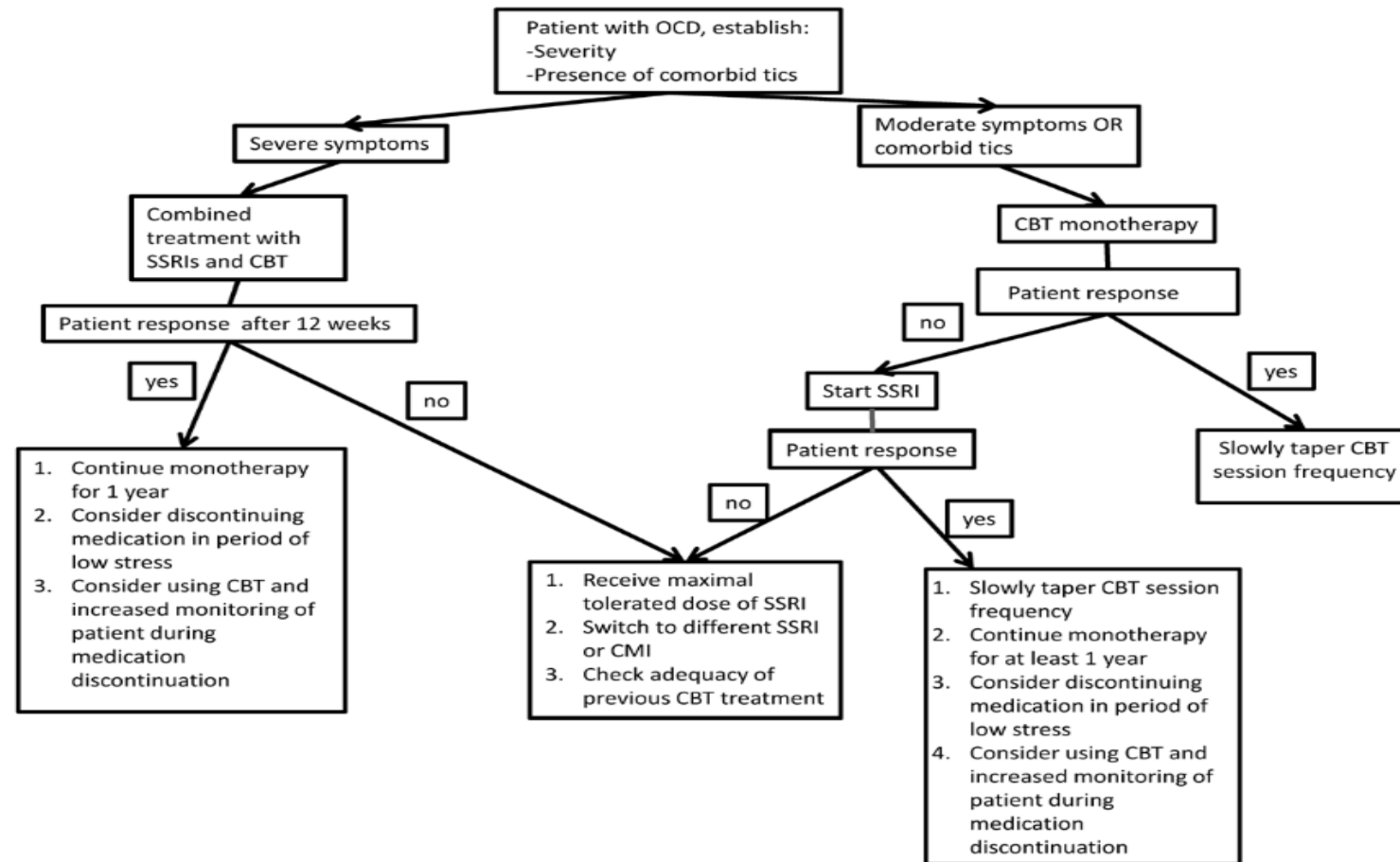
**Not well studied in OCD, presumed to be similar in efficacy to citalopram.

When First-line Treatments are Not Enough

- Neuroleptics*: Tics, poor insight, PDD, mood instability
 - Risperidone, aripiprazole, haloperidol
- Clomipramine: Good evidence for monotherapy (and with SSRIs)
- Limited, mixed, inconclusive evidence:
 - Glutamatergic: Riluzole, Topiramate, Lamotrigine, Memantine, N-acetylcysteine
 - Benzodiazepines: Not supported, though frequently used
 - SNRIs
 - Stimulants
 - Cannabinoids?
 - Neurosurgery/Deep Brain Stimulation/rTMS/dTMS

*Best evidence; predominantly from adult trials

Bloch, H. Michael. (2015). Assessment and Management of Treatment-Refractory Obsessive-Compulsive Disorder in Children.



Adapted from Coffey BJ 2019 Pediatric OCD; Child and Adolescent Psychopharmacology Slides

Quick Comment on COVID-19 Impact



PANDAS: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections



Earthworld.com

Clinical Case

- 6 y/o male with no previous history of psychiatric illness, family hx of OCD/tics on Dad's side, Mom has Hashimoto's thyroiditis
 - Independent, socially well adjusted, “cautious”
- “Constantly sick” with 7 strep infections since age 2

Clinical Case - PANDAS

- June 10th 2018
 - Woke up in middle of night and “**appeared possessed,**” increased **urinary frequency,** sudden **separation anxiety,** worsened **hand-washing/symmetry,** “**mean and oppositional,**” **rage episodes, joint pain,** eye rolling **tics,** and “**baby-talk**”
 - Tested positive for strep by culture, 1m Augmentin... Symptoms improved immediately!
- October 2018
 - No longer on antibiotics and close to baseline:
 - Few eye tics, mild anxiety, occasional hand-washing

PANDAS

- Rapid, new onset (or *severe* exacerbation) of obsessive-compulsive and/or tic symptoms in previously healthy child
- Symptom onset temporally associated with Group A Streptococcal (GAS) infection, that follows episodic course
 - Hypothesized to be a post-infectious autoimmune disorder (induced by a Group A Strep infection)
 - Autoimmune cells *cross-react* with proteins in the brain – leading to OCD/tics/other behavioral changes
 - First described by Dr. Susan Swedo and colleagues at NIMH investigating Sydenham's chorea and OCD in the 1990s

PANDAS - Clinical Criteria

1. Presence of DSM-based OCD, a tic disorder, or both
2. Pre-pubertal symptom onset
- 3. Episodic** course of symptom severity
 - Abrupt, explosive onset of symptoms or dramatic symptom exacerbations assigned to a specific day
4. Temporal association of symptom exacerbations with GABHS infection
 - Positive throat culture or streptococcal titers
5. Presence of associated neurologic abnormalities
 - Motoric hyperactivity and choreiform movements

PANDAS - Historical Context

- Sydenham's Chorea (SC) – “St. Vitus's dance”
 - Acute-onset movement disorder in children
 - Cardinal symptom of **rheumatic fever** (a **post-strep autoimmune disease**)
 - Patients also have significant, new-onset OCD symptoms
 - ~20% OCD and 50% OCB (da Rocha et al 2008)
 - Hypothesized to be the result “**molecular mimicry**”
- Those with SC often have:
 - Variety of behavioral symptoms, OCD, emotional lability, ADHD symptoms

Concerns with PANDAS

- Tics and OCD typically worsen during illness
- Conflicting literature
 - Exacerbations during non-strep periods
 - GAS with no symptom exacerbation
 - PANDAS-like picture without strep
 - Tics often present with sudden-onset
- What population are we examining?
 - Heterogeneous vs. homogeneous



PANS: Pediatric Acute-Onset Neuropsychiatric Syndrome



PANS Diagnostic Criteria

- Abrupt, dramatic onset of OCD or severely **restricted food intake**
- Symptoms not better explained by known neurologic/medical disorder
- Concurrent presence of additional severe/acute-onset neuropsychiatric symptoms from at least 2/7 categories:
 - Anxiety
 - Emotional (mood) lability and/or depression
 - Irritability, aggression, severe oppositionality
 - Regression – behavioral/developmental
 - Attention/concentration changes
 - Sensory/motor abnormalities
 - Somatic signs/symptoms (e.g. sleep disturbances, enuresis/inc. urinary frequency)

PANDAS/PANS Prevalence

- Jaspers et al 2017 (JCAP)
 - To determine frequency and features of those with PANDAS/PANS symptoms
 - 136 youth presenting at subspecialty pediatric OCD clinic (Canada)
 - **5% (~1-10%)** met proposed criteria*
- Features:
 - Little premorbid pathology
 - Greater family impact/more OCD-related impairment
 - Increased association with strep infections (lifetime)
 - Younger age compared to typical OCD onset
 - Increased urinary incontinence, increased autoimmune illness

Hot off the Press Research

- Mataix-Cols et al (2017) Molecular Psychiatry
 - Swedish birth cohort of 7.5million individuals
 - Individuals with OCD and TD/CTD had increased comorbidity with autoimmune disorders (AD) (43% and 36% respectively)
 - Familial link between AD and OCD/CTD
 - **76%** biological relatives of 45 children with PANS had at least one autoimmune or inflammatory disorder! (Gromark et al 2019 JCAP)
 - OCD and TD/CTD may share genetic risk factors with autoimmune disease
 - Immunological factors may play role in etiology **some** individuals with OCD/CTD

Hot off the Press

Orlovska et al (2017) JAMA Psychiatry

- Investigate link between OCD/tic disorders and infection
- 17y Danish cohort study with >1M children
- **Strep linked with increased OCD, tics, *any* mental disorder**
- **Non-strep throat infection linked with tics and *any* mental disorder**

Kohler-Forsberg et al (2018) JAMA Psychiatry

- Investigate link between infections requiring treatment and risk for mental illness
- Infections (hospitalization): Any mental illness diagnosis - HRR 1.8
 - OCD: HRR 2.7; TS: HRR 3.3
- Infections (antibiotic): Any mental illness diagnosis - HRR 1.4
 - OCD: HRR 2.4; TS HRR 3.1

Treatment



Current Guidelines

Consensus guidelines published during Summer 2017

1. Establish that PANS/PANDAS is the **correct diagnosis** (“diagnosis of exclusion”)
2. Provide **symptomatic** relief with **psychiatric** medications/**behavioral** interventions
3. Treat any **underlying infections**
 - *consider* use of prophylactic antibiotics
4. Treat any **inflammatory** components
5. Evaluate effectiveness
6. **Stop treatment when symptoms resolve**

Swedo et al (2017) *JCAP*

Treatment Guidelines Continued

3-pronged approach

- Psychiatric medications and behavioral treatment for symptom relief
 - Typical treatments for OCD **are** effective! (CBT, SSRIs)
- Antibiotics* to eliminate source of infection
 - ?Anti-inflammatory
- Anti-inflammatories (or immune-modulating) treatments to help immune system
- **“Education, supportive and behavioral therapies, and psychoactive medications are the mainstays of symptomatic treatment for PANDAS. Antimicrobials and immunomodulatory therapies may also be indicated”**
 - Need more prospective studies!

Swedo et al (2017) *JCAP*

Guideline highlights

- **Psychiatric:**

- OCD and other symptoms respond to same medications as in non-PANS
- Start low / go slow
- Psychoeducation and support

Thienemann et al (2017) *JCAP*

- **Immunomodulatory:**

- Start with NSAIDs for mild symptoms (up to 6 weeks)
 - 5-10mg/kg bid naproxen
 - 10mg/kg tid ibuprofen
- *Consider* early use of corticosteroids to abort or shorten flares

Frankovich et al (2017) *JCAP*

Guideline highlights

Antibiotics:

- Initial course of anti-strep treatment for newly diagnosed PANS and PANDAS patients (10 – 30d)
 - *Amoxicillin/Augmentin, Keflex, Azithromycin
- Chronic secondary prophylaxis for children with severe symptoms/recurrent GAS
 - If not GAS, prophylaxis (typically) not recommended
- Watch for other infections, but treat per standard guidelines
- Get standard immunizations(!)
- Get culture with symptom worsening if post-antibiotics
 - Antibody levels (>50% change)

Cooperstock et al (2017) *JCAP*

Systematic review – Treatment Studies to Date

- Limited studies thus far:
 - 4 RCTs, 1 cross-over, 2 open trials, 4 observational, 1 survey
 - Lots of case reports/series
- Inconclusive evidence for:
 - Antibiotics
 - Therapeutic plasma exchange
 - Tonsillectomy/adenoidectomy
 - IVIG
 - NSAIDs
 - Corticosteroids
- Issues:
 - Rigorously conducted research is scarce
 - High risk of bias
- Conclusion:
 - “Lack of evidence for treatment is based not on the inefficacy of the treatments, but on lack of systematic research”

Recent treatment studies

- **Antibiotics:**

- Azithromycin vs. placebo in double-blinded study
 - Better CGI-S, not CY-BOCS
 - Murphy et al (2017) JCAP

- **Anti-inflammatories**

- NSAIDS (ibuprofen, naproxen)
 - Two retrospective studies with positive findings
 - Flares shortened by 2.5-4 weeks
 - Spartz et al (2017) JCAP
 - Brown et al (2017) JCAP

- **Steroids:**

- One positive study
- Course shortened by 3.5weeks (from 11.4wks); early better
 - Brown et al (2017) JCAP

- **Immune-modulating**

- IVIG (mixed results)
 - Williams et al (2016) JAACP

Lab-work

- No smoking gun biomarkers
- Throat culture for active strep
 - Strep antibodies (ASO / anti-DNAse B): Need multiple data points
- Mycoplasma antibodies
 - Concern for false positives
- Other infectious causes:
 - Only if clinical syndrome that's consistent
- If multiple instances of infection, look for evidence of immune deficiency, inflammation, autoimmune markers
 - IgA, IgG, IgM immunoglobulins
 - IgG subclasses
 - ANA
 - ESR/CRP
 - TSH/T4
 - Vitamin D

Treatment

- Tailor treatment to the clinical severity of the patient
 - Mild Symptoms
 - Watchful waiting, CBT, NSAIDs
 - Moderate Symptoms
 - CBT, NSAIDs, +/-SSRIs, +/-Antibiotics
 - Severe Symptoms
 - CBT, typical psychiatric medications, NSAIDs, Antibiotics, ?steroids, ?other immune treatment

THANK YOU!



memegenerator.net

Conclusions

- “Insufficient evidence to clearly propose any treatment for PANDAS and related disorders” (Sigrá et al 2018, p 62)
- Lack of evidence for treatment is based not on the inefficacy of the treatments, but on lack of systematic research (Sigrá et al 2018, p 62)

Treatment Studies to Date

- 12 treatment studies in PANS/PANDAS to date
 - 4 double-blinded RCTs; 1 cross-over; 2 open-label; 4 observational
 - 1 retrospective online self-report
 - Treatments included: Penicillin, Azithromycin, IVIG, Therapeutic Plasma Exchange (TPE), Tonsillectomy, CBT, Steroids, NSAIDs
 - 11/12 had moderate or high risk of bias
- Inconclusive evidence: Abx, TPE, IVIG, NSAIDs, CBT, steroids
 - Evidence weak for tonsillectomy