



# 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

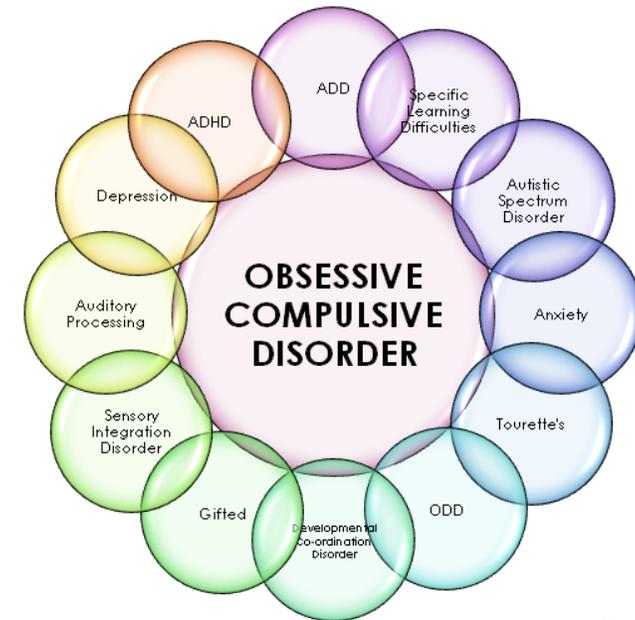
- Childhood-onset OCD responds best to a combination of medication (SSRIs) and behavioral therapy (exposure response prevention)
- PANDAS (pediatric autoimmune neuropsychiatric disorder associated with strep) and PANS – (pediatric acute-onset neuropsychiatric syndrome) currently have very limited evidence—based 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

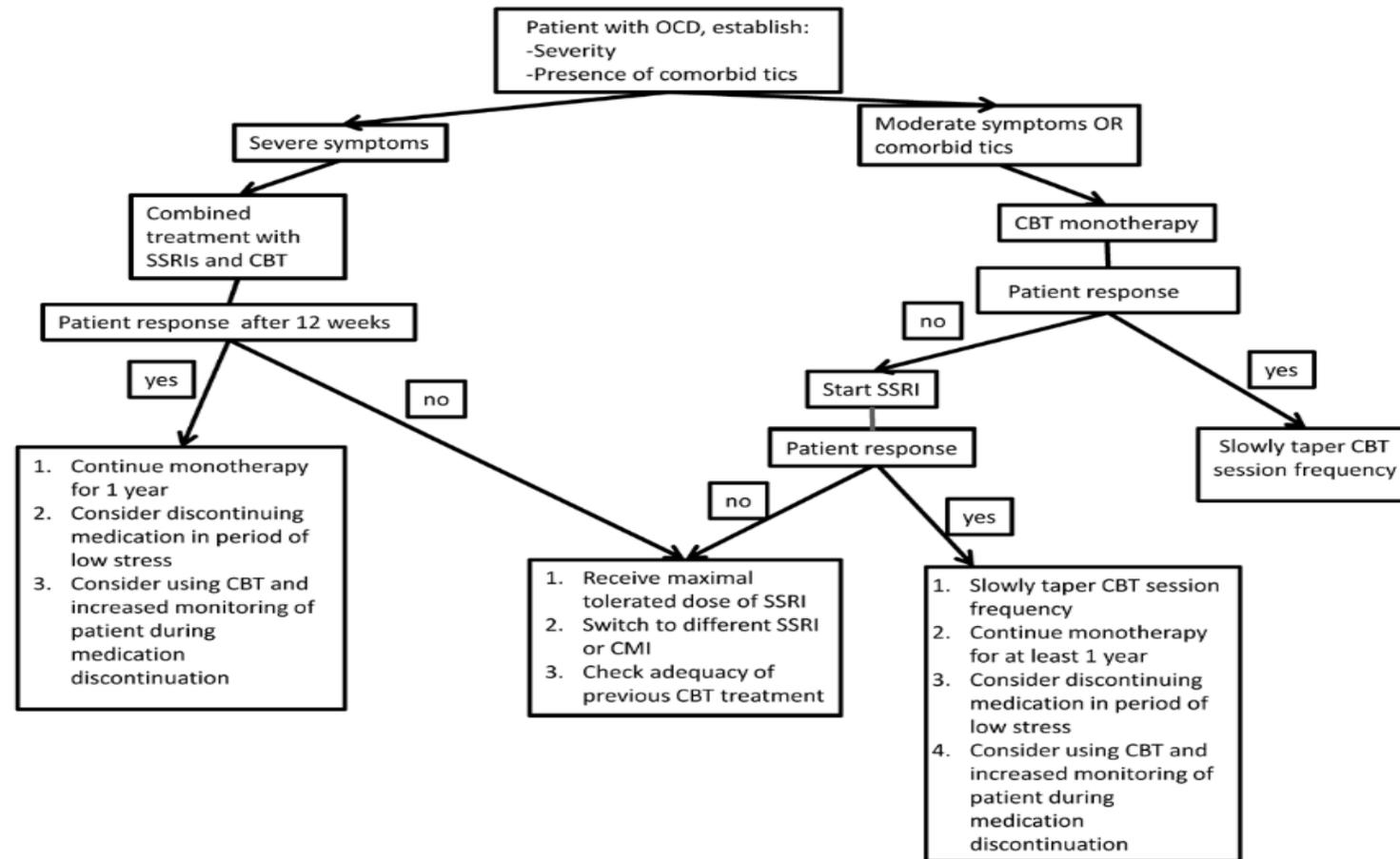
\*\*Not well studied in OCD, presumed to be similar in efficacy to citalopram.

# 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 10<sup>th</sup> 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 3.5 weeks (from 11.4 wks); 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