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Diagnosing Tourette Syndrome and Initial Considerations

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## Disclosure: John T. Walkup, MD
January 2019

<table>
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<th>Consultant</th>
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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.
Provisional Tic Disorder

- Motor and/or vocal tics
- Age of onset consistent with the other tic disorders i.e. < 18 years of age
- It is less than 1 year since the first tic started
- Can be ticcing in your office or not
Tic Disorder-NOS replaced by:

- Other specified tic disorder
  - Full diagnostic criteria for tic disorder not met, clinician indicates reason (e.g. onset after 18 years)

- Unspecified Tic Disorder
  - Full diagnostic criteria for tic disorder not met, clinician does not indicate reason
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, abilify, 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 (Prolinx®)
  - Pimozide (Orap®)
  - Haloperidol (Haldol®)

- **New Antipsychotics**
  - Risperidone (Risperdal®)
  - Aripiprazole (Abilify®)
  - Ecopipam
  - Ziprasidone (Geodon®)
  - Tetrabenazine/Deutetramethazine
  - 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
First Large Prospective Study

- Servello et al., JNNP, 2007
- 18 patients
- Vo-CM-PF thalamus
- Blinded on-off eval (but not reported in detail)
- F/U 3 – 17 months
- 2 complications: 1 from picking at incision, 1 abdominal hematoma
Tourette DBS Registry

- N= 185; 72% males
- Age = 29 years; range 13-58
- 31 institutions; 10 countries
- Implantation sites
  - centromedian 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 (8.2%)

Tic Suppression – “No legs”

- Baclofen – Singer et al.,
- Ziprasidone – Sallee et al.,
- Pergolide – Gilbert et al.,
- Glutamate agonists and antagonists – Singer et al.,
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
Marijuana

- The Basics
  - The plant
    - Using the plant
      - Smoke, vape, eat etc
    - Extracts from the plant
      - >400 chemicals in the plant; 61 unique compounds; 50-70% more cancer causing hydrocarbons
      - CBD and THC are the main ingredients, but
      - Research to understand the role of other chemicals
  - Pharmaceutical grade extracts
  - Compounding Dispensaries
    - Prescriber orders
      - Pharmacist compounds the pharmaceutical grade extracts in specific ratios
  - Synthetic compounds – illegal and legal
  - Synthetic analogs – receptor agonists or antagonists
Marijuana

- The data
- Lots of anecdotal reports and small studies done by “true believers”
  - Positive results
  - Negative results
- Generally poor for EVERY medical condition except epilepsy
- Data likely always to be poor
  - Illegal in the U.S.
  - If you are a research facility (e.g. a university) and you study an illegal drug you risk censure or criminal prosecution at the Federal level
- Drug companies can make synthetics and do a drug development program through the FDA
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
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.

PANDAS - Course of Illness

- First episode onset similar to SC
- Next episode onset closer to onset of infection?
- Other infections can trigger symptomatic exacerbation?
- Leads to chronic symptom picture
GABHS Infection

RF

GABHS infection

Sydenham’s Chorea
PANDAS - Course of Illness

- First episode onset similar to SC
- Next episode onset closer to onset of infection?
- Other infections can trigger symptomatic exacerbation?
- Leads to chronic symptom picture
PANDAS - Course of Illness

- GABHS infection
- PANDAS exacerbation
PANDAS - Course of Illness

- First episode onset similar to SC
- Next episode onset closer to onset of infection?
- Other infections can trigger symptomatic exacerbation?
- Leads to chronic symptom picture
PANDAS - Course of Illness

- Other infection
- GABHS infection
- PANDAS exacerbation
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
PANDAS Treatment

- Send patients with PANDAS to a nationally recognized center that is conducting clinical trials
- Don’t treat elevated antibody titers
- Don’t treat exacerbations of tics/OCD with antibiotics or immune treatments
- Use conventional treatments – medication and CBT
Summary

- Many treatment options for people with Tourette syndrome
- Many biological treatment approaches
  - Tics
  - Co-occurring conditions
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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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. Tics are usually brief, rapid movements (e.g., blinking, facial grimacing) or vocalizations (e.g., 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. Epidemiologic and clinical data indicate that Tourette disorder can be associated with considerable impairment and social isolation in school-aged children. Tics are commonly preceded by asymptomatic

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 endpoint 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
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; Habil. Liu, MPH; James Dzura, 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 endpoint compared with the control treatment (21.8 [6.59] to 19.3 [7.40]) (P < .001; effect size = 0.77). 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: NCT00231983

*Arch Gen Psychiatry.* 2012;69(8):795-803
CBITS Study Design

Assessment Schedule:

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<th>Week</th>
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<th>5</th>
<th>10</th>
<th>23</th>
<th>36</th>
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248 Subjects with TS or CTD

Psychoeducation Support

CBIT

Booster

Non-Responder

Responder

Non-Responder

Responder

Non-Responder

Responder
Responder Status at Week 10

(CG1-Impovement = 1 or 2)

CBIT

52.5%

PS
18.5%

T

CBIT
38.1

PS
6.4

T

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
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
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