Medication Management in Tic Disorders

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Discussion of off-label & investigational use:

Yes X No __

Outline

- Brief review of tics and Tourette syndrome (TS)
- Pharmacology for tics
- Pharmacology for OCD and ADHD when tics are also present

What are tics?

- Sudden, recurrent, non-rhythmic, movements or sounds
  - Unvoluntary
- Wax and wane over time
  - Treatment implications
- Often preceded by a premonitory urge/itch/tension
  - Somatic, sensory, or ideational symptoms that precede tics
  - Feeling of “not just right” or “incompleteness”
  - Temporarily relieved by performing the tic
- They “jump”
  - Change location, number, frequency, type, complexity severity

Mills et al., 2014
Hallett 2015

What is Tourette Syndrome?

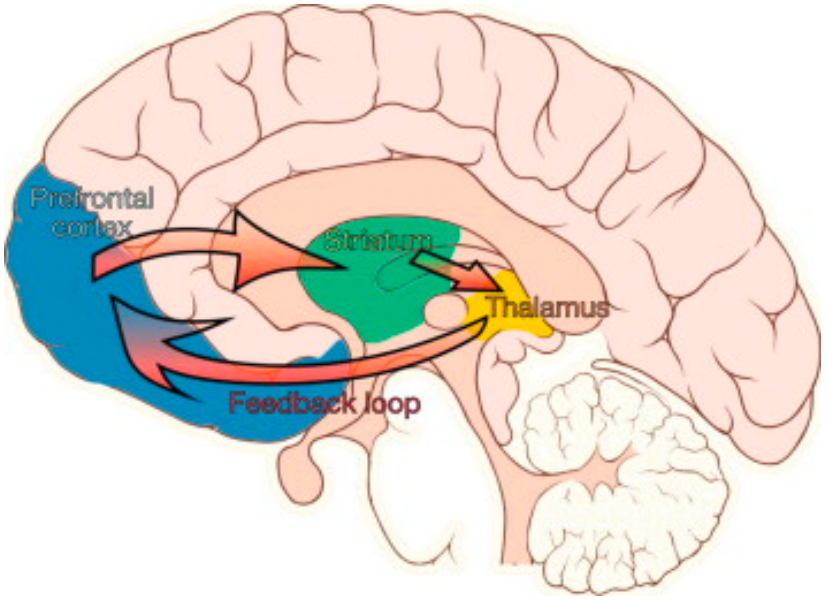
- Childhood-onset neuropsychiatric disorder characterized by tics
  - Estimated to be between 0.3% and 0.9% (Scharf et al 2015)
- Criteria:
  - At least Two motor and One vocal tic over the course of the illness
  - At least one year duration, though the tics can wax and wane in frequency
  - Onset before age 18
  - Not secondary to a substance or another medical condition

Other Tic Disorders

- Persistent (Chronic) Motor or Vocal Tic Disorder:
  - Same criteria as TS, but only motor OR vocal tics
  - Additional 1-2% of children
- Provisional Tic Disorder
  - Part of normal development? (~20-25% of kids)

TS Pathophysiology

- Dysfunction of fronto-striatal-thalamo-cortical circuits
  - Leads to disinhibition of the motor and limbic system
- Neurotransmitters in this circuit:
  - Glutamate
  - Serotonin
  - Dopamine
  - GABA



Beddows 2015 - http://scitechconnect.elsevier.com/neurobiology-basis-of-ocd/. Modified from original image, credits: Patrick J. Lynch and C. Carl Jaffe.

Treatment considerations in Tourette syndrome:

- Improvement with age
  - Rule of Thirds: 1/3 resolve, 1/3 improve, 1/3 stay the same
  - ~10% of patients have persistent, severe symptoms as adults
- Modifying factors (internal vs. external)

When to Treat Tics?

- When tics/urges are causing physical **pain/impairment**
- When tics are causing severe **social/functional problems**
- When tics lead to **psychological distress**, such as depressive and anxious symptoms, low self-esteem and/or social withdrawal

Childhood Psychosocial Morbidity

- Over 2/3 children with TS reported impaired peer relations, difficulties with friendships
  - Rated as less popular/more withdrawn by peers and teachers vs. healthy controls
  - Higher rates of peer victimization when compared to children with a “medical” illness (Type I diabetes) and healthy controls
- Quality of life in children with TS significantly worse than normative sample

(Eapen, Cavanna, Robertson 2016)

Treatments

- Behavioral
- **Pharmacologic**

healthncare.info

Overall Treatment Guidelines

- No studies comparing the effectiveness of behavioral and pharmacological treatments in patients with TS
- Treatment aims to reduce tic severity and frequency
- Often more important to manage the comorbid conditions in order to improve psychosocial functioning and (child) development
  - Intensity of tics does not have to equate with impairment

European Society for the Study of Tourette Syndrome, 2011

Pharmacotherapy

- Only FDA approved treatments: Pimozide, Haloperidol and Aripiprazole
- Broad range of clinical experiences, but actual evidence (based on RCTs) is limited

TS Pharmacology Overview

- Three “tiers” of tic medications
  - Tier 1: Alpha-2 agonists:
    - Clonidine, guanfacine, extended-release guanfacine
  - Tier 2: Atypical neuroleptics (antipsychotics)
    - Risperidone, aripiprazole, etc.
  - Tier 3: Typical neuroleptics (antipsychotics)
    - Haloperidol, pimozide, etc.

Doses of Medication

Table II. *Daily doses of frequently prescribed medications for Tourette syndrome.*

Medication (brand name)	Range of daily dosing
Haloperidol (Haldol)	0.25-4.0 mg
Pimozide (Orap)	0.5-8.0 mg
Risperidone (Risperdal)	0.125-3.0 mg
Aripiprazole (Abilify)	1.0-15.0 mg
Clonidine (Catapres)	0.025-0.4 mg
Guanfacine (Tenex)	0.25-4.0 mg

THOMSON REUTERS – Drugs of Today 2014, 50(2)

Alpha-agonists

- Clonidine, guanfacine
- “Blood pressure” medications
  - Indication in treating ADHD
  - Off-label, used for sleep, impulsivity, ?anxiety
  - Short-acting, extended-release, transdermal
- Least side effects
  - Sedation, dizziness, headache, low blood pressure
- Good for tics of limited severity**
  - Improvement about 30%
- **Caveat: May only be helpful if co-occurring ADHD
  - Recent negative study using extended-release guanfacine in children with chronic tics (Murphy et al., 2017)

Atypical Antipsychotics

- Risperidone, Aripiprazole (Dopaminergic/serotonergic)
  - (Class B: Ziprasidone, Olanzapine, Quetiapine)
- Other indications: Mood disorders (bipolar disorder, severe aggressive behavior/mood dysregulation in ASD, psychosis)
- Moderate side effects:
  - Metabolic symptoms (cholesterol, weight gain, glucose)
  - Akathisia, low blood pressure, GI, sedation
  - Low risk of tardive dyskinesia
  - Requires monitoring (blood)
- Moderate benefit:
  - 35-60% tic reduction

Typical Antipsychotics

- Haloperidol, Pimozide (Dopaminergic)
  - (Class B: Fluphenazine)
- Other indications: Psychotic disorders, severe bipolar disorder/mood dysregulation
- Potential for severe side effects:
  - Tardive dyskinesia, dystonia,
  - Sedation, weight gain, fogginess
  - Requires monitoring (EKG)
    - Often not tolerated 2o to side effects
- Largest benefit:
  - Haloperidol up to 80%; fluphenazine/pimozide up to 60%

Other Medications

- Benzodiazepines (clonazepam)
- Topiramate (anticonvulsant): Meta-analysis negative, but positive RCT in kids
- Baclofen (GABA modulator): Some positive effect
- Atomoxetine: Some benefit, at times exacerbates tics
- Nicotine: Some benefit
- Tetrabenazine: some positive effect, increased risk of depression
  - Trialing new VMAT-2 inhibitors
- Metoclopramide (mixed dopamine/serotonin antagonist)
- Botox: Only for simple motor tic
- Cannabinoids**

Thomas et al 2013
Egolf and Coffey 2014

Cannabanoids (Delta-9-THC)

- Anecdotal reports that marijuana may be helpful with tics and behavioral problems
- Whiting et al in JAMA (2015) suggested that "suggested that THC capsules may be associated with a significant improvement in tic severity in patients with Tourette syndrome"
- Two recent controlled trials with self and examiner scales
  - Statistically significant tic reduction without significant adverse effects (some short-term memory loss, rebound anxiety)
- Recent Cochrane study, however, states inability to draw definitive conclusions at this time
- NOT for children <21
  - Concern for association with psychosis

Curtis et al 2009
Mueller-Vahl 2012

OCD in TS

- 30-60% of TS pts meet DSM-IV criteria for OCD
  - Compared to 0.5-3.6% in general population
- Distinct symptoms:
  - Obsessions: symmetry, aggression, sexuality, religiosity
  - Compulsions: checking, touching, re-writing, evening
- Anxiety and depression more likely
- Patients with OCD + tics show less robust response to SSRIs compared to those without tics
  - Augmentation:
    - Haloperidol, risperidone, aripiprazole – positive trials

Gomes de Alvarenga et al 2012
Høolgaard D et al. 2012
Mansueto and Keuler 2005

ADHD in Tourette Syndrome

- 60-90% of TS patients have ADHD
  - Vs. 5.8-13.6% in males; 1.9-4.5% in females
- Tic disorders are more frequent in children with ADHD
- TS and ADHD is associated with:
  - Decreased quality of life (secondary to ADHD and OCD)
  - Worse social difficulties
  - Additional co-occurring disorders:
    - Oppositional defiant disorder, Intermittent explosive disorder

The TS Study Group (2002). Neurology
Peasgood et al (2016). Eur Child Adol Psych
Eddy et al (2012). Movement Dis.
Pringsheim et al (2017). Child Psych and Human Dev.

Treatment of ADHD and Tics (TACT): Targeted Combined Pharmacotherapy Study

- Multi-center treatment study in children with ADHD and Tourette/chronic tic disorder
  - Clonidine (alpha-agonist)
  - Methylphenidate (stimulant)
  - Combined (clonidine and methylphenidate)
  - Placebo
- Design: 136 children (ages 7-14);16 weeks
- Summarized results:
  - Tics and ADHD symptoms both did best with Combined alpha-agonist/stimulant

Tourette Syndrome Study Group (2002). Neurology.

TS and ADHD Pharmacotherapy

- If ADHD is mild and tics are problematic, can try alpha-agonist
  - Good for hyperactivity/impulsivity
- Solo stimulant use in patients with tics has traditionally been avoided, but
  - Meta-analysis by Cohen et al (2015)
    - No difference in tic worsening in stimulant vs. placebo group
    - No association between new onset or worsening of tics and stimulant use

Cohen et al. (2015) JAACAP

Summary

- For mild tics that need pharmacologic treatment, first try clonidine or guanfacine, especially if ADHD
  - Atypical or typical neuroleptics should be reserved for severe cases, used cautiously & monitored closely.
- New medications using different proposed mechanisms in the pipeline
- It is okay to use stimulants (case by case)
- SSRIs do not worsen tics
- Ultimate goal is to help patient develop and maintain appropriate self-esteem and coping skills

Questions?

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