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

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  • Rated as less popular/more withdrawn by peers and teachers vs. healthy controls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
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
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.**

<table>
<thead>
<tr>
<th>Medication (brand name)</th>
<th>Range of daily dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol)</td>
<td>0.25-4.0 mg</td>
</tr>
<tr>
<td>Pimozide (Orap)</td>
<td>0.5-8.0 mg</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>0.125-3.0 mg</td>
</tr>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>1.0-15.0 mg</td>
</tr>
<tr>
<td>Clonidine (Catapres)</td>
<td>0.025-0.4 mg</td>
</tr>
<tr>
<td>Guanfacine (Tenex)</td>
<td>0.25-4.0 mg</td>
</tr>
</tbody>
</table>
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
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

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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