# Management and Treatment Approach of Bothersome Tics

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## Objectives

- Review the phenomenology of tics
- Outline the range of effective management and treatment strategies for patients with bothersome tics, including both medication and non-medication approaches
- What's on the horizon?



## What is a tic?

- Tics Are Not:
  - Insects
  - Tic-tacs
  - Contagious
  - Sign of Mental Instability




- Phenomenology:
  - Sudden, brief, rapid, **repetitive, stereotyped, non-rhythmic** movements or utterances
  - Sensory or "premonitory urge", temporary suppressibility, release or relief phenomenon, "just rightism"

## What types of tics are there?

- Motor Tics → involuntary contraction of muscle. Typically in craniofacial distribution, though can involve trunk and limbs
- Vocal Tics → involuntary production of a sound
- Simple Tics → eye blinking, eye rolling, facial grimacing, nose flaring, neck movement, throat clearing, sniffing, grunting, squeaking
- Complex Tics → sequences of coordinated movement or sounds, such as bizarre gait, kicking, jumping, echopraxia, echolalia, copropraxia, coprolalia

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## Types of Tic Disorders

- Provisional Tic Disorder:
  - Formerly known as Transient Tic Disorder
  - Presence of motor or vocal tics for less than a year
  - Tics resolve within 1 year and do not recur
  - Common in children → ~10-20% prevalence
  - ~1% of those individuals will have persistence of tics for greater than 1 year

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## Types of Tic Disorders

- Chronic Motor Tic Disorder:
  - Presence of only motor tics for greater than 1 year
  - No vocal tics
- Chronic Vocal Tic Disorder:
  - Presence of only vocal tics for greater than 1 year
  - No motor tics
- Tourette Syndrome:
  - Combination of at least 2 or more motor tics and at least 1 vocal tic for greater than 1 year

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## Tourette Syndrome

- Background and Epidemiology:
  - Named after Dr. George Gilles de la Tourette in late 1800's
  - Initially regarded as a psychological condition → understanding of disease has transformed significantly over time → complex neurodevelopmental disorder with likely genetic component
  - Prevalence ~0.5-1%
  - Male:female → 4:1

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## Tourette Syndrome

- Clinical Features:
  - Onset of symptoms <18 years old
    - Average age of onset ~5-8 years old
    - Onset after age 21 is unusual and atypical
  - Tic severity peaks between 9-13 years old
  - Tics wax and wane (hour-to-hour, day-to-day, week-to-week)
  - Worse with stress, anxiety, heightened emotions, or anticipation
  - In general tics remain stable and/or improve with age in ~75% of individuals
  - High association with ADHD, OCD, Anxiety, Depression
    - Co-morbidities tend to persist into adulthood

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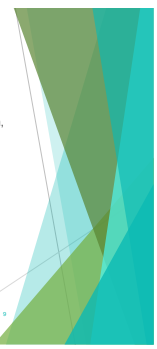
## Considerations in Treatment of Tourette Syndrome and Other Tic Disorders

- Most important question is whether to treat!
  - Consider impact of tics on activities, school, social interactions, self-esteem, etc.
- Education is often sufficient
- If treating, goal is tolerable suppression, not elimination of symptoms
- Treatment of tics to appease parents is not recommended
- Treat the most bothersome symptoms first
- Other considerations:
  - Tics wax and wane
  - Any new life event can be associated with worsening of tics
  - Tics typically remain stable and/or improve with age



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SPECIAL ARTICLE

# Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders

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## Abstract

### Objective

To make recommendations on the assessment and management of tics in people with Tourette syndrome and chronic tic disorders.

### Methods

A multidisciplinary panel consisting of 9 physicians, 2 psychologists, and 2 patient representatives developed practice recommendations, integrating findings from a systematic review and following an Institute of Medicine–compliant process to ensure transparency and unbiased

RELATED ARTICLE

Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders
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MORE ONLINE

*https://n.neurology.org/content/92/19/896



## Treatment of Bothersome Tics

- Non-Medications:
  - Comprehensive Behavioral Intervention For Tics (CBIT)
- Medications:
  - Alpha-2 Agonists:
    - Guanfacine, Clonidine
  - Topiramate
  - Anti-Dopaminergics:
    - Aripiprazole, Risperidone, etc.
  - Tetrabenazine
  - Botulinum Toxin
- Treatment of co-morbid OCD, Anxiety, Depression, etc.



## Comprehensive Behavioral Intervention for Tics (CBIT)

- Considered first line treatment intervention for bothersome tics
- A form of Habit Reversal Therapy (HRT)
- Methodology:
  - Trains patients to be aware of tics
  - Trains patients to develop a "competing motor response" when they feel the urge related to the bothersome tic
  - Make changes to day to day activities in ways that can be helpful in reducing tics
- Typically offered by psychologists, neuropsychologists, occupational therapists
  - Tourette Association of America has training program for providers
  - Typically one session per week for 8 weeks

## Empirical Support for CBIT

- RCT of 126 children ages 9-17 with TS or CTD
- 8 sessions of CBIT during 10 weeks of behavior therapy (n=61) or a control treatment consisting of supportive therapy and education (n=65)
- Behavioral intervention with CBIT led to significantly greater decrease in Yale Global Tic Severity Scale (24.7 to 17.1) compared with control treatment (24.6 to 21.1); p<0.001
- Significantly more children receiving behavioral intervention compared with those in the control group were rated as very much or much improved on the Clinical Global Impressions-Improvement scale (52.5% vs 18.5%, respectively; p<0.001)
- Drop out rate was low at 9.5% (12/126)
- Treatment gains were durable, with 87% available responders to behavioral therapy exhibiting continued benefit 6 months post treatment

*Piacentini, J., Woods, D.W., Scahill L., Wilhelm, S., Peterson, A.L., Chang, S., Ginsburg, G.S., Deckersbach, T., Dziura, J., Levi-Pearl, S., Walkup J.T., 2010, Behavior Therapy for Children with Tourette Disorder: A Randomized Controlled Trial. Journal of the American Medical Association, 303:1929-1937.

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## Empirical Support For CBIT

- RCT of 122 adults ages 16-69 with TS or CTD
- 8 sessions of CBIT or 8 sessions of supportive therapy over 10 weeks
- Behavioral Intervention with CBIT resulted in significantly greater decrease on the Yale Global Tic Severity Scale (24.0 to 17.8) compared with 8 sessions of supportive control treatment (21.8 to 19.3); p < .001
- Significantly more adults receiving CBIT were rated as being very much improved or much improved on the Clinical Global Impression-Improvement scale compared to supportive treatment (38.1% v 6.8%, respectively; p < .001)
- Drop out was 13.9% regardless of which treatment condition
- Treatment gains were durable, with continued benefit to 6 months post-treatment

*Wilhelm, Peterson, Piacentini, Woods, Deckersbach, Sukhodolsky, Chang, Liu, Dziura, Walkup, Scahill. (2012). Randomized Trial of Behavior Therapy for Adults with Tourette Syndrome . Arch Gen Psychiatry, 69, 795-803.

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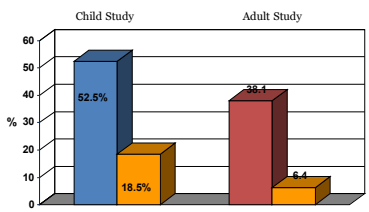
## Responder Status at Week 10

(CGI-Improvement = 1 or 2)



## Alpha-2 Agonists

- MOA → agonist binding at alpha-2 receptors within the CNS
- Considered first line pharmacologic therapy for treatment of tics
- Also effective for ADHD symptoms
- Potentially less potent but fewer side effects than dopamine blockers
- Most common side effects are sedation, orthostatic hypotension, bradycardia, dizziness, and constipation
- Clonidine (Catapres):
  - Maximum dose 0.4-0.6mg daily
  - Kapvay is extended release form
- Guanfacine (Tenex):
  - Maximum dose is 4mg daily
  - Intuniv is extended release form
  - Tends to be less sedating than Clonidine

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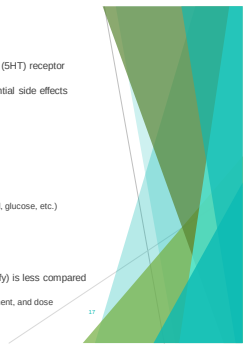
## Anti-Dopaminergics

- MOA → primarily block dopamine ($D_2$) receptors, with less serotonin (5HT) receptor blockade
- Are not considered first line anymore for treatment of tics given potential side effects compared to other treatment options available (i.e. alpha-2 agonists)
- Typical Antipsychotics:
  - Haloperidol (Haldol), Pimozide (Orap)
- Atypical Antipsychotics:
  - Risperidone (Risperdal), Aripiprazole (Abilify)
- Side effects:
  - Sedation
  - Metabolic Syndrome (weight gain, changes in blood pressure, cholesterol, glucose, etc.)
  - Akathisia
  - Extra-pyramidal side effects:
    - Tardive syndromes (i.e. dyskinesia, dystonia)
    - Parkinsonism
- Risk of extra-pyramidal side effects with atypicals (Risperidone, Abilify) is less compared to the typicals (Haldol, Pimozide), though still possible
  - Risk of extra-pyramidal side effects increases with age, duration of treatment, and dose



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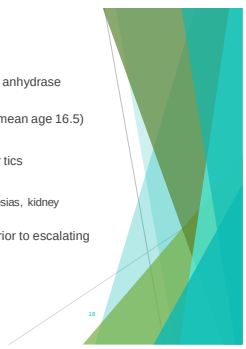
## Topiramate (Topamax)

- MOA → likely multiple mechanisms, including carbonic anhydrase inhibition and potentiate GABAA inhibition
- One phase III study in 29 children and adults with TS (mean age 16.5)
- Mean dose of Topiramate ~118mg during study
- Study showed mild improvement in outcome scores for tics
- High drop out rate due to side effects
  - Cognitive dulling, reduced appetite, weight loss, paresthesias, kidney stones
- Good option after CBIT and/or alpha-2 agonists, and prior to escalating to anti-dopaminergics



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## Tetrabenazine

- Rarely ever used to treat tics at this point due to risk of side effects and other better available options
- MOA → Vesicular monoamine transport 2 ($VMAT_2$) inhibitor → depletes presynaptic formation of dopamine
- Side Effects:
  - Balance Difficulty
  - Akathisia
  - Parkinsonism
  - Prolongation of QTc
  - Worsening depression and suicidality (Black Box Warning)

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## Botulinum Toxin

- MOA → Reduces release of presynaptic acetylcholine → overall reduction in contraction of the muscle
- Benefit within 1-2 weeks; wears off after 3 months
- Reduces risk of systemic side effects
- Side effects dependent upon area/region of injection → most common is weakness
- Helpful for simple motor tics → i.e. eye blinking, neck extension
- Difficult for more complex motor tics with multiple muscles and direction of movement involved

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## Medical Marijuana

- There are very limited, well designed, clinical trials with large sample sizes looking at compounds involving THC and/or CBD in treating patients with tics
- Two Studies Involving THC:
  - Muller-Vahl KR, Schneider U, Koblenz A, et al (Class II Study):[1]
    - Randomized, double-blinded, cross over study of 12 adults with TS in 2002
    - Single dose THC (5, 7.5mg, or 10mg) vs placebo
    - Tic severity rated over a single day, and cross-over to alternate treatment occurred 4 weeks later
    - No significant differences between treatments and clinician-rated measure on the Yale Global Tic Severity Scale (YGTSS)
  - Muller-Vahl KR, Schneider U, Prevedel H, et al (Class III Study):[2]
    - Randomized, double-blinded, placebo-controlled study of 24 adults with TS in 2003
    - THC group (10mg/daily) vs placebo
    - Treatment period was for 6 weeks, with 6 clinical visits for assessment using a self-rating scale (i.e. Tourette Syndrome Symptom List) and examiner rating scale (i.e. Yale Global Tic Severity Scale)
    - Seven patients dropped out or had to be excluded
    - No significant difference between THC and placebo group on the Yale Global Tic Severity Scale (YGTSS)

1.) "Muller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. Pharmacopsychiatry. 2002; 35: 57-61.

2.) "Muller-Vahl KR, Schneider U, Prevedel H, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized. Journal of Clinical Psychiatry. 2003; 64: 459-65.

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## What's On The Horizon?

- Newer $VMAT_2$ Inhibitors:
  - Deutetrabenazine (Austedo)
  - Valbenazine (Ingrezza)
- Ecopipam
- ABX-1431

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## Newer $VMAT_2$ Inhibitors

- Deutetrabenazine (Austedo):
  - Contains deuterium → attenuates metabolism which lengthens half life and reduces peak side effects (i.e. fatigue, somnolence)
  - Dosed twice daily
  - Approved for both tardive dyskinesia in adults and chorea associated with Huntington's Disease
  - Contains same black box warning as Tetrabenazine
  - **ARTISTS 1 phase II/III and ARTISTS 2 phase III studies were negative in pediatric patients with moderate-to-severe tics**
- Valbenazine (Ingrezza):
  - Similar in structure to Tetrabenazine/Deutetrabenazine
  - Dosed once daily
  - Approved for Tardive Dyskinesia
  - Did not worsen underlying mood disorders in tardive trials
  - **T-Forward → phase II study was negative in both adult and pediatric patients with tics**

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## Ecopipam

- Novel $D_1$ receptor blockade → most anti-psychotics are $D_2$ receptor blockade
- Phase 2b study:
  - Multicenter, placebo-controlled, double-blind, randomized, parallel-group study in 149 pediatric subjects (between ages 6-18) with TS
  - Subjects randomized 1:1 to either ecopipam hydrochloride (HCl) or matching placebo for a 12 week treatment period (4 week titration and then 8 week maintenance)
  - Ecopipam had a significant effect from baseline to week 12 on the Yale Global Tic Severity Score—Total Tic Score (YGTSS-TTS), with a mean difference of -3.4 (p=0.011)
  - Mean change from baseline to week 12 on the Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S) score was significant (p=0.001), as was the YGTSS global score (p=0.004).
  - Treatment-related adverse events occurred in 34% of patients on ecopipam and in 21% on placebo.
    - The most common side effects on ecopipam were headache (9.2%), insomnia (5.3%), fatigue (6.6%), somnolence (6.%), and restlessness (5.3%).
    - No weight gain or other metabolic adverse events occurred with ecopipam.
  - Study Drawbacks → small sample size and duration of treatment was short (8 weeks)
- Currently in process for planning Phase 3 study in near future

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## ABX-1431

- Novel MOA → Monoacyglycerol lipase (MGLL) inhibitor
- Inhibition of MGLL by ABX-1431 can modulate endocannabinoid system selectively in areas where circuits are activated
- Phase 2 study:
  - 8-week multicenter, randomized, placebo-controlled, double blinded clinical trial at two dose levels in 49 adults with moderate-to-severe TS followed by optional 4-week open lab safety extension.
  - YGTSS-TTS scores improved in both active treatment and placebo groups
  - The mean (95% CI) treatment difference at week 8 of 3.0 ($P$ = 0.043) favored the placebo group, and thus the study did not meet its primary endpoint
  - Conclusion → No evidence that ABX-1432 has efficacy in suppressing tics



## Summary

- Tourette Syndrome is a complex neuropsychiatric condition
- Tics tend to remain stable and/or improve with age
- Psychiatric co-morbidities tend to persist with age
- Treat the most bothersome symptom first!
- Consider both non-pharmacologic (CBT) and pharmacologic for treatment of bothersome tics
- Also assess and treat co-morbid conditions (Anxiety, Depression, OCD, etc.)



## References


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Questions?