MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Tourette's Disorder and Tics: What's New?
Child and Adolescent Psychopharmacology:

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Disclosures (Last 12 Months)

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

- American Academy of Child and Adolescent Psychiatry: Honoraria
- Emalex: Research Support
- Psychiatry Academy/Harvard Medical School: Honoraria
- NIMH: Research Support
- Partners Healthcare: Honoraria
- Skyland Trail: Advisory Board
- Teva/Nuvelution: Research Support; Scientific Advisory Board
- Tourette Association of America: Co-Chair, Medical Advisory Board; TAA-CDC Partnership

Off-label indications will be discussed

Tourette's Disorder and Tics: Learning Objectives

At the end of this session, the participant should be able to:

1. Review recent updates on **epidemiology, genomics and clinical phenomenology** of tics and Tourette's Disorder

2. Become familiar with **tic spectrum disorders**

3. Evaluate potential **new pharmacological treatments** for Tourette's Disorder

4. Apply updates to **clinical practice**

Prevalence of Tic Disorders: Systematic Review and Meta-analysis

(*Knight, T. et al.; Pediatr Neurol; 2012; Aug;47(2):77-90)*

- **Methods**: MEDLINE and EMBASE databases.
- **Results:** 35 studies (1985-2011) Incidence or prevalence of tic disorders.
- 13 studies: **Children**: **prevalence of TS 0.77%** (95% confidence interval, 0.39-1.51%). **Prevalence is higher in boys**: 1.06% boys were affected (95% confidence interval, 0.54-2.09%) vs. 0.25% girls (95% confidence interval, 0.05-1.20%).
- **Transient tic disorder: most common tic disorder: 2.99%** (95% confidence interval, 1.60-5.61%).
- 2 studies: A**dults: TS prevalence 0.05%** (95% confidence interval, 0.03-0.08%). Prevalence of tic disorders was higher in all studies performed in **special education populations.**
- **Conclusion**: Tic disorders are more common in children than adults, in boys than girls, and in special education populations.

Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies

(Yu, D. et a.l Am J Psych; 2019; 17(63); 217-227)

Objective: GWAS meta-analysis and probed aggregated **TS polygenic risk** to test whether TS and related tic disorders have an underlying shared genetic etiology.

Methods: GWAS meta-analysis, gene-based association, and genetic enrichment analyses were conducted in 4,819 TS cases and 9,488 controls.

Replication of top loci was conducted in an independent population-based sample (706 case subjects, 6,068 control subjects).

Relationships between TS PRS, other tic disorders, ascertainment, and tic severity were examined.

Results: GWAS identified **one significant locus within *FLT3* on chromosome 13, rs2504235**, although this association was not replicated in the population-based sample.

Genetic variants significantly explained 92.4% TS heritability.

TS-associated genes were significantly preferentially expressed in **dorsolateral prefrontal cortex (DLPC).**

Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies

(Yu, D. et al Am J Psych; 2019; 17(63); 217-227)

Results: TS PRS predicted both **TS and tic spectrum disorders** in the population-based sample. TS PRS also significantly correlated **with worst-ever tic severity** and was higher in case subjects with a **family history of tics** than in simplex case subjects.

Conclusions: Modulation of gene expression through cortico-striatal circuits, is implicated as a fundamental mechanism in TS pathogenesis.

At a genetic level, tic disorders represent a **continuous spectrum of disease,** supporting the unification of TS and other tic disorders in future diagnostic schemata.

TS PRSs derived from sufficiently large samples may be useful in the future for predicting **conversion of transient tics to chronic tic disorders, as well as tic persistence and lifetime tic severity.**

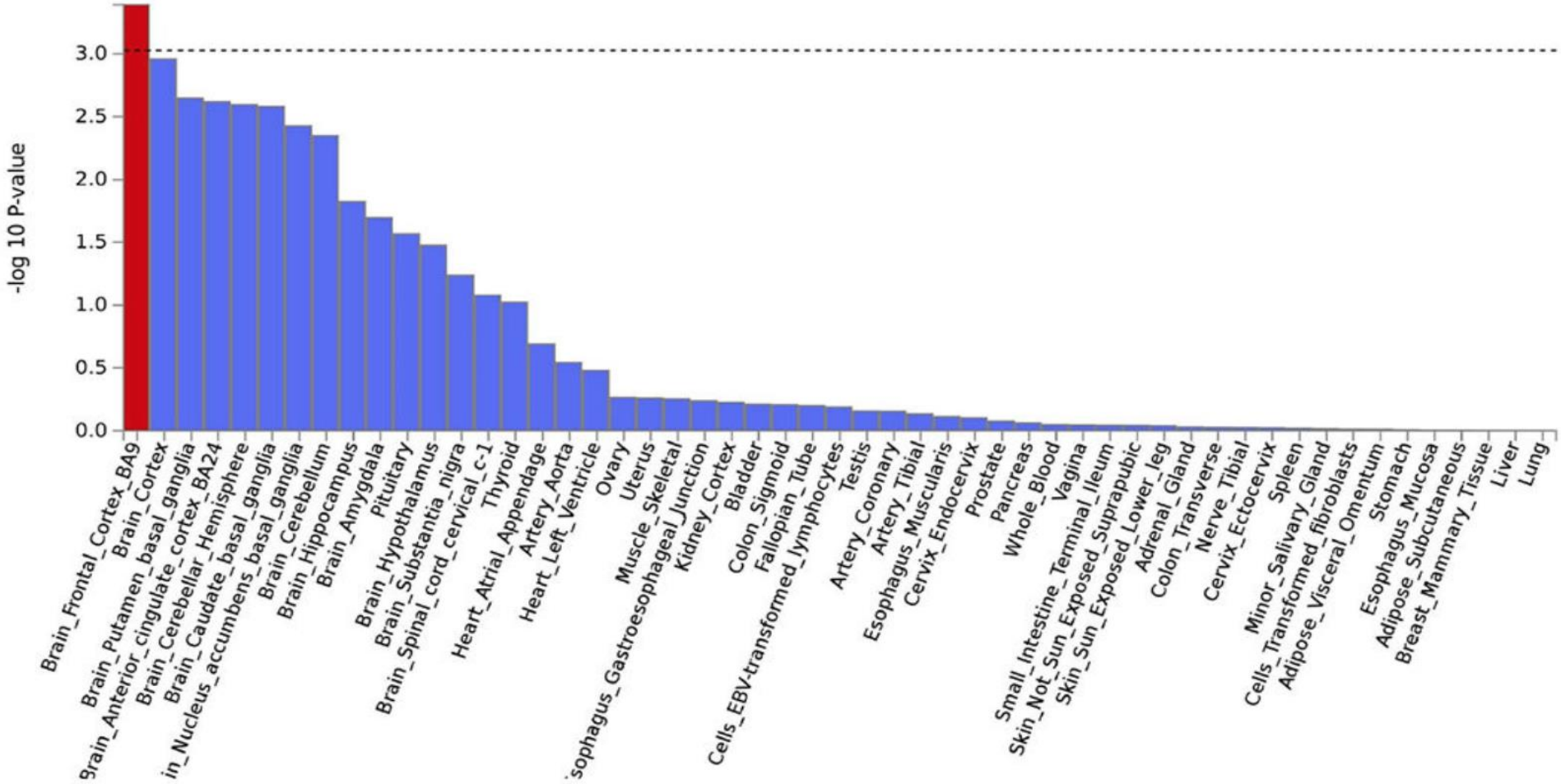
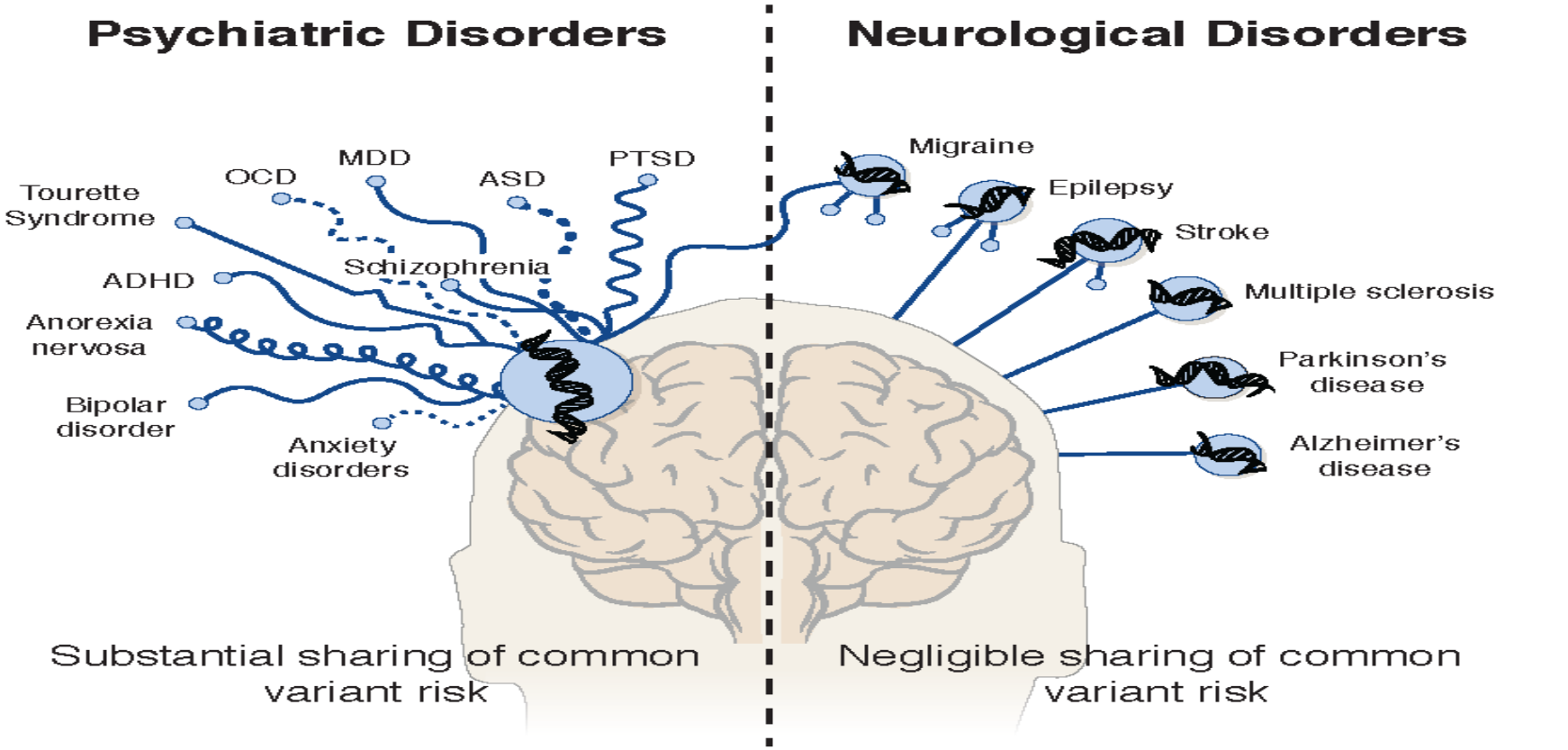


Figure 3.
Gene expression enrichment analysis of genome-wide Tourette syndrome polygenic risk in 53 adult human tissues.

Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. Yu, Am J Psych, 2019

From a genetic standpoint, TS is a psychiatric disorder (C. Mathews, 2018, AACAP)



Anttila V. et al. Analysis of Shared Heritability in Common Disorders of the Brain. **Science.**

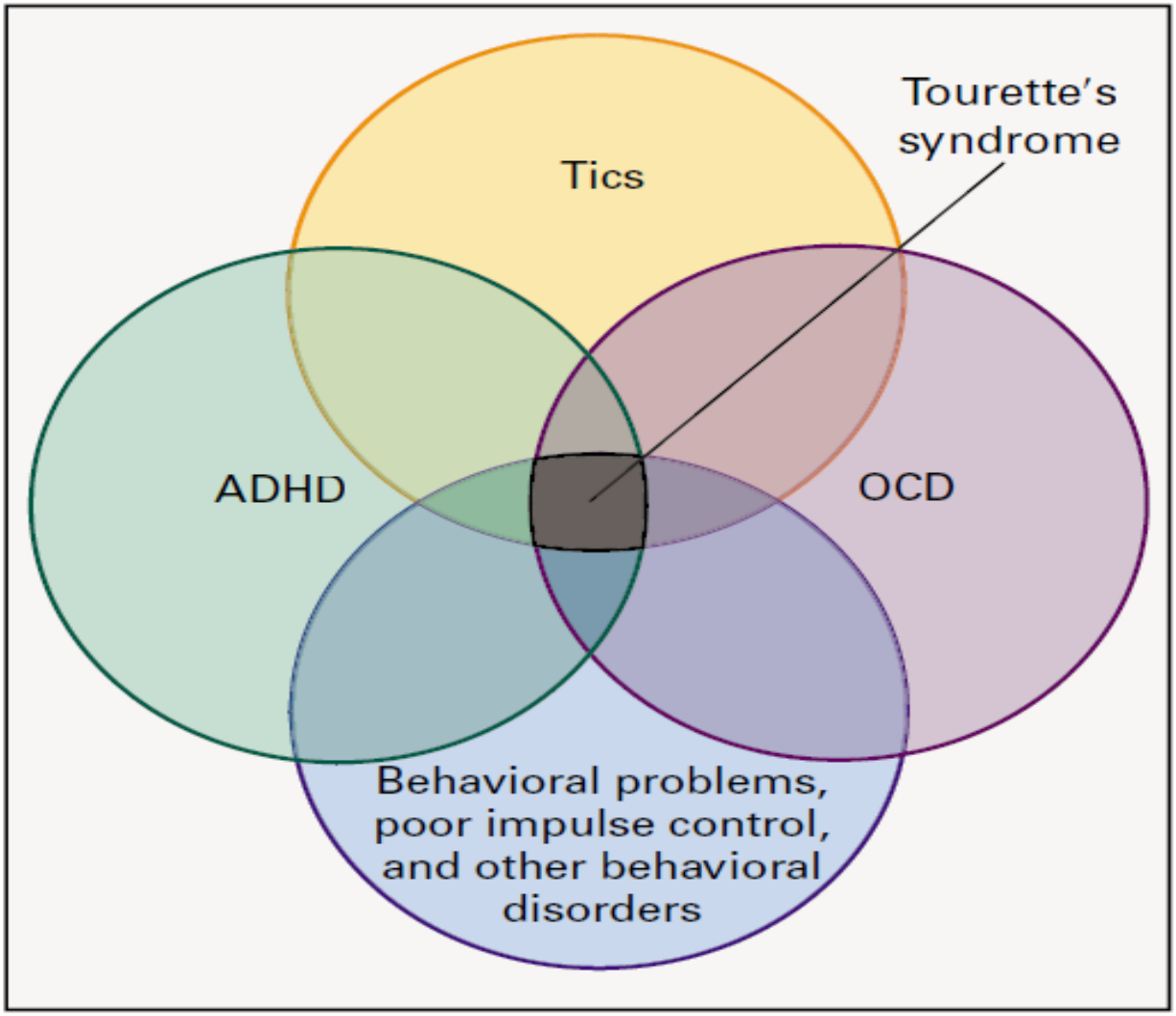


Figure 1. Clinical Hallmarks of Tourette's Syndrome.

The diagnosis is based on the occurrence of tics along with behavioral disorders, including attention-deficit–hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD). Other behavioral disorders include anxiety and mood disorders, learning disorders, sleep disorders, conduct and oppositional behavior, and self-injurious behavior.

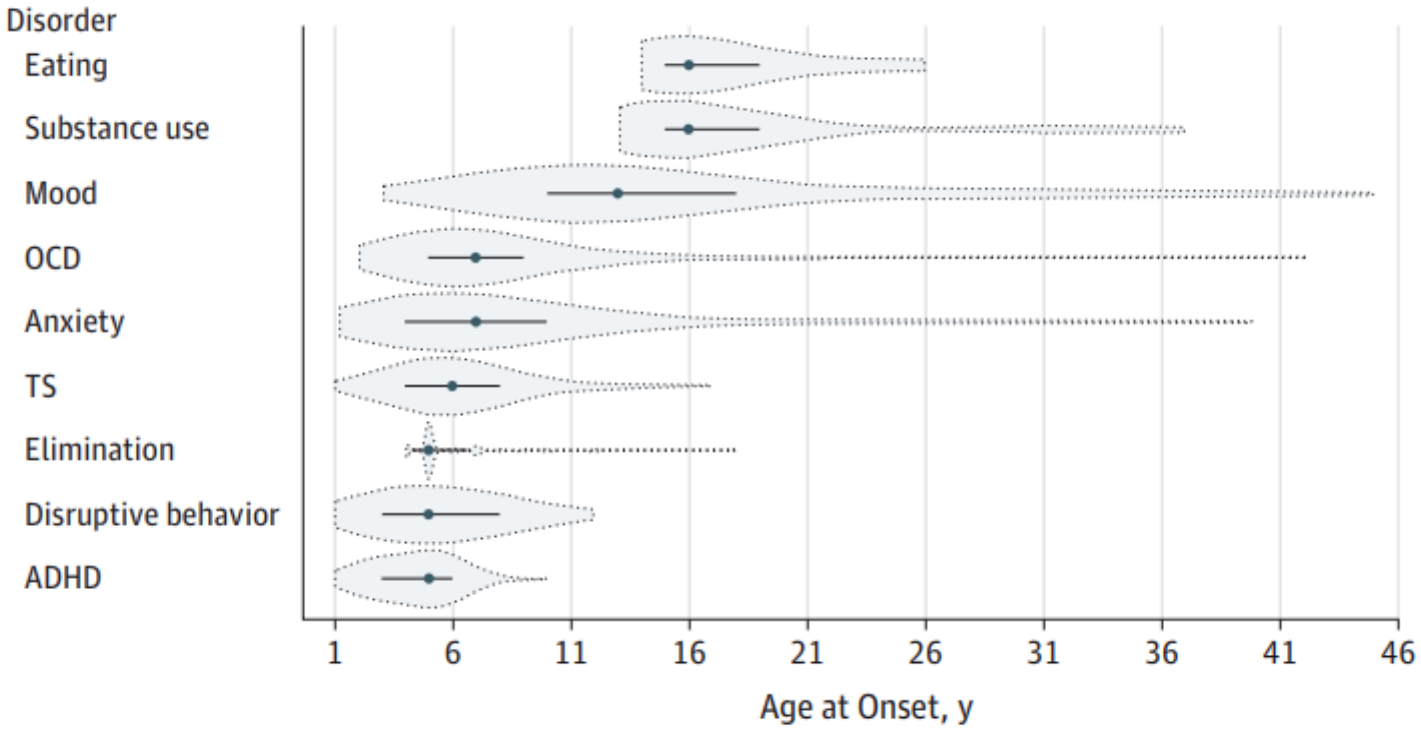
Jankovic J.NEJM; 2001.

Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in TS

(*Hirschtritt, ME et al. (2015). JAMA Psychiatry; April; Volume 72; 4)*

- **DESIGN:** Structured diagnostic interviews with TS (n =1374) and TS-unaffected family members (n=1142).
- **RESULTS**: Lifetime prevalence **of any psychiatric comorbidity among individuals with TS was 85.7%**; **57.7%** had 2 or more psychiatric disorders. 72.1% met criteria for OCD or ADHD. Other disorders: ie mood, anxiety, and disruptive behavior, each occurred in about 30%.
- **Age of greatest risk for onset of most comorbid psychiatric disorders was between 4 and 10 years.**
- TS was associated with increased risk of anxiety (odds ratio [OR], 1.4; P = .04) independent of comorbid OCD and ADHD; high rates of mood disorders (29.8%) may be accounted for by OCD (OR, 3.7; P < .001).
- **CONCLUSION**: Psychiatric comorbidities are common among individuals with TS, and most comorbidities begin early in life.

Figure 2. Ages at Onset for Comorbid Disorders Among Individuals With Tourette Syndrome (TS)



Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in Tourette Syndrome

(Hirschtritt ME et al. JAMA Psychiatry; April 2015; Volume 72; 4)

Tic disorders revisited: Introduction of the Term "Tic spectrum disorders"

(*Muller-Vahl. K. Eur Child Adol Psych 2019; 28; 1129-1135)*

- **Aim**: Compare persistent/chronic motor tic disorder (CMTD) and TS clinical phenomenology.
- **Methods**: Retrospective chart analysis: 1018 adult and child patients with persistent tic disorders. Tic severity was assessed using Shapiro Tourette Syndrome Severity Scale (STSS).
  Results: Groups **did not differ in any clinical or demographic** variables. Patients **only differed in tic severity**: CMTD patients had lower severity, lower prevalence of complex motor tics, and lower comorbidity compared to TS patients.
- **Conclusion**: Both disorders exist on **a symptom severity continuum** with TS a more severe and CMTD a less severe form. Recommendation is for tic spectrum disorders.

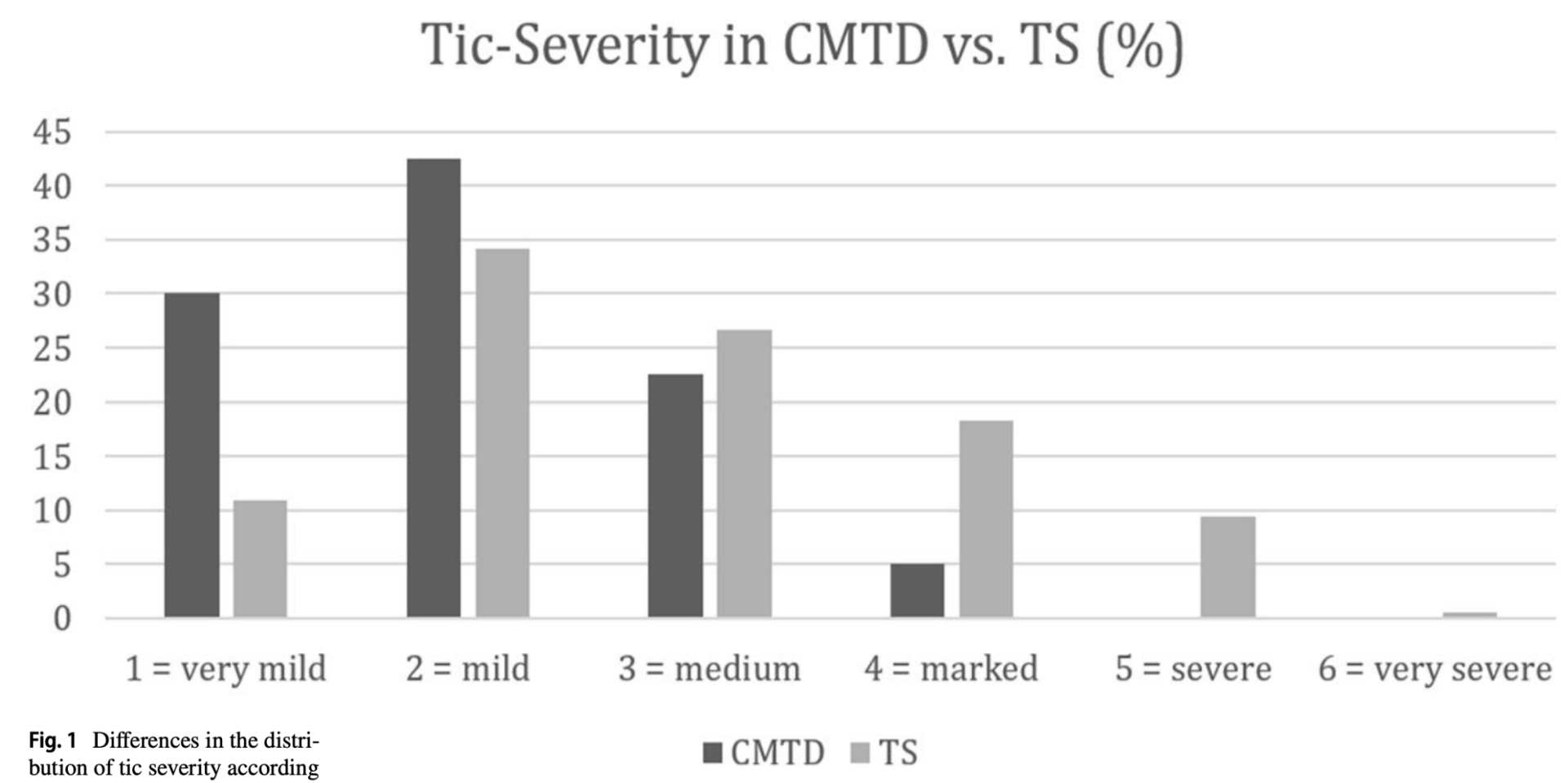


Fig. 1 Differences in the distribution of tic severity according to the GSR of the STSS for the CMTD and TS groups. *STSS-GSR* Shapiro Tourette-Syndrome Severity Scale Global Severity Ratings, *CMTD* chronic motor tic disorder, *TS* Tourette syndrome

Tic disorders revisited: Introduction of the Term "tic spectrum disorders"

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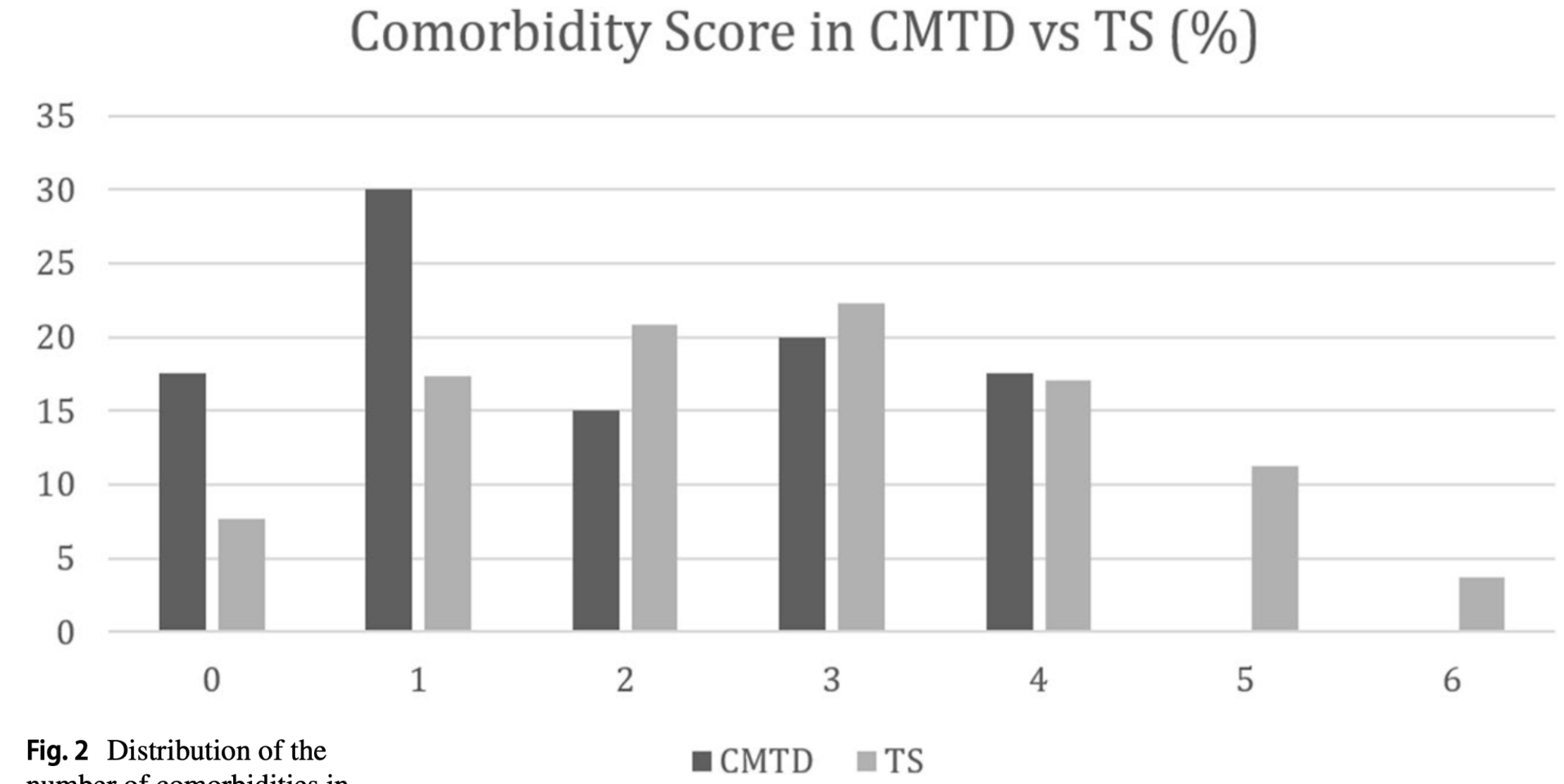

Fig. 2 Distribution of the number of comorbidities in the CMTD and TS groups. Comorbidity score ranges from 0 = none to 6; *CMTD* chronic motor tic disorder, *TS* Tourette syndrome

Tic disorders revisited: Introduction of the Term "tic spectrum disorders"

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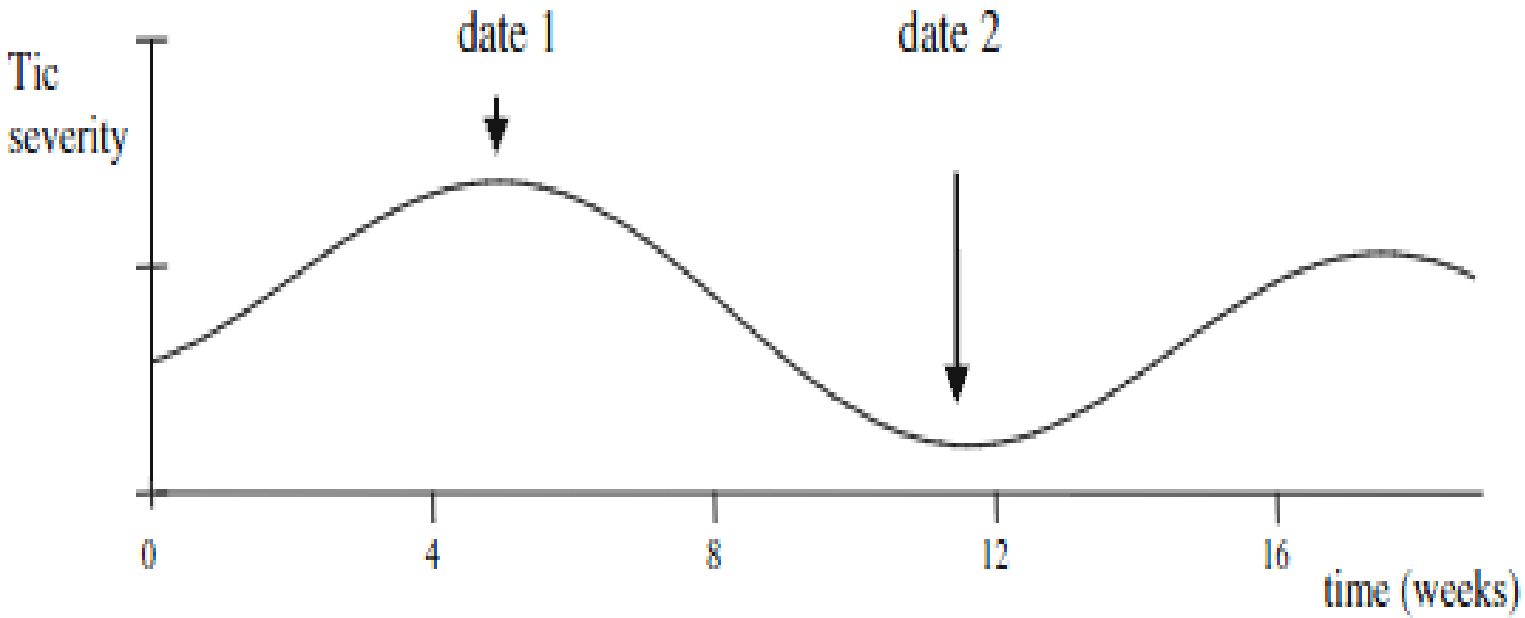


The Challenges of Treating Tics!

Roessner, V. et al. Eur Child Adolesc Psychiatry (2011); 20:173-196

Tics/Tourette's Disorder: Treatment Overview

Only formally approved (labeled) treatments for TD:

- **D2 dopamine antagonists**: neuroleptics
- Haloperidol (Haldol) and pimozide (Orap)
- DA partial agonist/antagonist:
- Aripiprazole (Abilify) (Physicians Desk Reference, 2020)

Haloperidol: effective for tics, superior to placebo

(Shapiro et al. 1968, 1978)

Pimozide: effective for tics, superior to placebo and haloperidol (Shapiro et al. 1983, 1984; Sallee et al. Am J Psych. 1997)

Aripiprazole: effective for tics, superior to placebo (Yoo et al; 2013)

Other interventions

- Psychoeducation; referral to the Tourette Association **<tourette.org>**
- *Habit reversal therapy (Comprehensive Behavioral Intervention for Tics)
- Individual/ family therapy; educational consultation

Daily Doses of Frequently Prescribed Medications

(Egolf, A. Coffey, B. Current Pharmacotherapeutic Approaches to the Treatment of Tourette Syndrome: Drugs Today; 2014 Feb; 50 (2):159-79. doi: 10.1358/dot.2014.50.2.2097801).

Medication	Range of daily dosing
Haloperidol	0.25-4.0mg
Pimozide	0.5-8.0mg
*Risperidone	0.125-3.0mg
Aripiprazole	1.0-15.0mg
*Clonidine	0.025-0.4mg
*Guanfacine	0.25-4.0mg

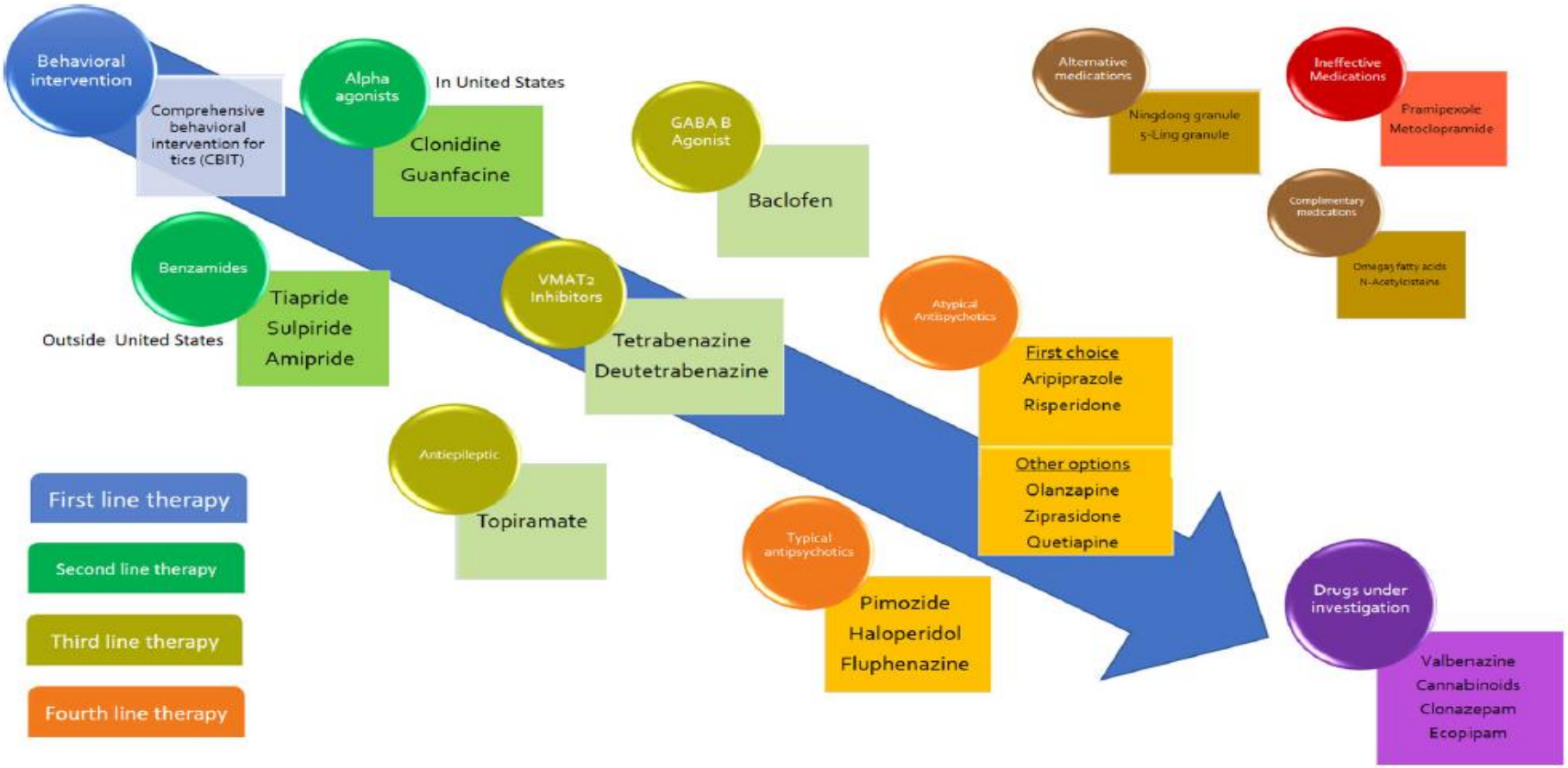


Fig. 1 Tourette syndrome treatment algorithm. Therapies follow a progression that starts with the intervention that has no side effects and concludes with the medications that can have the most severe side effects. Medication selection should follow this progression. Note that there is more than one medication category in each progressive line of therapy, so more than one option is available in each tier. Complimentary medications are available and have evidence for their use as an add-on therapy and not as single agents. Alternative medications are available and have some evidence for their efficacy, but are not widely used and cannot yet be recommended. Drugs under investigation show promise in the treatment of tics, but still need further studies before their use can be recommended. *VMAT2* vesicular monoamine transporter-2

Quezada, J. Current Approaches and New Developments in the Pharmacological Management of Tourette Syndrome. 2018.

Tics, Tourette's Disorder and Moderators or Predictors of Response: What Is Known?

What is known about **moderators and predictors** of treatment response in children and adolescents with persistent tic disorders and Tourette's disorder?

What is known specifically about **response to medication**?

Not much……..!!!

Moderators and Predictors of Response to Behavior Therapy in TS

(Sukhodolsky, D. et al. Neurology 88; March 2017; 1029-1036)

Methods: Data from adult (N=122) and child (N=126) CBT trials comparing CBIT to PST were combined for moderator analyses.

Demographic and clinical characteristics, baseline tic medication and comorbid disorders were tested as possible moderators or predictors.

Results: **Tic medication** significantly moderated response to CBIT vs. PST. Participants showed tic reduction after CBIT regardless of medication, but **only participants on medication showed reduction of tics after PST**. Other demographic and clinical variables did not moderate response.

Across both treatments, **greater tic severity (p=0.005) and positive expectancy** (p=0.01) predicted **greater** tic improvement.

Anxiety disorders (p=0.042) and premonitory urge severity (p=0.005) predicted **lower** tic reduction.

Conclusion: Although those on medication showed improvement on CBIT, the difference in response between CBIT and PST was greater for those **not on medication**. ADHD, OCD or anxiety disorders did not moderate treatment response.

Moderators and Predictors of Response to Behavior Therapy in TS

(Sukhodolsky, D. et al. Neurology 88; March 2017; 1029-1036)

Demographics and clinical characteristics: 6 sites. N=248.

Mean age of participants; 21 years. Males: 67-75%. White, non-Hispanic: 80-85%.

Diagnosis: 89% TS.

Comorbid diagnoses: ADHD 36-42%; OCD 17-20%; Anxiety 28-31%.

Medication: 30-32%. A2As: 14%; antipsychotics; 7-11%.

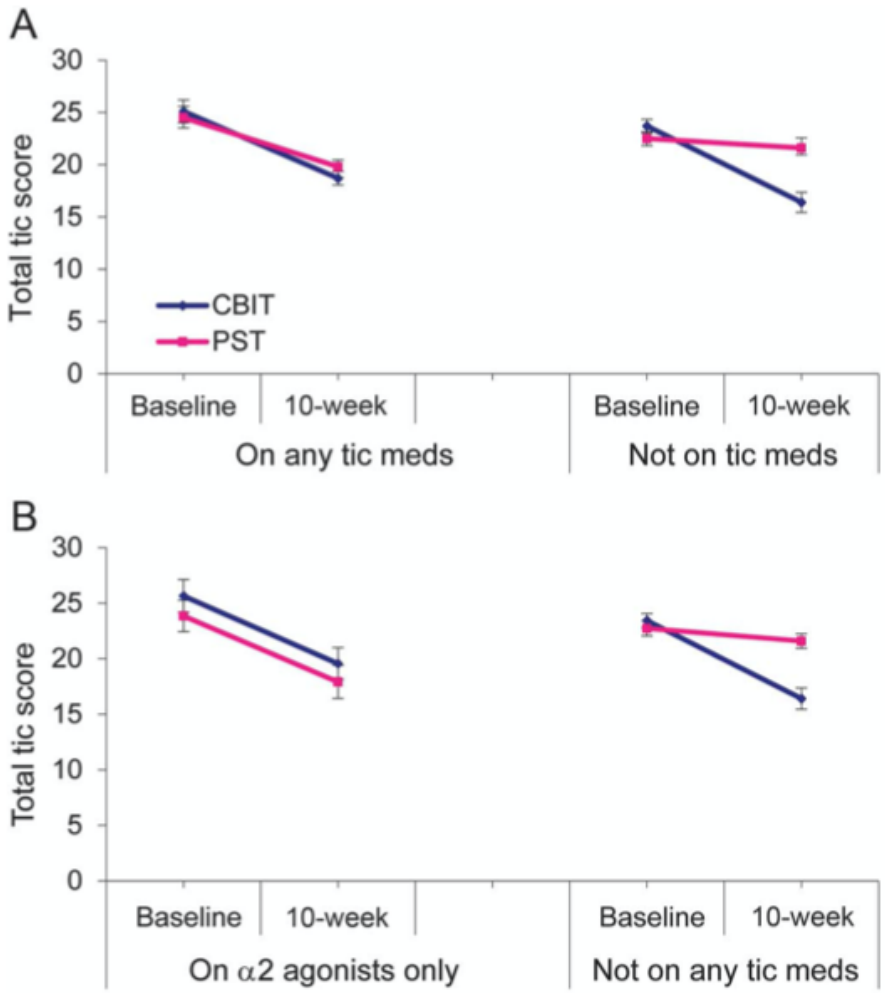
Baseline characteristics as potential moderators of treatment response

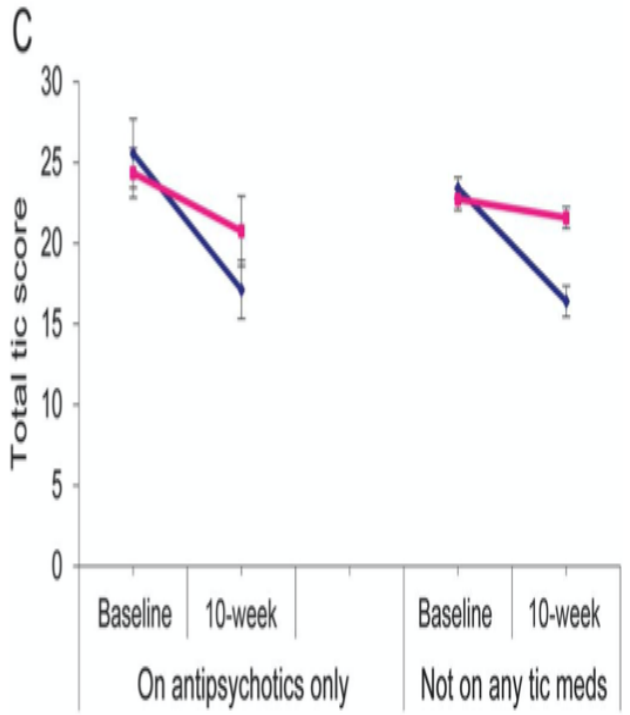
Any tic medication: $p<0.01$

Antipsychotics; A2As; both or no medications (4 groups): $p<0.02$

Not significant: Comorbid disorders, tic phenomenology, demographic and clinical characteristics; family functioning; treatment expectancy

Figure Moderating effects of tic medication on Yale Global Tic Severity Scale (YGTSS) Total Tic score





(A) Change from baseline in participants on any tic-suppressing medication (n = 77) to those not on tic medication. (B, C) Change in YGTSS in participants receiving α2 agonists only (n = 37) and antipsychotic medication only (n = 25). Error bars represent standard errors. CBIT = Comprehensive Behavioral Intervention for Tics; PST = psychoeducation and supportive therapy.

Sukhodolsky, D et al. Moderators and predictors of response to behavior therapy for tics in Tourette syndrome. 2017.

THE NEW YORKER

"I'm not going to shoot the messenger, but I'm also not going to renew his grant."

Canada Day

TUESDAY
JULY 1

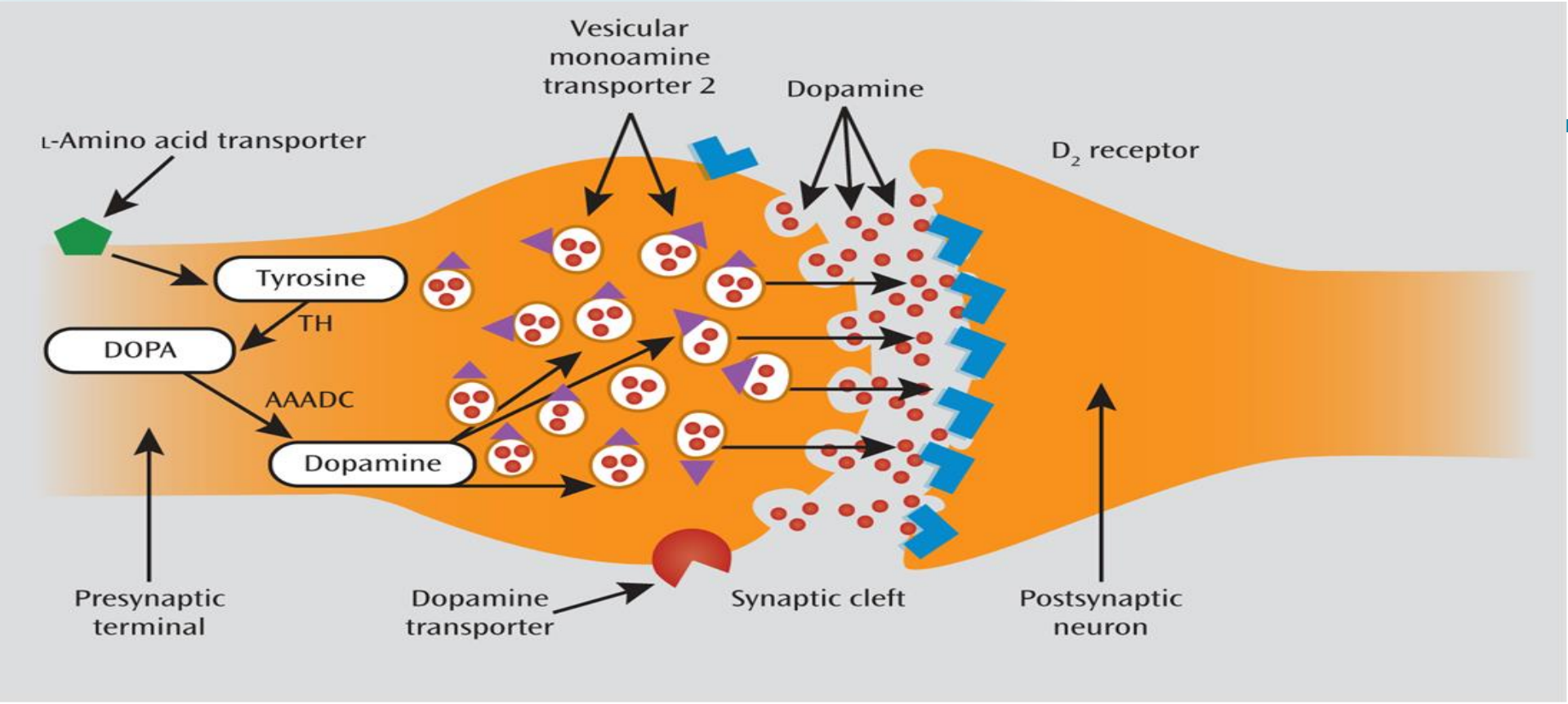
Novel Agents For Tics and Tourette'sDisorder: What's New?

This is an exciting period for investigation of novel treatments for Tourette Syndrome……!!

Several novel compounds have been or are currently under investigation:

- **VMAT2 Inhibitors**
- **D1 Dopamine Receptor Antagonist**
- **Cannabis Related/Cannabinoid Compounds**

Mechanism of VMAT2 Inhibition in Hyperkinetic Movement



- **VMAT-2 inhibition depletes dopamine, reducing involuntary movements**
- **Clinically validated by efficacy of VMAT-2 inhibitors (reserpine, tetrabenazine)**

Fusar-Poli P et al. *Am J Psychiatry* 2012;169:264-272.

Deutetrabenazine in Tics associated with Tourette syndrome

(*Jankovic J, Jimenez-Shahed J, Budman C, Coffey B. et al. Tremor Other Hyperkinet Mov. 2016; 6. doi: 10.7916/D8M32W3H*)

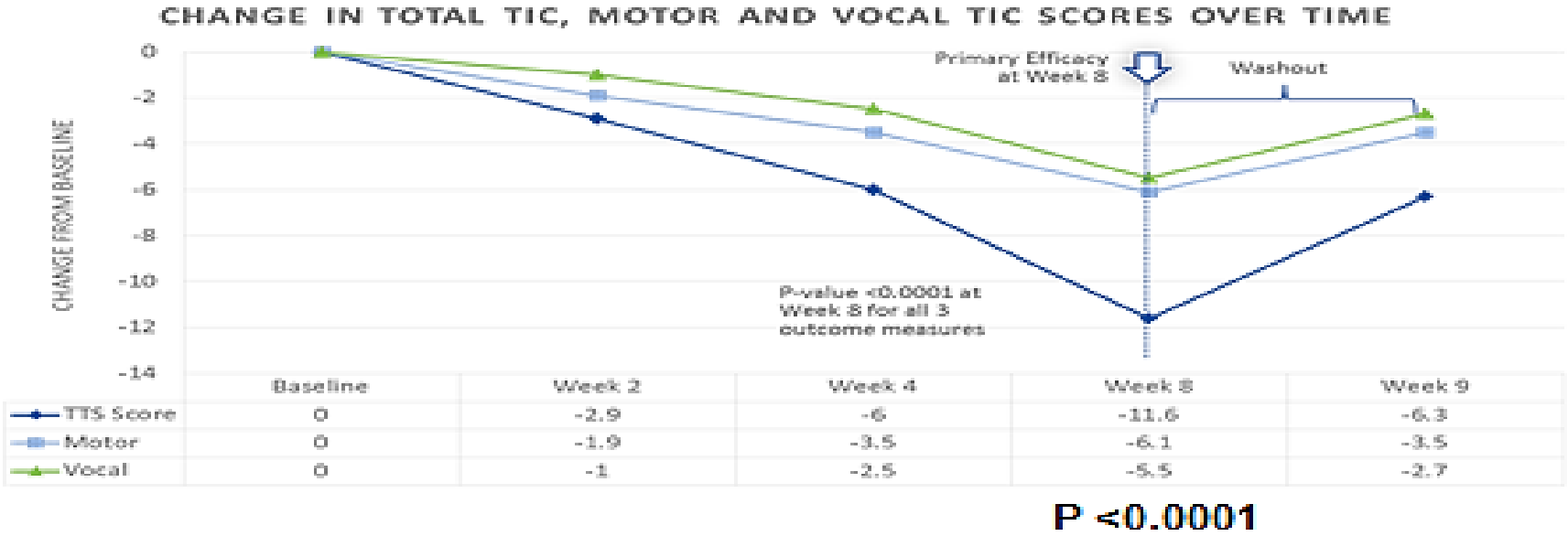
*

- **Background:** SD-809 (deutetrabenazine), **an inhibitor of vesicular monoamine transporter type 2 (VMAT2)**, depletes presynaptic DA and may have utility in treatment of various hyperkinetic movement disorders, including tics
- **Methods:** N=23 adolescent patients (mean age 16 years; range: 12-18) with moderate-to-severe tics associated with TS. In an open-label design, TS patients were titrated over 6 weeks to a dose up to 36 mg/day. Titration phase was followed by a maintenance phase at this dose for 2 weeks. independent evaluators assess tic severity. Mean dose at Week 8 = 32 mg (Range: 18-36 mg)

	Baseline (N=23)	Week 8 (N=20)	Change	P-value*
Mean TTS Score	31.6	20.8	-11.6	<0.0001
Meant TS CGI	4.7	3.6	-1.2	<0.0001

Deutetrabenazine in Tics associated with Tourette syndrome

(Jankovic J, Jimenez-Shahed J, Budman C, Coffey B. et al. Tremor Other Hyperkinet Mov. 2016; 6. doi: 10.7916/D8M32W3H0

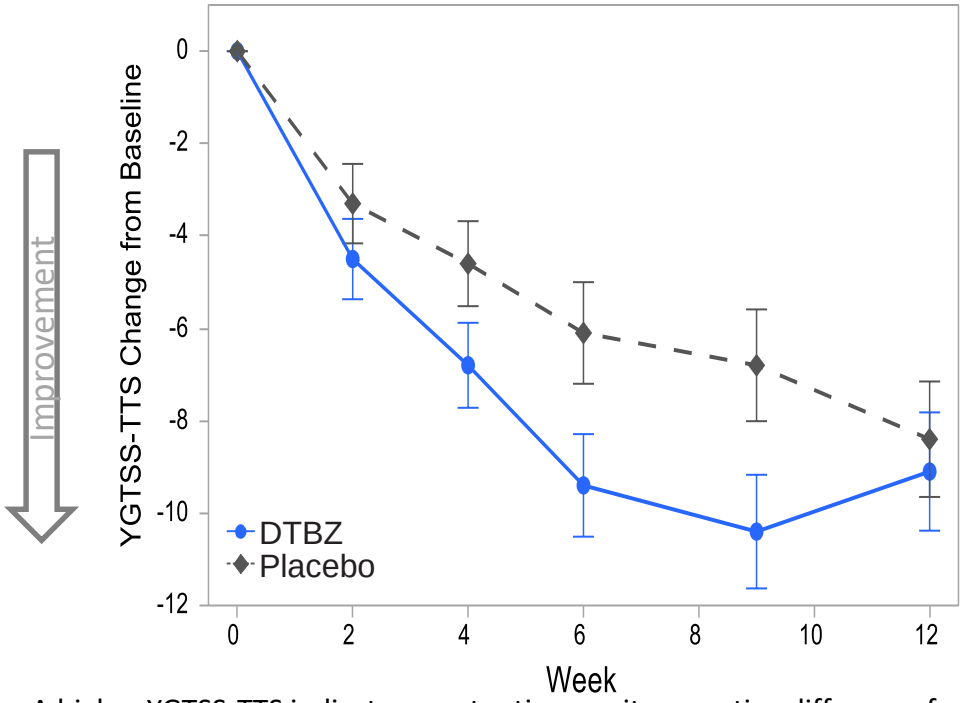


	Baseline	Week 2	Week 4	Week 8	Week 9
TTS Score	0	-2.9	-6	-11.6	-6.3
Motor	0	-1.9	-3.5	-6.1	-3.5
Vocal	0	-1	-2.5	-5.5	-2.7

- **Treatment-Emergent Adverse Events: 15/23 (65.2%)**
- Most common AEs were headache, fatigue, irritability and somnolence
- **AE: None serious or severe**
- Results supported further development of SD-809 for treatment of TS.
- A large Phase II/III global trial has recently been completed.

ARTISTS 1: YGTSS-TTS Change From Baseline by Visit

N=119. Although a favorable trend during titration was noted, the primary endpoint was not met



Change from baseline to Week 12	DTBZ (N=58)	Placebo (N=59)
LS mean (±SE)	-9.1 (±1.28)	-8.4 (±1.25)
LS mean difference vs. placebo (95% CI)	-0.7 (-4.1, 2.8)	
Cohen's d	-0.073	
P value	0.692	

A higher YGTSS-TTS indicates greater tic severity; negative difference favors DTBZ.

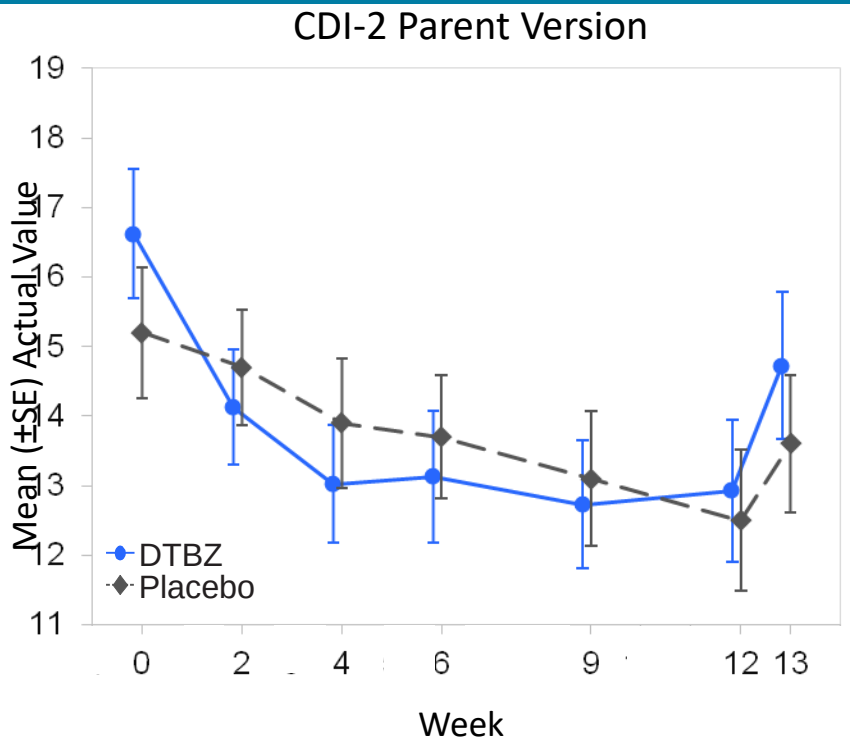
CI, confidence interval; DTBZ, deutetrabenazine; LS, least squares; SE, standard error; TTS, Total Tic Score; YGTSS, Yale Global Tic Severity Scale.

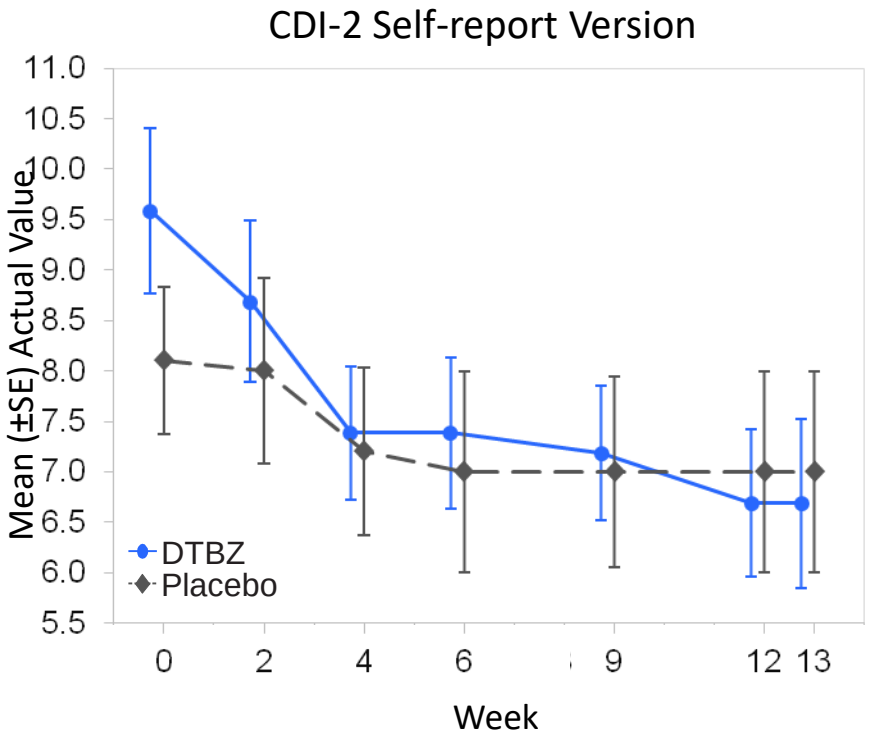
ARTISTS 1: Most Common (>5% Overall) Treatment-emergent Adverse Events

	DTBZ (N=58) n (%)	Placebo (N=59) n (%)	Total (N=117) n (%)
Headache	6 (10.3%)	6 (10.2%)	12 (10.3%)
Fatigue	7 (12.1%)	3 (5.1%)	10 (8.5%)
Nausea	4 (6.9%)	5 (8.5%)	9 (7.7%)
Weight increased	7 (12.1%)	1 (1.7%)	8 (6.8%)
Upper respiratory tract infection	0	7 (11.9%)	7 (6.0%)
Somnolence	5 (8.6%)	1 (1.7%)	6 (5.1%)
Vomiting	3 (5.2%)	3 (5.1%)	6 (5.1%)

DTBZ, deutetrabenazine.

ARTISTS 1: Children's Depression Inventory (Parent and Self-report Versions)

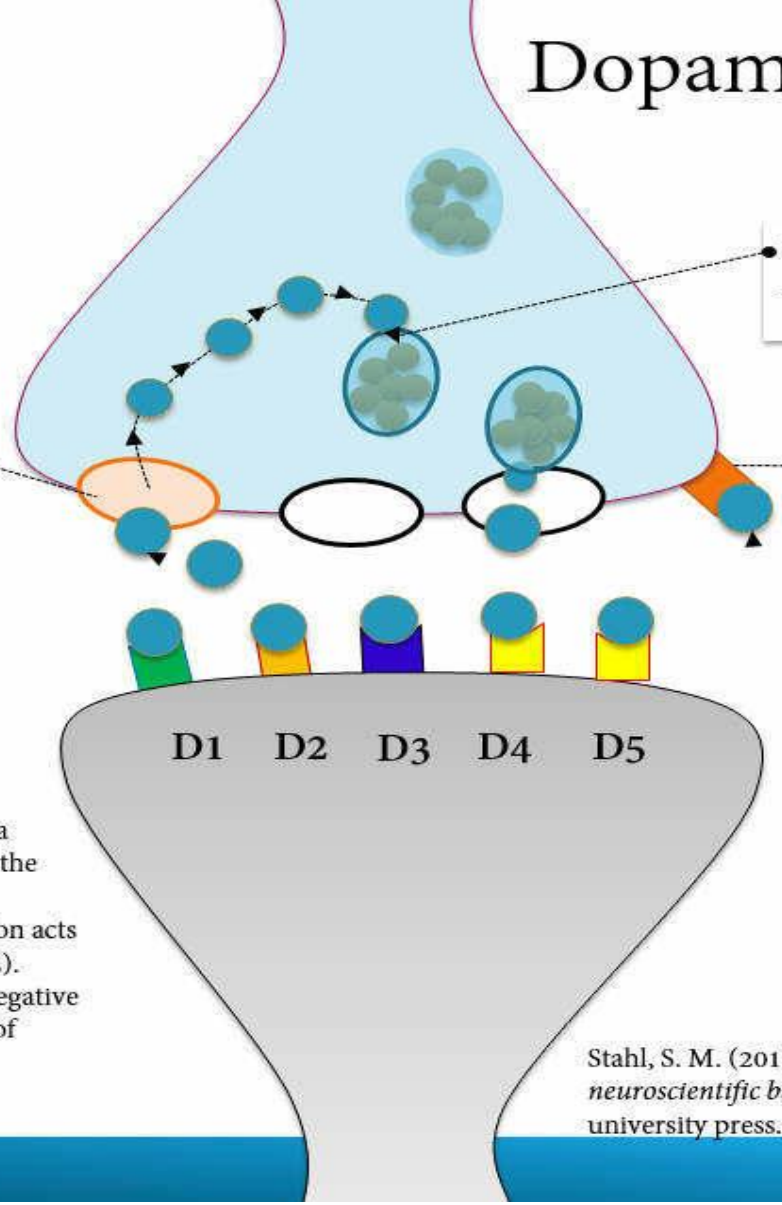




CDI, Children's Depression Inventory; SE, standard error.

psych scene
EXCELLENCE IN PSYCHIATRY

Dopamine receptors



1. Dopamine is stored into synaptic vesicles via the VMAT2 and stored until its release into the synapse
2. Dopamine released during neurotransmission acts on 5 types of postsynaptic receptors (D1-D5).
3. The presynaptic D2 autoreceptor acts as a negative feedback mechanism regulating the release of dopamine from the pre-synaptic neuron.

Stahl, S. M. (2013). *Stahl's essential psychopharmacology: neuroscientific basis and practical applications*. Cambridge university press.

Under Investigation: Ecopipam (Phase 2/3)
Sponsor: Emalex Biosciences

- **Ecopipam**: a potent, **selective antagonist of D_1 receptor** family; a first-in-class drug that selectively blocks the actions of dopamine at its receptor.
- **D_1-receptor super-sensitivity** may be a mechanism for the repetitive behaviors associated with Tourette Syndrome.
- **What is new?** First in class drug; positive results in early phase studies.
  Strengths: May provide new insight into dopamine receptor system involvement in TS and/or OCD.

Ecopipam, a D1 Receptor Antagonist, for Treatment of Tourette Syndrome in Children: A Randomized, Placebo-controlled Crossover Study

(*Gilbert, D. et al. Movement Disorders, Vol. 33, No. 8, 2018; 1272-1280)*

- **Method:** N=40 youth 7- 17 years with TS and YGTSS– total tic score (TTS) of ≥20 were enrolled and randomized to either ecopipam or placebo for 30 days, followed by a 2-week washout and then crossed to the alternative treatment for 30 days
- Primary outcome measure was TTS.
- **Results**: Relative to placebo, reduction in TTS was greater for ecopipam at 16 days (mean difference, -3.7; 95% CI, -6.5 to -0.9; P = 0.011) and 30 days (mean difference, -3.2; 95% CI, -6.1 to -0.3; P = 0.033).
- Adverse events: predominantly mild to moderate, with only 5 rated severe (2 for ecopipam and 3 for placebo).
- **Conclusions**: Ecopipam reduced tics and was well tolerated. This placebo-controlled study of ecopipam supported further clinical trials in children and adolescents with Tourette syndrome.
- A large North American trial is currently under way.

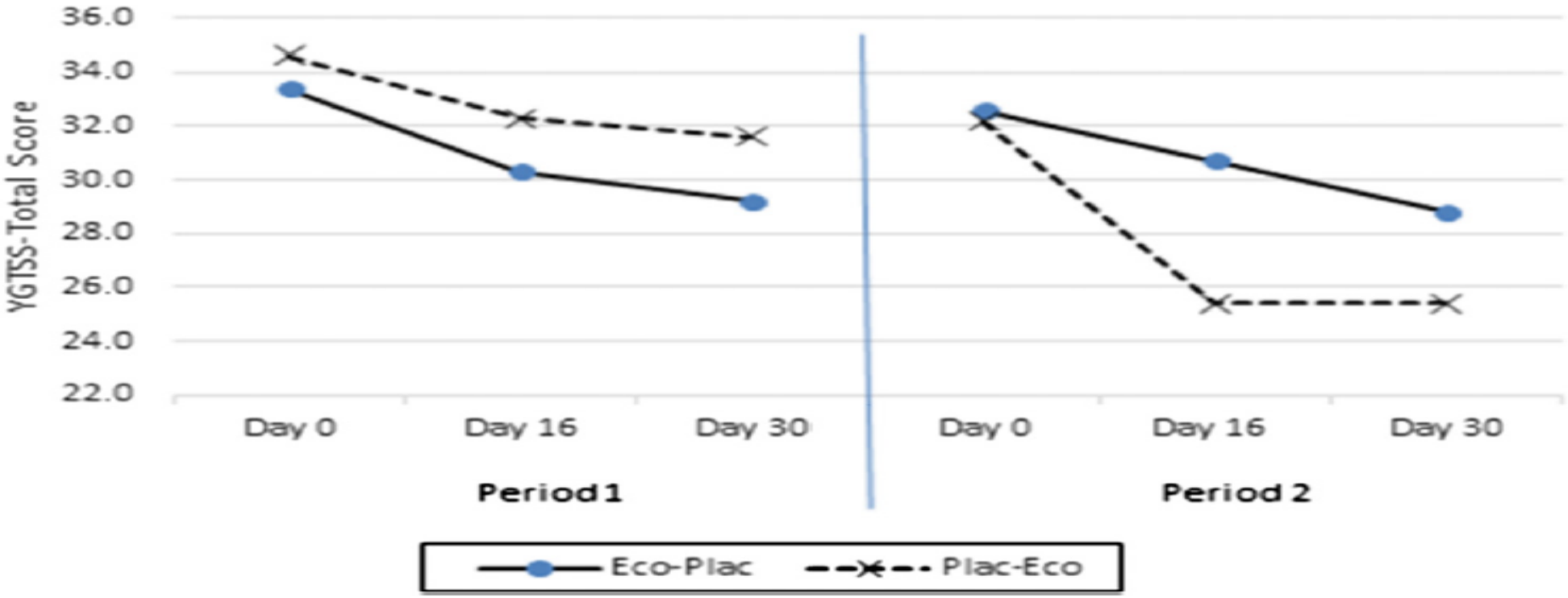


FIG. 2. Treatment effects by period. YGTSS, Yale Global Tic Severity Scale; YGTSS-total score, motor and phonic tic scores, the primary outcome for the trial; Eco-Plac, ecopipam in period 1, followed by placebo in period 2; Plac-Eco, placebo in period 1, followed by ecopipam in period 2. Means are from the raw data. For estimates of mean treatment effects and standard error from intention-to-treat analysis, accounting for period, subject level baseline, period level baseline, see results. [Color figure can be viewed at wileyonlinelibrary.com]

Gilbert, L. D.. Ecopipam, a D1 Receptor Antagonist, for Treatment of Tourette Syndrome in Children: A Randomized, Placebo-controlled Crossover Study. 2018.

Endocannabinoids and Tourette's Disorder

Highest density of **central cannabinoid (CB1**) receptors: frontal cortex, BG, cerebellum, hypothalamus, hippocampus, and nucleus accumbens……all areas implicated in pathophysiology of TD.

Endocannabinoids bind to CB1 receptors and impact: monoamines (DA), and excitatory (glutamate) and inhibitory (GABA) neurotransmitters.

Evidence suggests that **delta THC increases intra-cortical inhibition**; thus THC may reduce central TS disinhibition through modulation of neurotransmitter release, including DA.

Two early RCTs (2002; 2003) by Dr. Kirsten Muller-Vahl in 36 adults with TD reported that dronabinol was more effective than PBO in tic reduction.

Treatment of Gilles de la Tourette Syndrome with Cannabis-Based Medicine: Results from a Retrospective Analysis and Online Survey (Milosev, L. et al Cannabis and Cannabinoid Res; 4 (4). 2019; 265-274).

- **Introduction:** Study was designed to investigate efficacy and safety of Cannabis-based medicine (CBM) in GTS and compare effects of different CBM.
- **Methods**: Retrospective data analysis; all adult patients at clinic who had used CBM for GTS were asked to complete an online survey about CBM treatment.
- **Results:** N=98 patients had used CBM (most often street cannabis followed by nabiximols, dronabinol, medicinal cannabis) for GTS.
- Of 38 patients who could judge: 66% preferred treatment with medicinal cannabis, 18% dronabinol, 11% nabiximols, and 5% street cannabis.
- CBM resulted in subjective improvement of tics (about 60% in 85% of treated cases), comorbidities (55% of treated cases, most often OCB/OCD, ADHD, and sleep disorders), and quality of life (93%).
- Effects of CBM appear to persist in the long term. Adverse events occurred in half of the patients, but they were rated as tolerable.
- **Conclusion**: CBM might be effective and safe in the treatment of tics and comorbidities at least in a subgroup of adult patients with GTS.

Treatment of Gilles de la Tourette Syndrome with Cannabis-Based Medicine: Results from a Retrospective Analysis and Online Survey

(Milosev, L. et al Cannabis and Cannabinoid Res; 4 (4). 2019; 265-274).

Figure 1

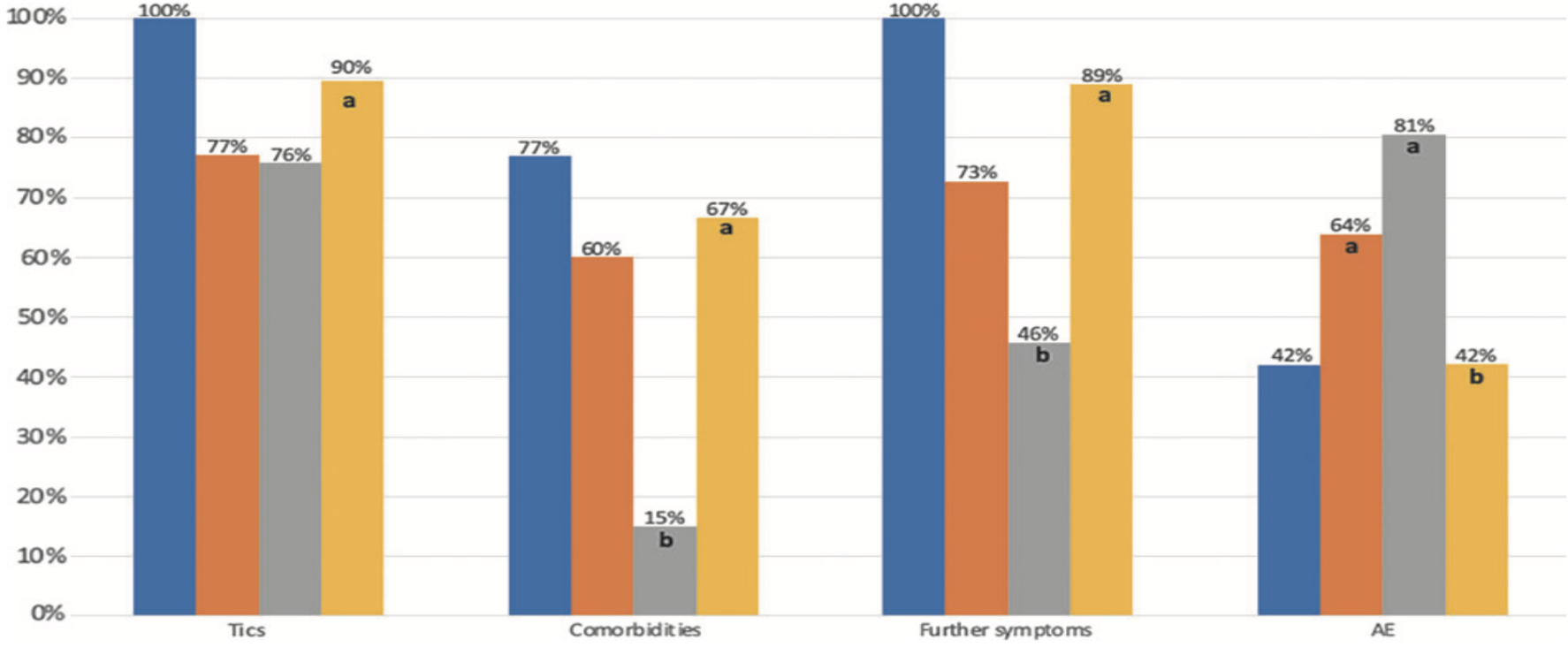


FIG. 1. Part 1 (retrospective analysis): percentages of patients reporting improvement of tics, comorbidities, and further symptoms and confirming AEs depending on the type of CBM. Percentages refer to varying number of patients' statements. Data based on small sample sizes ranging from 86 to 156 statements obtained from 12 to 67 patients. Absolute values are given in Table 5. [a]Significantly higher than expected under the assumption of independence, [b]significantly lower than expected under the assumption of independence. Statistical comparisons were conducted via chi-square test and one-way ANOVA. Contrasts were corrected for multiple comparisons via Bonferroni correction. AEs, adverse events; ANOVA, analysis of variance; CBM, cannabis-based medicine.

Under Investigation

Cannabinoid Medications for Tourette Syndrome

Safety and Efficacy of Cannabis in Tourette Syndrome (Phase 2) Sponsor: University Health Network, Toronto

Design: RCT x-over pilot to compare efficacy and safety of **3 vaporized cannabis products** with different THC and CBD contents, and placebo, in adults with TS.

Subjects randomized to one of 4 treatment arms; each receives **single dose** of one of 3 cannabis products + placebo with order determined by treatment assignment.

Efficacy of a Therapeutic Combination of Dronabinol and PEA for Tourette Syndrome Sponsor: Therapix/Yale

Proof of concept study for dronabinol (delta THC) and PEA (palmitoylethanolamide) for adults with TS.

PEA=endogenous cannabinoid and dietary supplement with anti-inflammatory properties. PEA+ dronabinol may stimulate cannabinoid receptors, inhibit metabolic degradation, and increase THC uptake ("Entourage" Effect)

Combination may reduce dronabinol adverse effects.

Design: 12 week open label trial; N=16 participants, ages 18-60 with treatment resistant TS.

THE NEW YORKER

"I forget. If I have an adverse reaction, do I call my doctor or my lawyer?"

Passover ends/
/Easter (Orthodox)

SATURDAY/SUNDAY
APRIL 11/12

Summary: Tics and Tourette's Disorder: What's New?

Polygenic risk scores (PRS) –predict persistence and severity of tics and Tourette's Disorder.

Persistent motor tics – less severe than Tourette's; similar comorbidities and treatment.

Treatment moderators: Tics reduced after **CBIT** regardless of medication; **medication only** showed reduction of tics after PST.

There are **3 FDA approved medications** in US for treatment of tics and Tourette's Disorder. All are neuroleptics and carry potential for significant adverse effects.

Off label agents (alpha 2 agonists) are recommended as first line pharmacotherapy for better safety and tolerability.

N**ovel agents** under investigation or in the pipeline may hold promise as pharmacotherapy for tics and Tourette's Disorder.

VMAT2 inhibitors: Results of large phase 2B/3 were disappointing, but tolerability was good. Represents improvement over tetrabenazine.

D1 antagonist: multicenter trial underway.

Cannabinoids: under study in Germany, US and Canada in adults.

Tune in next year!!

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