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Tics and Tourette's Disorder
Child and Adolescent Psychopharmacology

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Barbara J. Coffey, MD, MS

Professor and Chair, Department of Psychiatry and Behavioral Sciences

Division Chief, Child and Adolescent Psychiatry

Director, UHealth Tics, OCD and Related Problems Program

University of Miami Miller School of Medicine

Disclosures

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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
- American Physicians Institute: Honorarium
- Duke University: Honorarium
- Emalex: Research Support
- Florida Department of Health: Children's Medical Services: Contract
- Galen Mental Health: Advisory Board
  Mount Sinai West: Honorarium
- New Venture Fund: Research Support
- NIMH/NINDS: Research Support
- Noema: Research Support
- Talkiatry: Honorarium
- Tetra: Research Support
- Tourette Association of America: Scientific Advisory Board; TAA-CDC Partnership
- University of Cincinnati: Honorarium
- University of Texas: Honorarium
- Zynerba: Research Support

Off-label indications will be discussed

Tics and Tourette's Disorder: Learning Objectives

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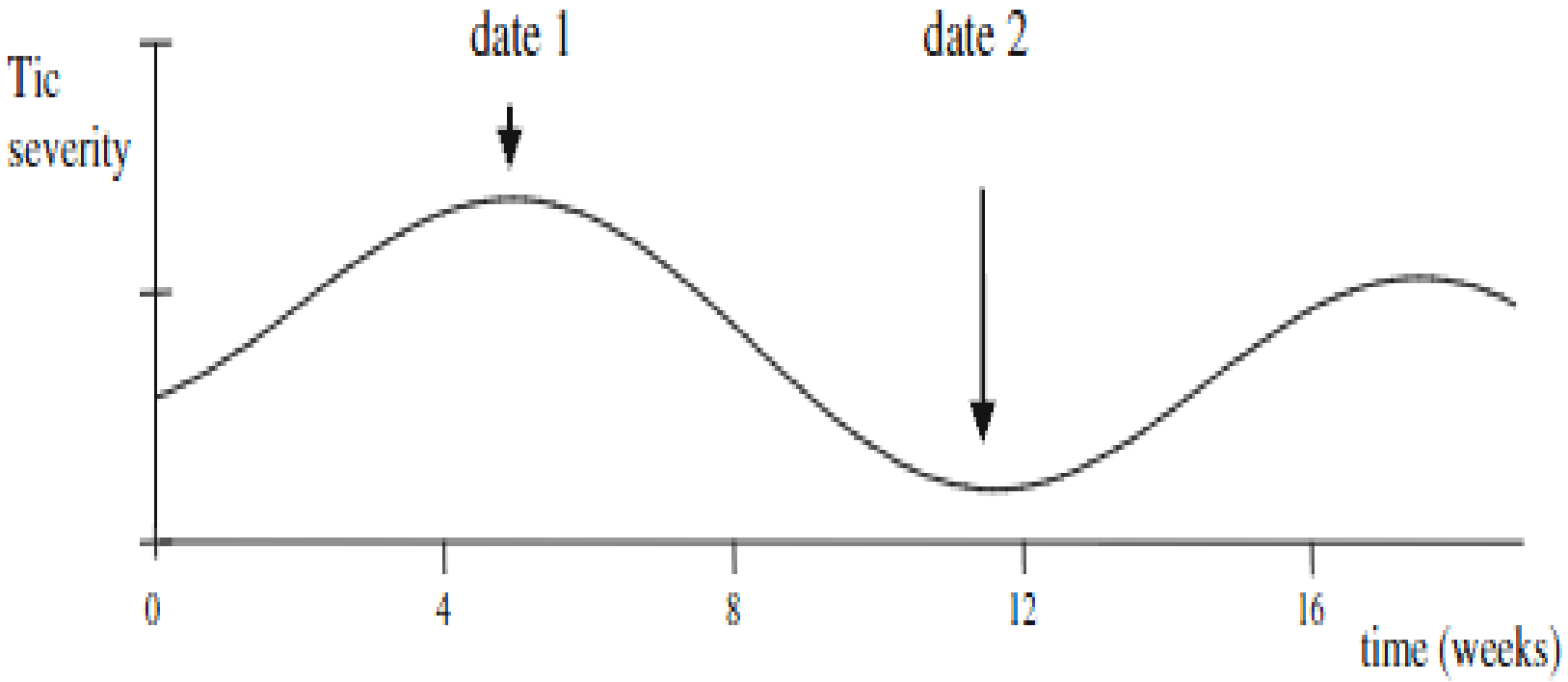
- At the end of this session, the participant should be able to:
  - **Review recent findings** on the underlying genomics, diagnostic and classification data, and psychiatric comorbidity on tics and Tourette's disorder.
  - **Discuss approved and off label treatments** for Tourette's and tic disorders
  - Preview **potential new medications** in the pipeline or under investigation for treatment of tics
  - **Develop an evidence-based treatment** approach for youth with tics and Tourette's Disorder



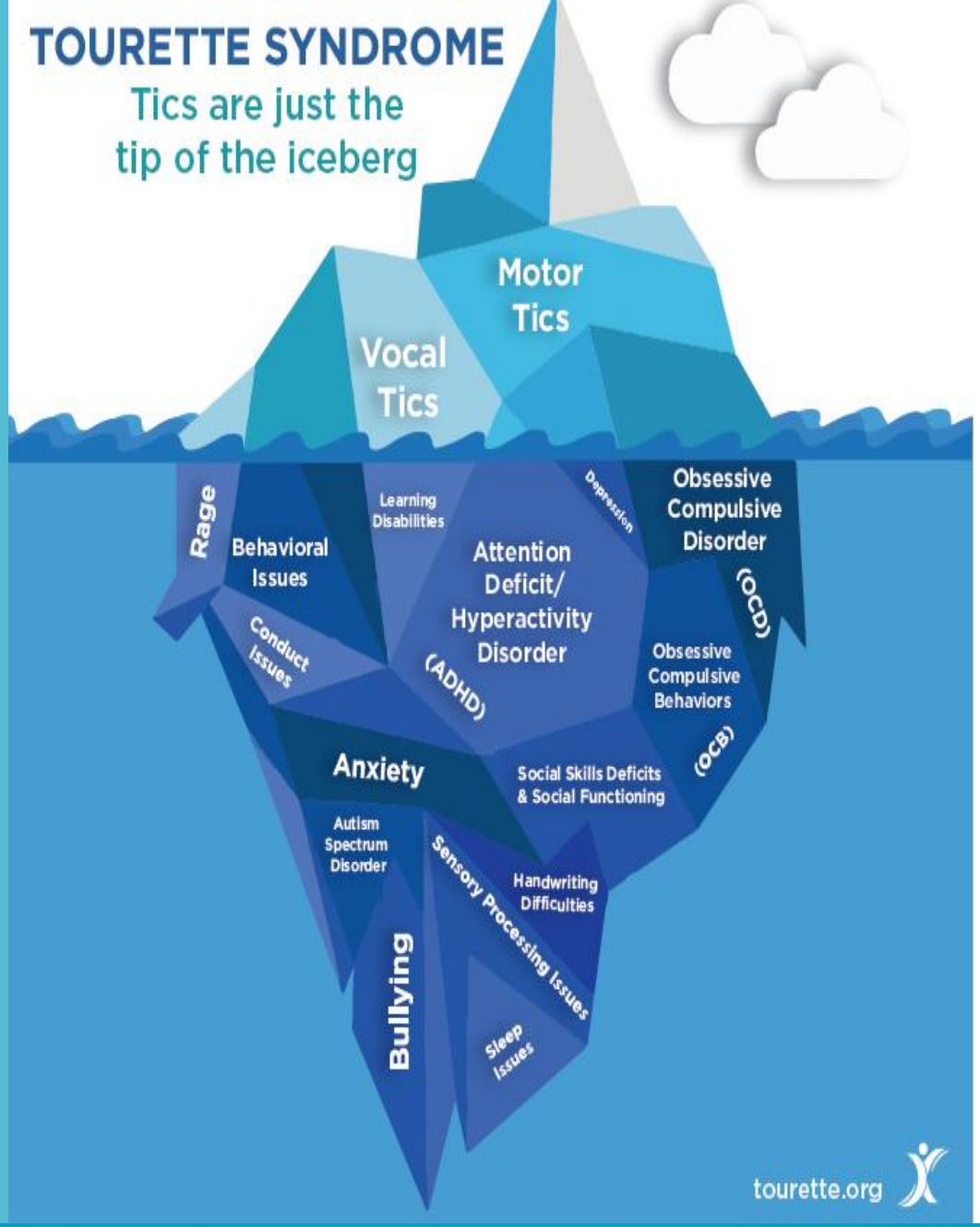
The Challenges of Treating Tics!

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

- **Co-occurring psychiatric symptoms/disorders** are common in Tourette's disorder

- They are significantly more common than in the general population

- These conditions contribute to the **distress, impairment and reduced quality of life that** individuals with Tourette's disorder experience



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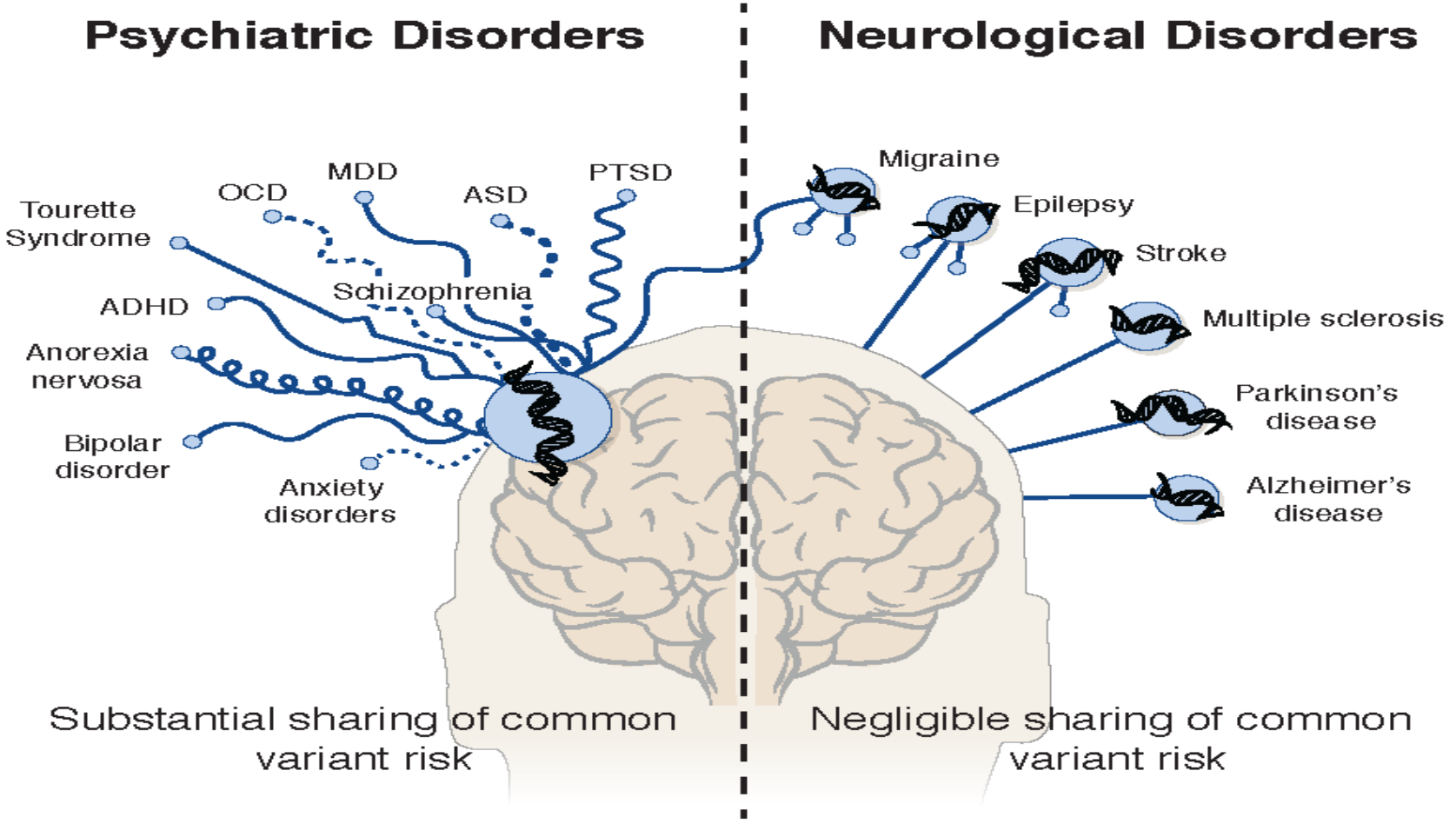
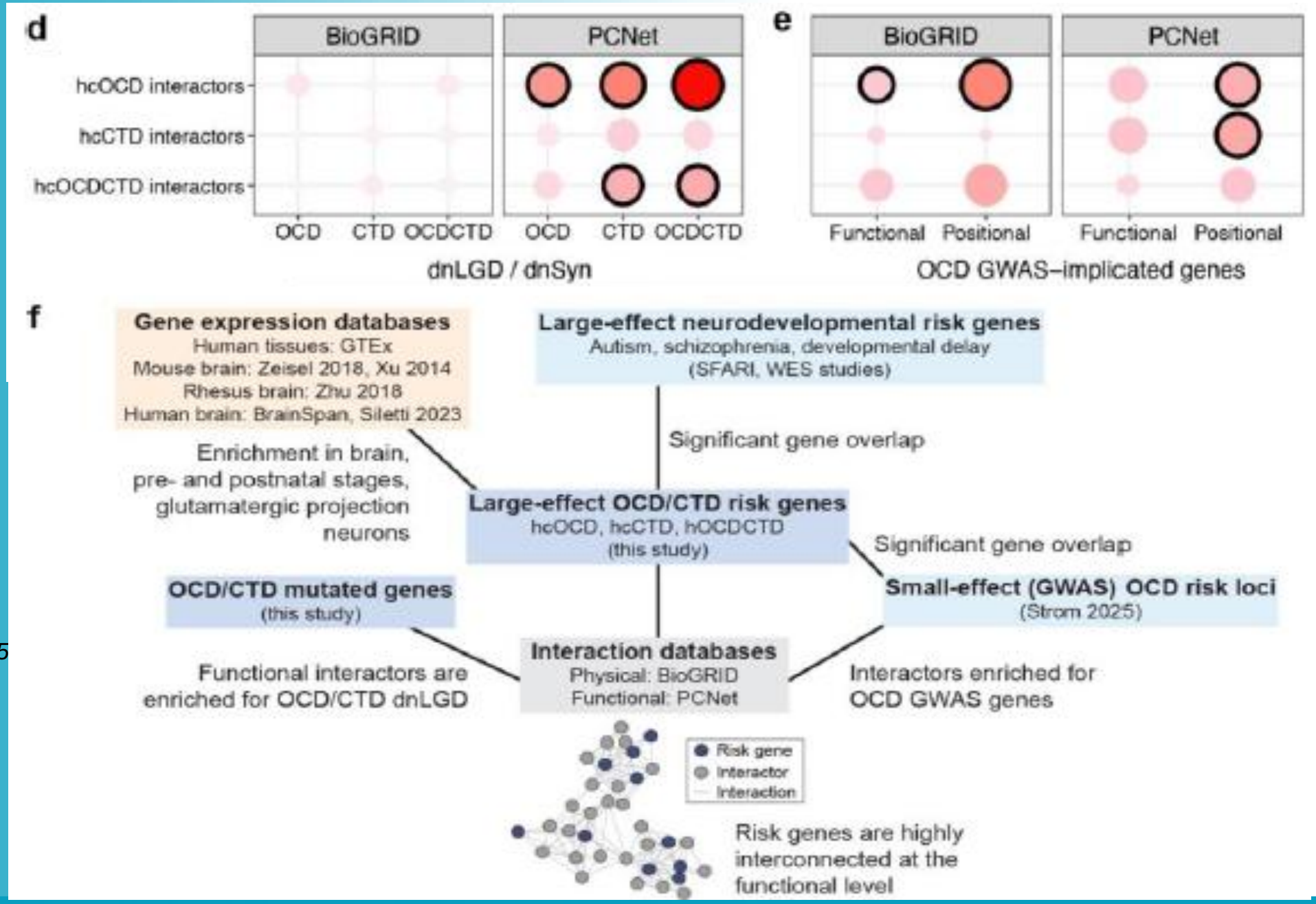
From a genetic standpoint, Tourette's is a psychiatric disorder (*C. Mathews, 2018, AACAP*)



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

Rare coding mutations identify 36 large-effect risk genes in 2 obsessive-compulsive disorder and chronic tic disorders



(*Wang, B., Tran, M. N., Wang, S.,et al. (2025, October 14). (Version 1) [Preprint]. medRxiv. https://doi.org/10.1101/2025.10.10.25337672)*

We've All been Wrong about Provisional Tic Disorder

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(Grossen, S. C., Arbuckle, A. L., Bihun, E. C., et al.. (2024). Comprehensive Psychiatry, 134, Article 152510. https://doi.org/10.1016/j.comppsych.2024.152510)

Background: Provisional Tic Disorder (PTD) is common in childhood. Wisdom among clinicians is that PTD is short-lived and mild, with at most a few tics, and rarely includes complex tics, premonitory phenomena or comorbid illnesses. However, such conclusions come from clinical experience, with biased ascertainment and limited follow-up.

Methods: Prospective study of **89 children with tics starting 0–9 months ago** (median 4 months), fewer than half from clinical sources. **Follow-up at 12 (± 24, 36, 48) months after the first tic**.

Results: At entry, **many children had ADHD (39), anxiety disorder (27), OCD (9) or enuresis (17).** All had at least two current tics, with a mean total since onset of 6.9 motor and 2.0 phonic tics. Forty-one (41) had experienced a complex tic, and 69 could suppress some tics.

Tics were clinically meaningful: **64 had tics severe enough for a clinical trial**, **and 76 families sought medical attention for the tics**. At 12 months, 79 returned, and 78 still had tics. Of these, 29 manifested no tics during history and extended examination, but only via A/V monitoring when the child was alone. Only 12/70 now had plans to see a doctor for tics. **Most who returned at 2–4 years still had tics** known to the child and family, but medical impact was low.

Conclusions: Our results do not contradict previous data but **overturn clinical lore**. The data strongly argue against the longstanding but arbitrary tradition of separating tic disorders into recent-onset versus chronic.

Tics and Tourette's disorder, Self-Harm, Suicidal Thoughts and Behavior: A Mental Health Crisis with Differences Between Boys and Girls

(M. Loreta Lopez; Mary Elizabeth Gorora; Jessica D. Leuchter et al.)

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Objective: To examine sex differences in the frequency and correlates of self-injurious behavior and compulsive self-harm tics compared with suicidal ideation and behavior in youth with tic disorders and Tourette's disorder.

Methods: This cross-sectional study analyzed data from the 2022 TAA online caregiver survey (N = 533 children with tic disorders; 68% male, 32% female). Outcomes included self-injurious behavior, self-harm tics, suicidal ideation and attempts, psychiatric comorbidities, and tic-related pain.

Results: Females had **later tic onset** ($p = .004$), more adolescent diagnoses ($p < .001$), and **higher depression** ($p < .001$) and **tic-related pain** ($p = .006$), while males were diagnosed earlier ($p = .006$) and had **higher ADHD** comorbidity ($p = .018$).
Females were more likely to report **self-injurious ideation ($p = .014$), behavior ($p < .001$), and recent suicidal ideation ($p < .001$). Inadequately treated females had higher rates of lifetime self-injury ($p < .001$) and suicide attempts (prior $p = .022$; recent $p = .004$).**

Conclusions: These findings highlight **important sex differences in psychiatric comorbidities, self-injury, and suicidality** among youth with tic disorders, underscoring the need for early recognition and targeted clinical monitoring, particularly in females. Limitations include caregiver-report bias, cross-sectional design, missing data, and difficulty distinguishing intentional self-harm and suicidal ideation from self-injurious tics or OCD symptoms.

Tics and Tourette's disorder, Self-Harm, Suicidal Thoughts and Behavior: A Mental Health Crisis with Differences Between Boys and Girls

(*M. Loreta Lopez; Mary Elizabeth Gorora; Jessica D. Leuchter et al.)*

Table 1. Demographics

Demographics		Male	Female
		n (%)	n (%)
Race	Native America/Alaskan Native	9 (2.7%)	5 (3.2%)
	Asian	11 (3%)	4 (2.6%)
	Black or African American	3 (1%)	7 (4.5%)
	Native Hawaiian or Pacific Islander	2 (1%)	0 (0.0%)
	Mixed Race	18 (5%)	12 (7.7%)
	White	288 (87%)	128 (82.1%)
	Total	*331 (100%)*	*156 (100.0%)*
Ethnicity	Hispanic or Latino	28 (8%)	13 (8.3%)
Age Group	Under 5 years old	5 (1%)	4 (2.4%)
	5-8 years old	56 (16%)	30 (18.2%)
	9-12 years old	147 (42%)	46 (27.9%)
	13-17 years old	142 (41%)	85 (51.5%)
	Total	*350 (100%)*	*165 (100.0%)*

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Tics and Tourette's disorder, Self-Harm, Suicidal Thoughts and Behavior: A Mental Health Crisis with Differences Between Boys and Girls

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Table 2. Age tics were first noticed and age at diagnosis by sex

Age Group	Male, n (%)	Female, n (%)	Difference in Proportions	z Score	p Value
Age First Noticed	*n=359*	*n=173*			
Under 5 years old	150 (41.8%)	62 (35.8%)	+6.0%	1.32	.185
5–8 years old	156 (43.5%)	67 (38.7%)	+4.8%	1.05	.293
9–12 years old	40 (11.1%)	27 (15.6%)	–4.5%	–1.47	.143
13–17 years old	13 (3.6%)	17 (9.8%)	–6.2%	–2.90	.004
Age at Diagnosis	*n=357*	*n=170*			
Under 5 years old	43 (12.0%)	19 (11.2%)	+0.8%	0.25	.803
5–8 years old	190 (53.2%)	71 (41.8%)	+11.4%	2.74	.006
9–12 years old	102 (28.6%)	40 (23.5%)	+5.1%	1.30	.194
13–17 years old	22 (6.2%)	40 (23.5%)	–17.3%	–6.06	<.001

Tics and Tourette's disorder, Self-Harm, Suicidal Thoughts and Behavior: A Mental Health Crisis with Differences Between Boys and Girls

(M. Loreta Lopez; Mary Elizabeth Gorora; Jessica D. Leuchter et al.)

Table 3. Tic pain frequency and severity by sex

Pain Measure	Male, n (%)	Female, n (%)	Difference in Proportions	z Score	p Value
Pain Frequency	*n=345*	*n=171*			
Never	76 (22.0%)	23 (13.5%)	+8.5%	–2.19	.029
Rarely	64 (18.6%)	31 (18.1%)	+0.5%	–0.12	.905
Sometimes	128 (37.1%)	59 (34.5%)	+2.6%	–0.49	.622
Often	61 (17.7%)	47 (27.5%)	–9.8%	2.73	.006
Always	16 (4.6%)	11 (6.4%)	–1.8%	0.98	.326
Pain Measure	**Male, n (%)**	**Female, n (%)**	**Difference in Proportions**	**z Score**	**p Value**
Pain Severity	*n=333*	*n=167*			
0 (no pain)	82 (24.6%)	22 (13.2%)	+11.4%	–3.20	.001
1	11 (3.3%)	11 (6.6%)	–3.3%	1.54	.123
2	26 (7.8%)	11 (6.6%)	+1.2%	–0.41	.681
3	45 (13.5%)	28 (16.8%)	–3.3%	0.98	.327
4	38 (11.4%)	24 (14.4%)	–3.0%	0.96	.337
5	62 (18.6%)	18 (10.8%)	+7.8%	–2.40	.016
6	22 (6.6%)	19 (11.4%)	–4.8%	1.94	.053
7	25 (7.5%)	19 (11.4%)	–3.9%	1.36	.173
8	17 (5.1%)	13 (7.8%)	–2.7%	1.07	.284
9	5 (1.5%)	2 (1.2%)	+0.3%	–0.27	.786
10 (worst pain)	0 (0.0%)	0 (0.0%)	—	—	—

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Table 4. Self-harm, suicidal ideation, and suicide attempts by sex

Measure	Male, n/N (%)	Female, n/N (%)	Difference in Proportions	z Score	p Value (z score)	Pearson χ^2 (df=1)	p Value (chi square)
Self-harm Ideation (Lifetime)	126/358 (35.2%)	80/173 (46.2%)	−11.0%	−2.45	.014	5.995	.014
Self-harm Attempt (Lifetime)	92/358 (25.7%)	71/172 (41.3%)	−15.6%	−3.64	<.001	13.244	<.001
Suicide Ideation (Recent)	41/356 (11.5%)	39/173 (22.5%)	−11.0%	−3.32	<.001	11.028	<.001
Suicide Ideation (Prior)	61/339 (18.0%)	50/162 (30.9%)	−12.9%	−3.25	.001	10.528	.001
Suicide Attempt (Recent)	24/360 (6.7%)	19/173 (11.0%)	−4.3%	−1.52	.129	2.935	.087
Suicide Attempt (Prior)	32/349 (9.2%)	28/172 (16.3%)	−7.1%	−2.39	.017	5.716	.017

Tics and Tourette's disorder, Self-Harm, Suicidal Thoughts and Behavior: A Mental Health Crisis with Differences Between Boys and Girls

(*M.L Lopez; M.E. Gorora; J. D. Leuchter et al.*)

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Table 5. Treatment inadequacy, self-harm, and suicidal attempt by sex

Measure	Male, n/N (%)	Female, n/N (%)	Difference in Proportions	z Score	p Value (z score)	Pearson χ^2 (df=1)	P Value (chi square)
Self-harm Attempt (Lifetime)	41/137 (29.9%)	41/77 (53.2%)	–23.3%	–3.37	<.001	11.342	<.001
Suicide Attempt (Recent)	6/137 (4.4%)	10/77 (13.0%)	–8.6%	–2.30	.022	5.279	.022
Suicide Attempt (Prior)	11/134 (8.2%)	17/77 (22.1%)	–13.9%	–2.86	.004	8.173	.004

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New TICS Surveillance Study (TAA-CDC Partnership) 2026

Goals:

Describe the public health impact of persistent tic disorders (PTD) and Tourette syndrome (TS) among diverse populations of children, adolescents, and young adults (ages 4-26 years) identified in clinical settings.

Document priority outcomes associated with PTD/TS:

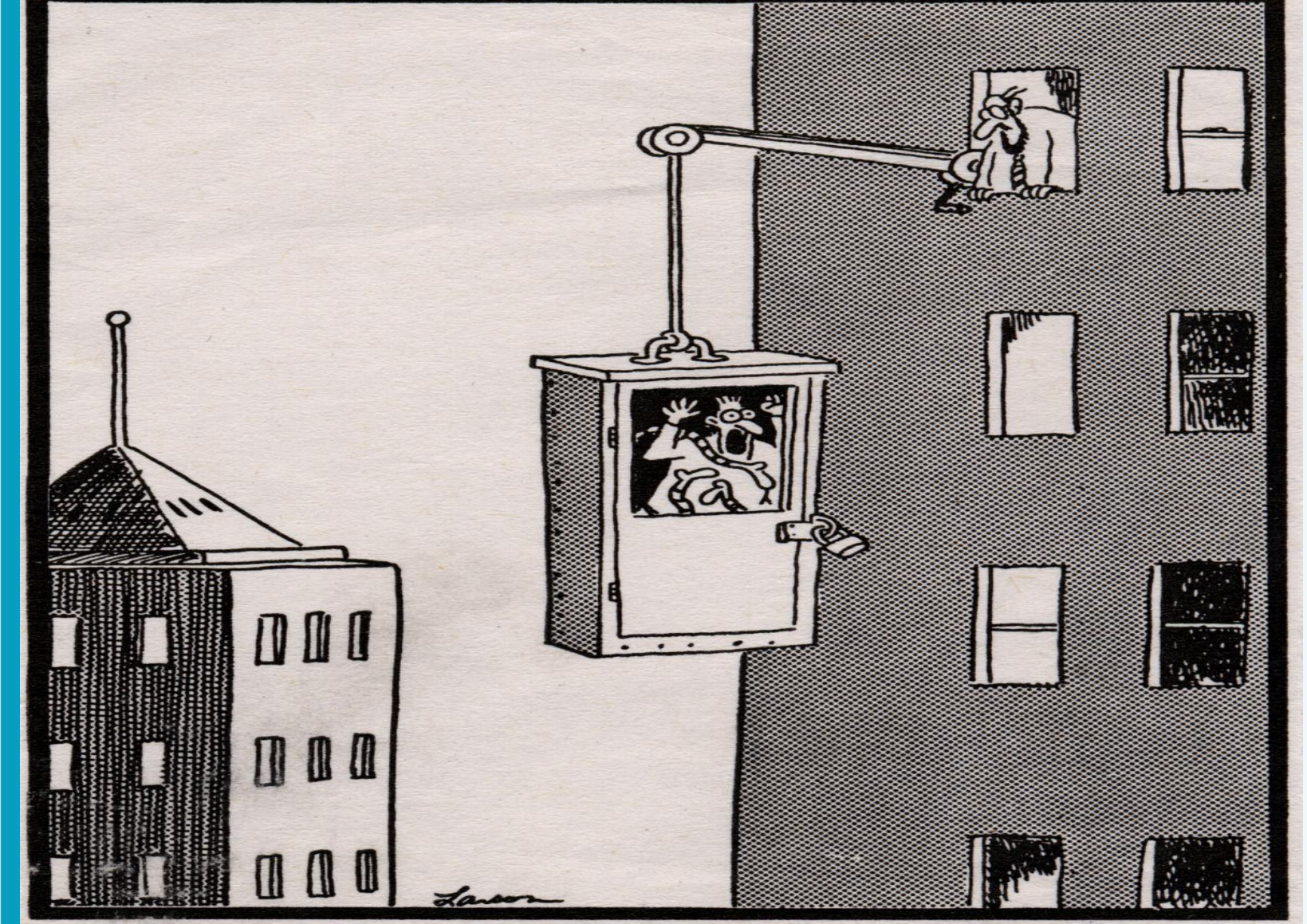
Cost (e.g., education level, employment, healthcare)

****Suicidality**

Transition to adult health care

Prevalence of co-occurring conditions and modifying influences

Improve capacity for collaboration and data sharing
Compliment and supplement existing data on this population



Professor Gallagher and his controversial technique of simultaneously confronting the fear of heights, snakes, and the dark

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Comprehensive Behavioral Intervention for Tics Study (CBIT)

(Piacentini, J. Woods, D. Scahill, L. et al. JAMA; 2010; 303 (19):1929-1937)

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Three phases:

1) Awareness training

2) Competing response training

3) Social support

Two parallel studies compared behavior therapy to supportive therapy (ST)

Child study: 126 children (ages 9-17) with TD/CTD; JAMA; 2010

Adult study: 120 children and adults (ages 16+) with TD/CTD: Arch Gen Psych; 2012

Tics/Tourette's Disorder: Psychopharmacology Treatment Overview 2026

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Only formally approved (labeled) medication for TD:

- **D2 dopamine antagonists: neuroleptics**
- *Haloperidol (Haldol) and pimozide (Orap)*
- ***DA partial agonist/antagonist:***
- *Aripiprazole (Abilify)* (Physicians Desk Reference, 2026)

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 of America
- ***Habit reversal therapy (Comprehensive Behavioral Intervention for Tics)**
- Individual/ family therapy; educational consultation

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Why A Need for New Psychopharmacological Treatments for Tourette's?

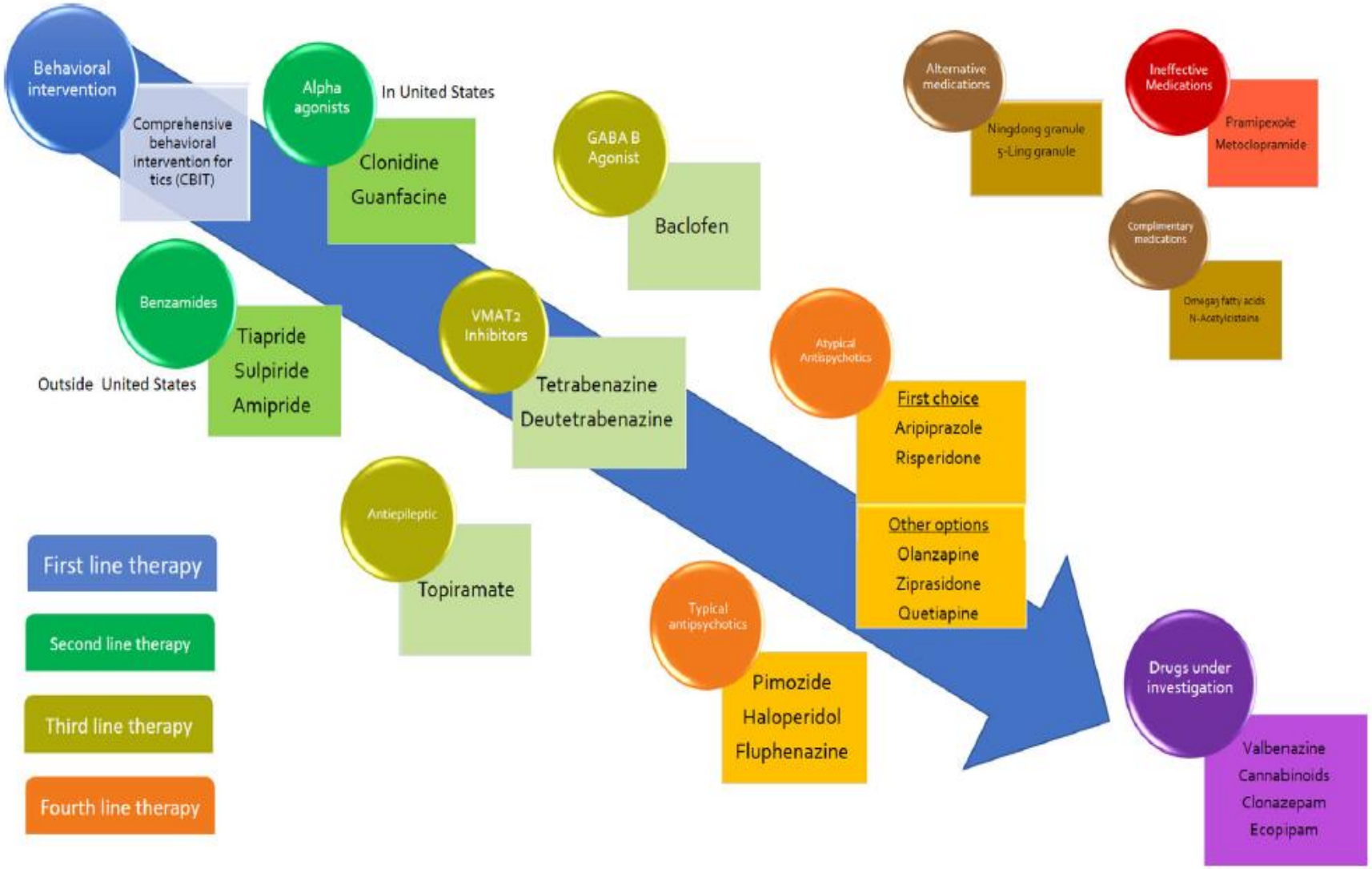
Labeled for indication: **D2 dopamine blockers** have potential major adverse effects.

First generation neuroleptics: **extrapyramidal effects**

Second generation antipsychotics: **metabolic effects**

Off label agents: alpha adrenergic agonists: less effective; response moderated by ADHD. Fatigue, somnolence, and cardiovascular effects.

Comprehensive Behavioral Intervention for Tics (CBIT): lack of trained therapists; duration of treatment



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

Table 1 Currently available treatments in Tourette syndrome

Treatment	AAN recommendation (level of evidence) [4]	Potential side effects	Special considerations
CBIT	B	None	Dependent on patient motivation
Alpha agonist	B	Sedation, bradycardia	May be more effective with comorbid ADHD, requires tapering to avoid rebound hypertension
Topiramate	B	Cognitive language problems, somnolence, weight loss, nephrolithiasis	–
Antipsychotics	C	Weight gain, extrapyramidal side effects, tardive dyskinesia, QTC prolongation	Requires cardiac monitoring, requires tapering to avoid withdrawal dyskinesia, tardive syndrome
VMAT2 inhibitors	–	Drowsiness, depression, parkinsonism	Often costly and not covered by insurance, do not carry a risk of tardive dyskinesia
BoNT	C	Temporary weakness, hypophonia at the site of injection	Useful for bothersome focal tics or phonic tics
Cannabis-based medications	C	Dizziness, dry mouth, fatigue, impaired driving ability	Not recommended for children. Adult use only and where legislation allows
DBS	B	Hardware infection/removal, worsening of psychiatric conditions	For refractory cases, all patients should be screened by a multidisciplinary board before implantation

CBIT = comprehensive behavioral intervention in tics; VMAT2 = vesicular monamine transporter 2; BoNT = botulinum neurotoxin; DBS = deep brain stimulation

Daily Doses of Frequently Prescribed Medications: Practical Approach

(*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

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

TUESDAY
JULY 1

Canada Day

psych scene
EXCELLENCE IN PSYCHIATRY

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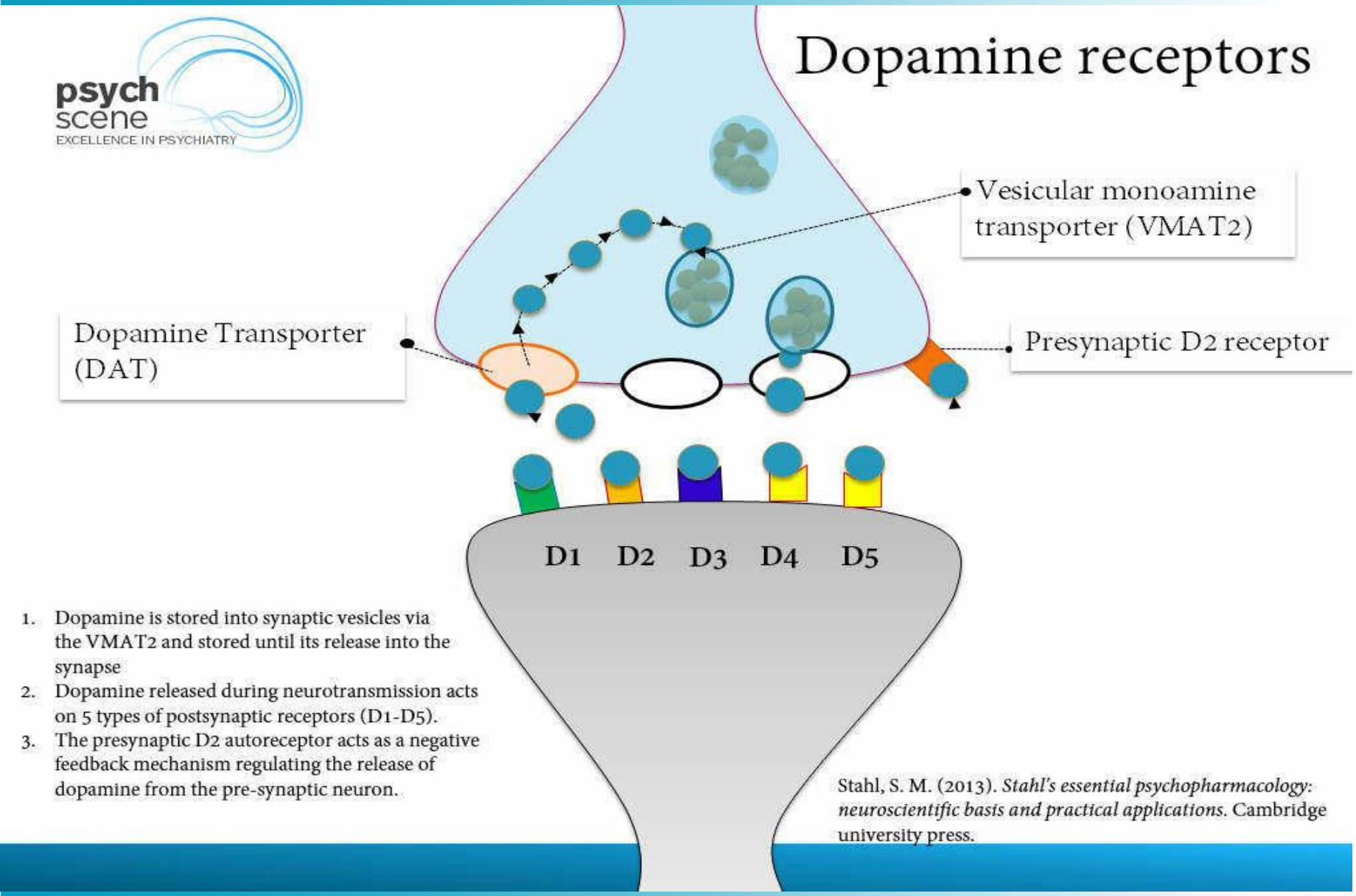
Dopamine receptors



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.

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)*

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- **Method:** N=40, age 7 to 17, with TS and YGTSS– total tic score (TTS) ≥20 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 -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 study supported further clinical trials in children and adolescents with TS.

TABLE 1. Demographics and baseline characteristics

Descriptive characteristics of the population	n = 40
Age (years), mean ± SD	12.9 ± 2.8)
Sex, n (%)	
Male	32 (80)
Female	8 (20)
Race/ethnicity, n (%)	
White	33 (82.5)
African American	3 (7.5)
Biracial	2 (5)
Asian	1 (2.5)
Hispanic	1 (2.5)
Comorbidity, n (%)	
ADHD	26 (65)
OCD	17 (43)

ADHD, attention deficit/hyperactivity disorder; OCD, obsessive compulsive disorder; SD, standard deviation.

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

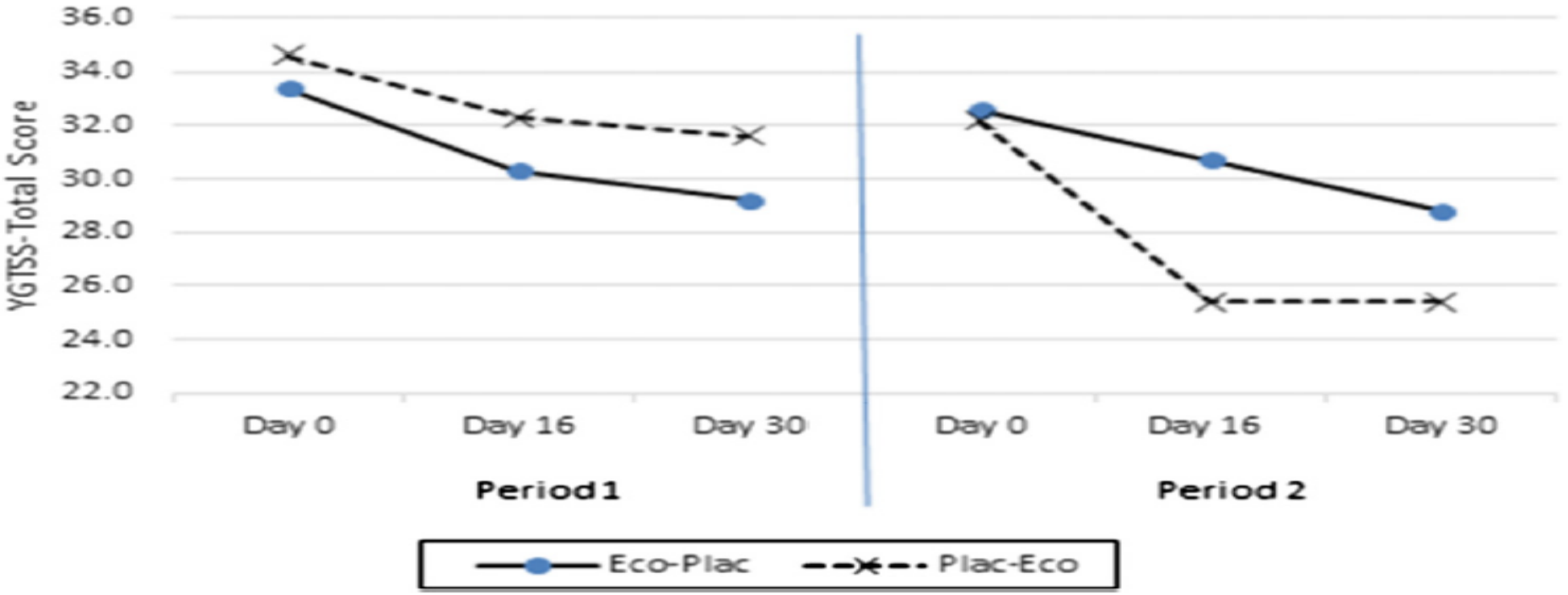

FIG. 2. Treatment effects by period. YGTSS, Yale Global Tic Severity Scale; YGTSS-total score, motor and phonic tic scores, the primary outcome for the trial; Eco-Plac, ecopipam in period 1, followed by placebo in period 2; Plac-Eco, placebo in period 1, followed by ecopipam in period 2. Means are from 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.

Ecopipam for Tourette Syndrome: A Randomized Trial

(Gilbert DL, Dubow JS, Cunniff TM, et al, Pediatrics. 2023;151(2): e2022059574. doi:10.1542/peds.2022-059574)

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TABLE 1 Baseline Characteristics (Safety Population)

	Placebo (n = 77)	Ecopipam (n = 76)
Age, years, mean ± SD	12.6 ± 2.6	12.6 ± 2.8
6 to 11 y, n (%)	26 (33.8)	27 (35.5)
12 to <18 y, n (%)	51 (66.2)	49 (64.5)
Male, n (%)	53 (68.8)	59 (77.6)
Race, n (%)		
White	72 (93.5)	66 (86.8)
Black/African American	3 (3.9)	6 (7.9)
Asian	2 (2.6)	1 (1.3)
Other	0	3 (4.0)
Wt, kg, mean ± SD	56.1 ± 21.5	58.2 ± 25.8
North America, n (%)	60 (77.9)	64 (84.2)
Europe, n (%)	17 (22.1)	12 (15.8)
Medical history, n (%)		
Attention-deficit/hyperactivity disorder	30 (39.0)	39 (51.3)
Depression	5 (6.5)	4 (5.3)
Obsessive-compulsive disorder	11 (14.3)	14 (19.4)
Medication use, n (%)		
Antipsychotics (previous)	20 (26.0)	20 (26.3)
Antidepressants (concomitant)	19 (24.7)	23 (30.1)
Baseline tic scores mean ± SD		
YGTSS-TTS	34.7 ± 5.6	34.6 ± 6.3
YGTSS-GS	66.4 ± 11.6	68.0 ± 13.0
CGI-TS	4.8 ± 0.68	4.8 ± 0.94

SD, standard deviation.

Ecopipam for Tourette Syndrome: A Randomized Trial

(Gilbert DL, Dubow JS, Cunniff TM, et al, Pediatrics. 2023;151(2): e2022059574. doi:10.1542/peds.2022-059574)

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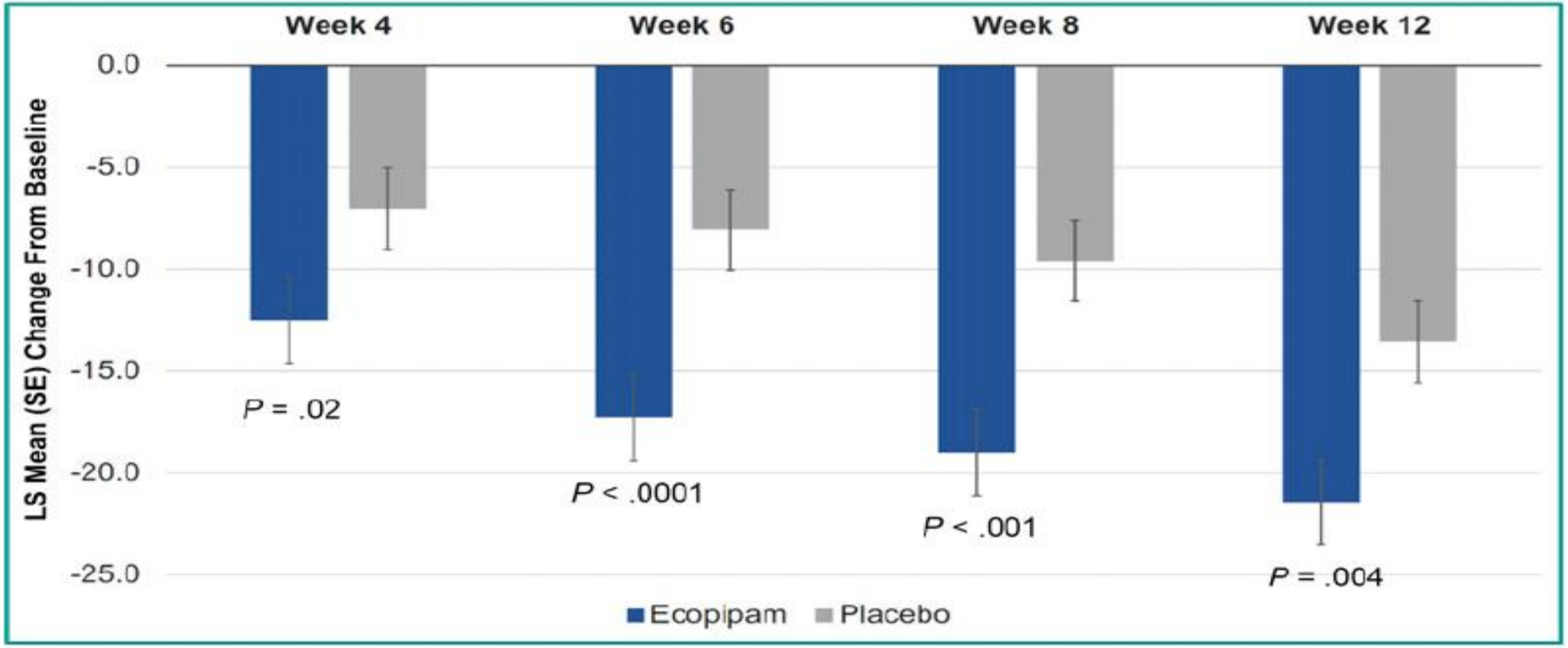

FIGURE 2

(A) YGTSS-TTS LS mean (SE) change from baseline to week 4, 6, 8 and 12 and (B) YGTSS-GS LS mean (SE) change from baseline to week 4, 6, 8, and 12. *P* values from MMRM analysis.

Ecopipam for Tourette Syndrome: A Randomized Trial

(Gilbert DL, Dubow JS, Cunniff TM, et al, Pediatrics. 2023;151(2): e2022059574. doi:10.1542/peds.2022-059574)

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TABLE 2 Incidence of Treatment-Emergent AEs (At Least 5% Greater Incidence With Ecopipam, Safety Population)

	Number (%) of Subjects	
	Placebo (n = 77)	Ecopipam (n = 76)
Headache	7 (9.1)	12 (15.8)
Insomnia	2 (2.6)	10 (13.1)
Fatigue	0	6 (7.9)
Somnolence	2 (2.6)	6 (7.9)
Anxiety	0	4 (5.3)
Nausea	1 (1.3)	4 (5.3)
Restlessness	0	4 (5.3)
Any AE	38 (49.4)	47 (61.8)
Treatment-related AE	16 (20.8)	26 (34.2)
AE leading to withdrawal	1 (1.3)[a]	4 (5.3)[b]
Serious AE	1 (1.3)[c]	2 (2.6)[d]

Treatment-related AEs were AEs with relationship to treatment as "Possibly Related" or "Probably Related."

[a] Suicidal ideation based on C-SSRS defined as nonspecific suicidal thoughts or active suicidal ideation without intent to act.

[b] 4 subjects with nausea, anxiety, depressed mood, self-injurious ideation, suicidal ideation, tic.

[c] Suicidal ideation.

[d] Coronavirus disease 2019 infection, vomiting.

Safety and Effect of 12-Month Ecopipam Treatment in Pediatric Patients with Tourette Syndrome

(Gilbert, D. L., Kim, D. J. B., Miller, M. M., Atkinson, S. D., Karkanias, G. B., Munschauer, F. E., Wanaski, S. P., & Cunniff, T. M. (2025). Safety and effect of 12-month Ecopipam treatment in pediatric patients with Tourette syndrome. Movement Disorders Clinical Practice, 12(8), 1157–1166. https://doi.org/10.1002/mdc3.70091)

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Objective: Evaluate long term safety

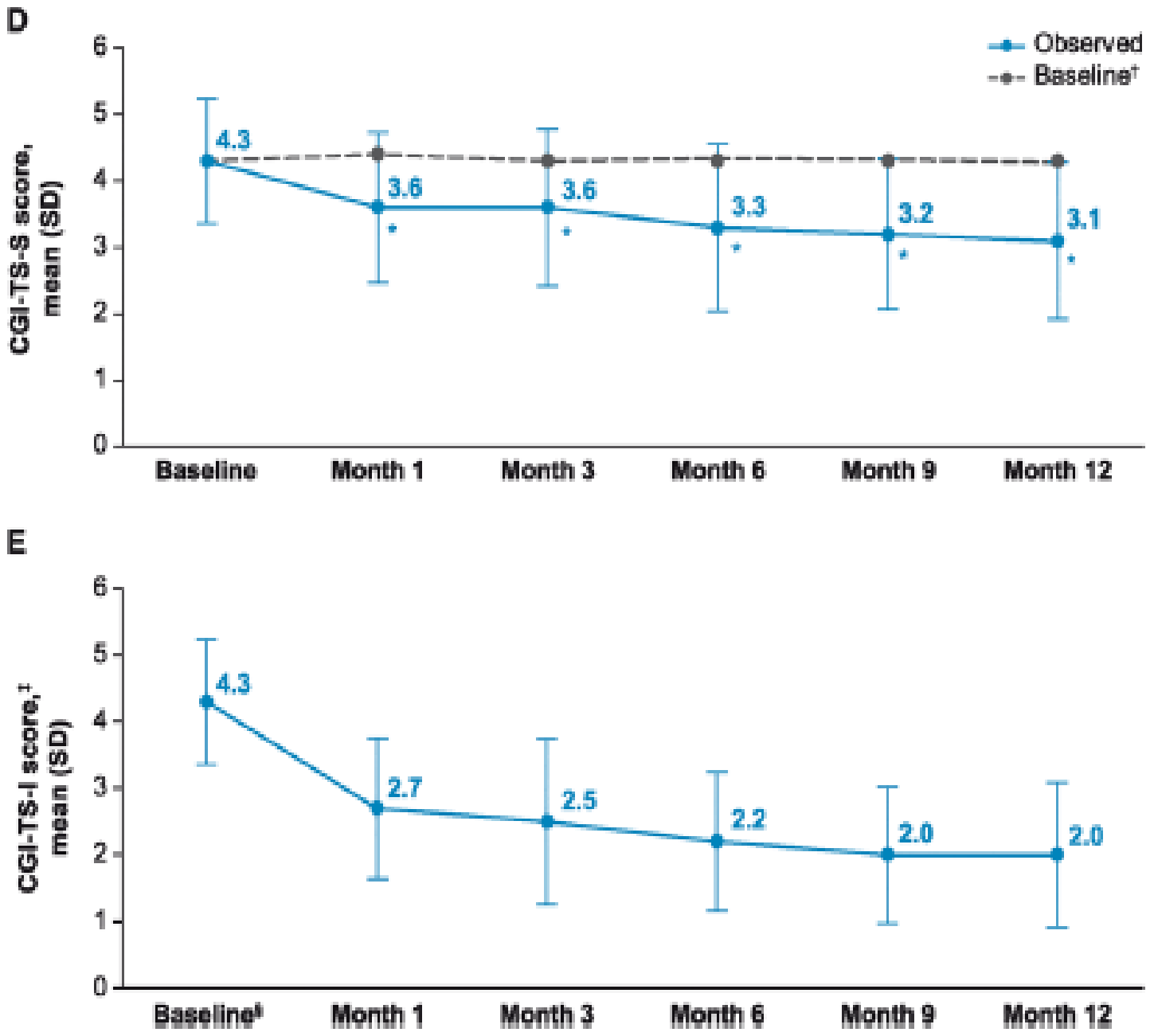
Methods: Participants from parent study (Phase 2b) ages 6-17 were enrolled for 12 months open label extension. Dose was titrated to 1.8 mg/kg and visits were monthly.

Results: N=122 youth enrolled and 80% completed. Most common AEs were nasopharyngitis (14%) and anxiety (9%).

At 12 months: no significant weight gain, changes in HgA1C or cholesterol were noted. No EPS were observed. Significant improvements were noted in tic severity and quality of life.

Conclusion: 12 months of ecopipam was well tolerated and no new adverse effects were noted. Tic severity and quality of life significantly improved.

Safety and Effect of 12-Month Ecopipam Treatment in Pediatric Patients with Tourette Syndrome (*Gilbert, D. L., Kim, D. J. B., Miller, et al. 2025)*



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Efficacy and Safety of Fixed-Dose Deutetrabenazine in Children and Adolescents for Tics Associated With Tourette Syndrome: A Randomized Clinical Trial

(JAMA Network Open.2021;4(10):e2129397.doi:10.1001/jamanetworkopen.2021.29397)

- Original Investigation | Neurology
- Barbara Coffey, MD, MS; Joseph Jankovic, MD; Daniel O. Claassen, MD; Joohi Jimenez-Shahed, MD; Barry J. Gertz, MD, PhD; Elizabeth A. Garofalo, MD;
- David A. Stamler, MD; Maria Wieman, MPH; Juha-Matti Savola, MD, PhD; Mark Forrest Gordon, MD; Jessica K. Alexander, PhD; Hadas Barkay, PhD; Eran Harary, MD

ARTISTS 1: YGTSS-TTS Change From Baseline by Visit

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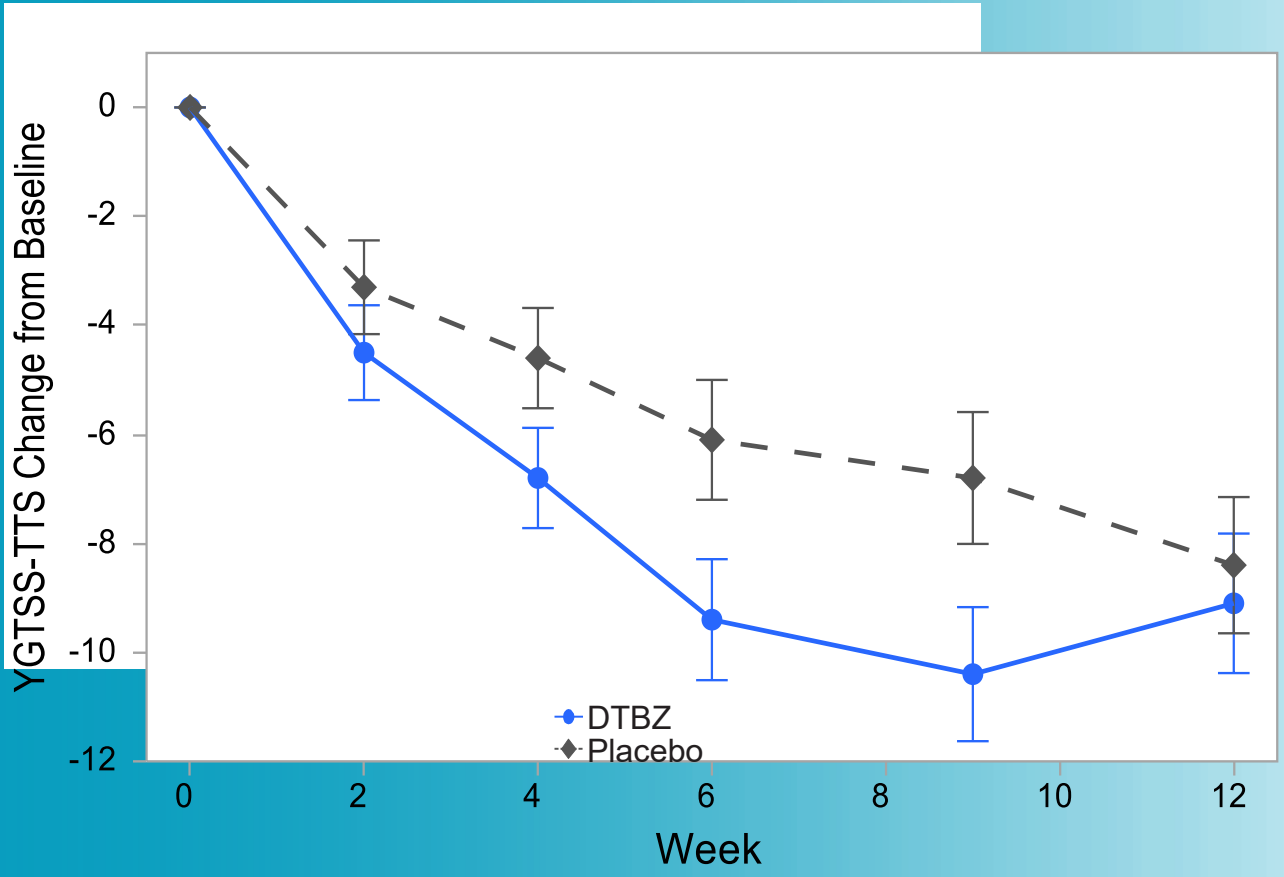
Although a favorable trend during titration was noted, the primary endpoint was not met



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.

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Endocannabinoids and Tourette Syndrome?

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The endocannabinoid system plays a role in **motor inhibition**.

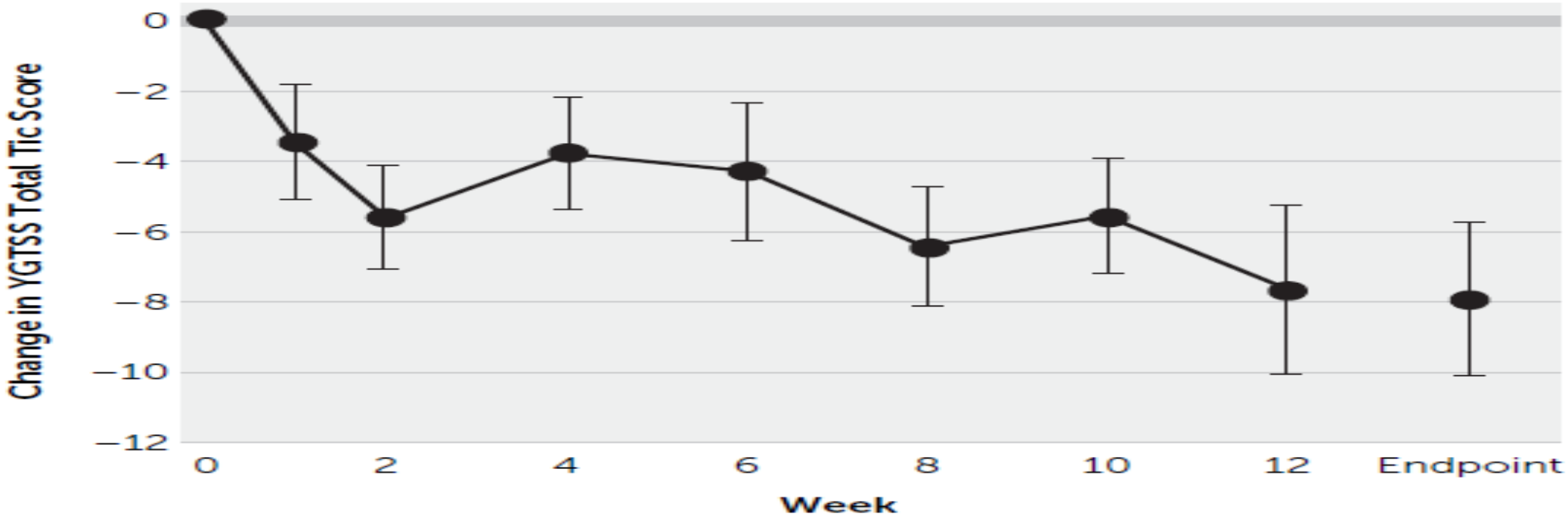
Highest density of **central cannabinoid (CB1**) receptors: frontal cortex, basal ganglia, cerebellum, hypothalamus, hippocampus, and nucleus accumbens……all areas implicated in pathophysiology of TS.

***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 TS reported that dronabinol was more effective than PBO in tic reduction.

FIGURE 1. Change in tic severity with THX-110 in 16 adults with Tourette's syndrome[a]



Bloch, M. H., Landeros-Weisenberger, A., Johnson, J. A., & Leckman, J. F. (2021). A Phase-2 Pilot Study of a Therapeutic Combination of Δ⁹-Tetrahydracannabinol and Palmitoylethanolamide for Adults With Tourette's Syndrome. The Journal of neuropsychiatry and clinical neurosciences, 33(4), 328–336. https://doi.org/10.1176/appi.neuropsych.19080178

CANNA-TICS: Efficacy and safety of oral treatment with nabiximols in adults with chronic tic disorders – Results of a prospective, multicenter, randomized, double-blind, placebo controlled, phase IIIb superiority study

(Müller-Vahl, K. R., Pisarenko, A., Szejko, N., er all A. (2023). Psychiatry Research, 323, Article 115135. https://doi.org/10.1016/j.psychres.2023.115135)

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Aim: Cannabis-based medicines might be a promising new treatment for patients with (TS)/chronic tic disorders (CTD) resulting in improvement of tics, comorbidities, and quality of life.

Methods: Randomized, placebo-controlled, study aimed to examine efficacy and safety of the cannabis extract nabiximols in adults with TS/CTD (n = 97, randomized 2:1 to nabiximols: placebo).

Primary efficacy endpoint: tic reduction ≥ 25% on TTS of the Yale Global Tic Severity Scale after 13 weeks of treatment.

Results: A larger number of patients in the nabiximols vs. placebo group (14/64 (21·9%) vs. 3/33 (9·1%)) met responder criterion; superiority of nabiximols could formally not be demonstrated.

Substantial trends for improvements of tics, depression, and quality of life were observed.

Exploratory subgroup analyses revealed **an improvement of tics in males, patients with more severe tics, and patients with comorbid attention deficit/hyperactivity disorder.** There were no relevant safety issues.

Conclusion: Data further supports role of cannabinoids in the treatment of CTDs.

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CANNA-TICS: Efficacy and safety of oral treatment with nabiximols in adults with chronic tic disorders – Results of a prospective, multicenter, randomized, double-blind, placebo controlled, phase IIIb superiority study

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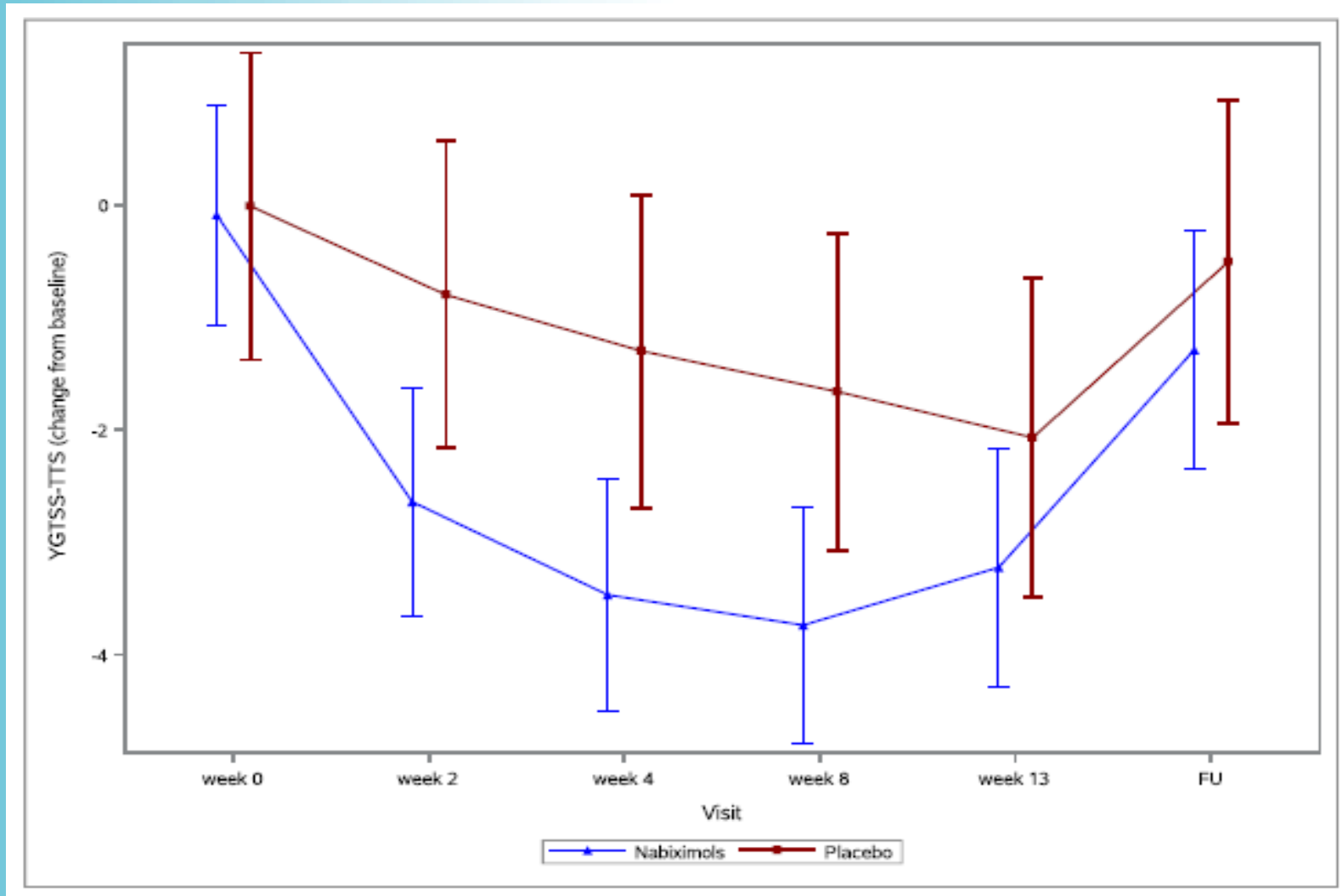
(Müller-Vahl, K. R., Pisarenko, A., Szejko, N., Haas, et al. Psychiatry Research, 323, Article 115135. https://doi.org/10.1016/j.psychres.2023.115135)

Fig. 2. Tic Severity during the course of the study after treatment with Nabiximols compared to placebo. Displayed are least square means of the change from baseline to follow-up visit (FU) of the Total Tic Score (YGTSS-TTS) derived from the mixed linear model. In the model repeated measures with a first-order autoregressive covariance structure, baseline values and center were included. Missing values are not replaced. FU is the follow-up visit 4 weeks after end of treatment.



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

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- Progress has been made in the past several years on better understanding of underlying genetic, phenomenological and psychiatric comorbidity in tic disorders and Tourette's.
- **Provisional tics** may be similar in phenomenology to persistent tics.
- Better understanding of the role of **pain, suicidal thoughts and behaviors, especially in girls**, is needed.
- Yet, effective treatment has lagged. To this day, there are still only **3 FDA approved medications** in the US, and all have significant adverse effects.
- There is clearly a **need for more effective and better tolerated** treatments.
- **CBIT** is recommended as the first line treatment for children, adolescents and adults.
- **Off label** agents (alpha 2 agonists) are recommended as first line pharmacotherapy.
- For the first time in decades, **novel agents** may hold promise as pharmacotherapy for tics and Tourette's Disorder.
- **Ecopipam:** D1 receptor antagonist is first in class with specific development program for TS. Phase 2 and Phase 3 study results are promising.
- VMAT2 inhibitors may be helpful for some individuals with Tourette's, **used off label,** as they are well tolerated.
- **Cannabis related compounds** are numerous; impact of THC and CBD need to be dissected. Positive results may point to an endocannabinoid system dysfunction in TS. Despite current public (and teen!!) clamor for use, more scientific data is needed.