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

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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
- Emalex: Research Support
- Harvard Medical School /Psychiatry Academy: Honoraria
- New Venture Fund: Research Support
- NIMH/NINDS: 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

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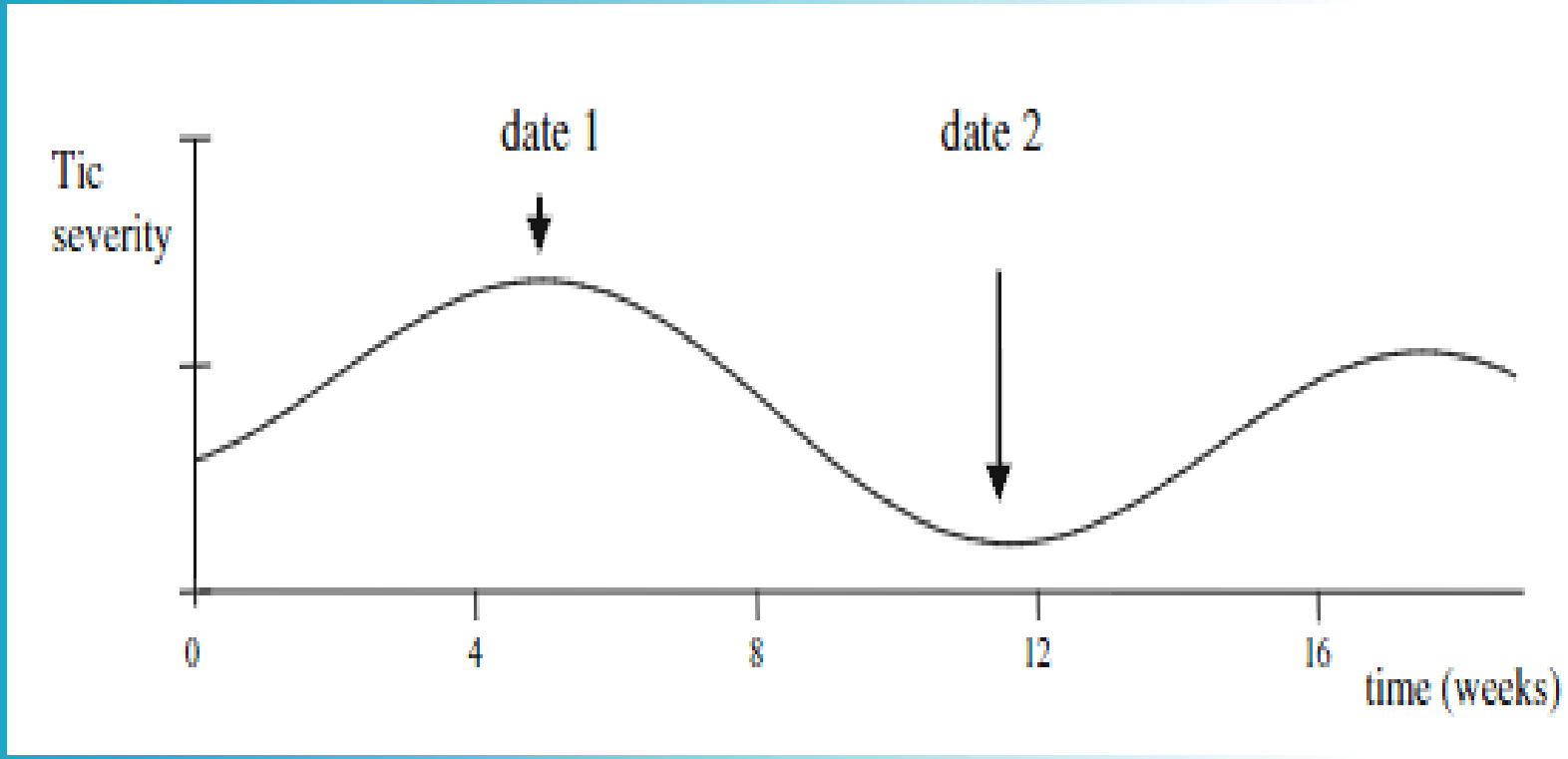
- At the end of this session, the participant should be able to:
  - **Discuss approved and off label treatments** for Tourette's and tic disorders
  - Preview **potential new drugs** in the pipeline or under investigation for treatment of tics
  - Interpret **relevance of clinical trial** findings for application to treatment of youth with tics and Tourette's Disorder



The Challenges of Treating Tics!

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

Tics/Tourette's Disorder: Treatment Overview

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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, 2019)

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
- ***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).

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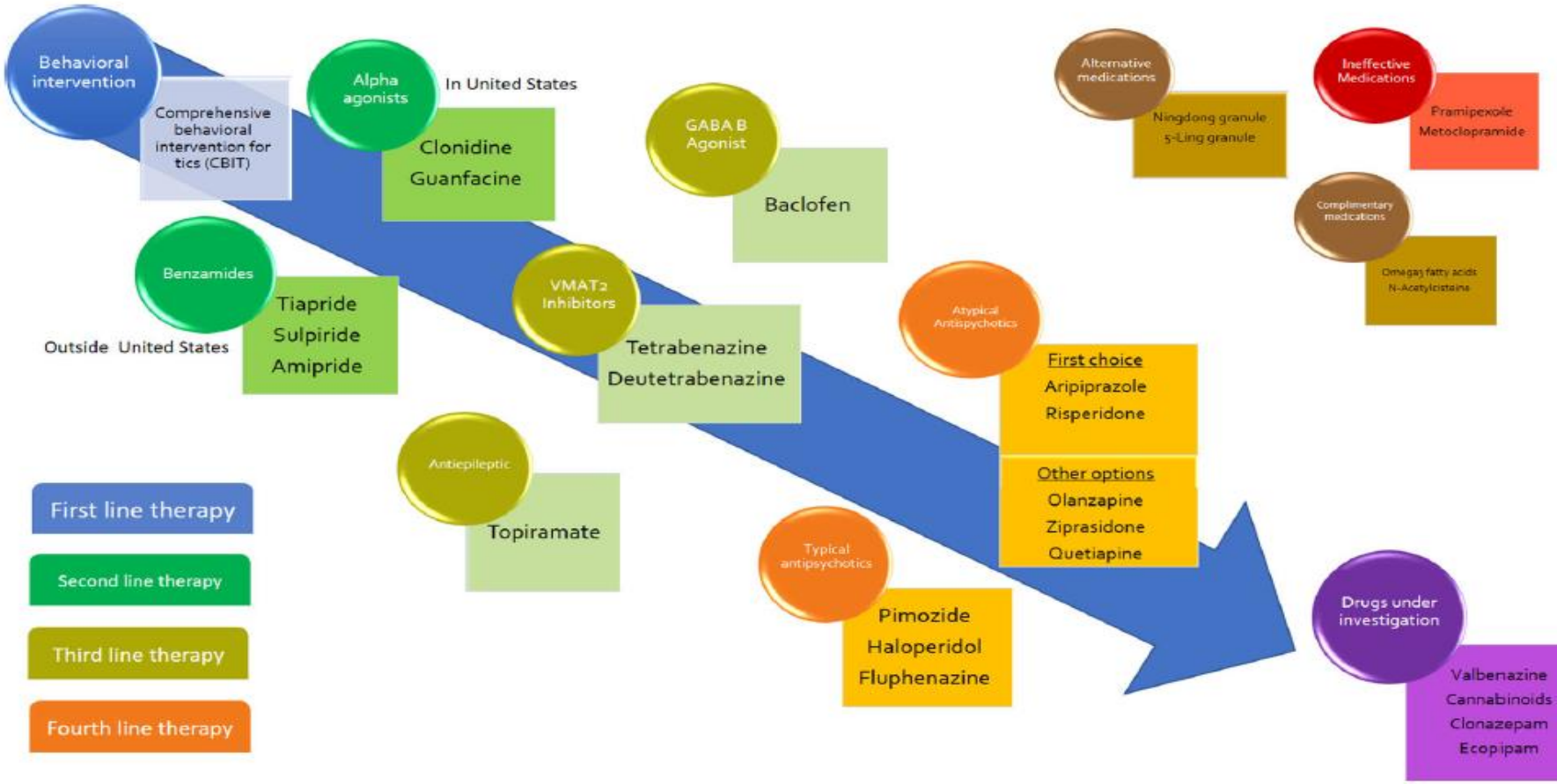
Medication	Range of daily dosing
Haloperidol	0.25-4.0mg
Pimozide	0.5-8.0mg
*Risperidone	0.125-3.0mg
Aripiprazole	1.0-15.0mg
*Clonidine	0.025-0.4mg
*Guanfacine	0.25-4.0mg



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Complimentary medications are available and have evidence for

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T2 vesic-

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

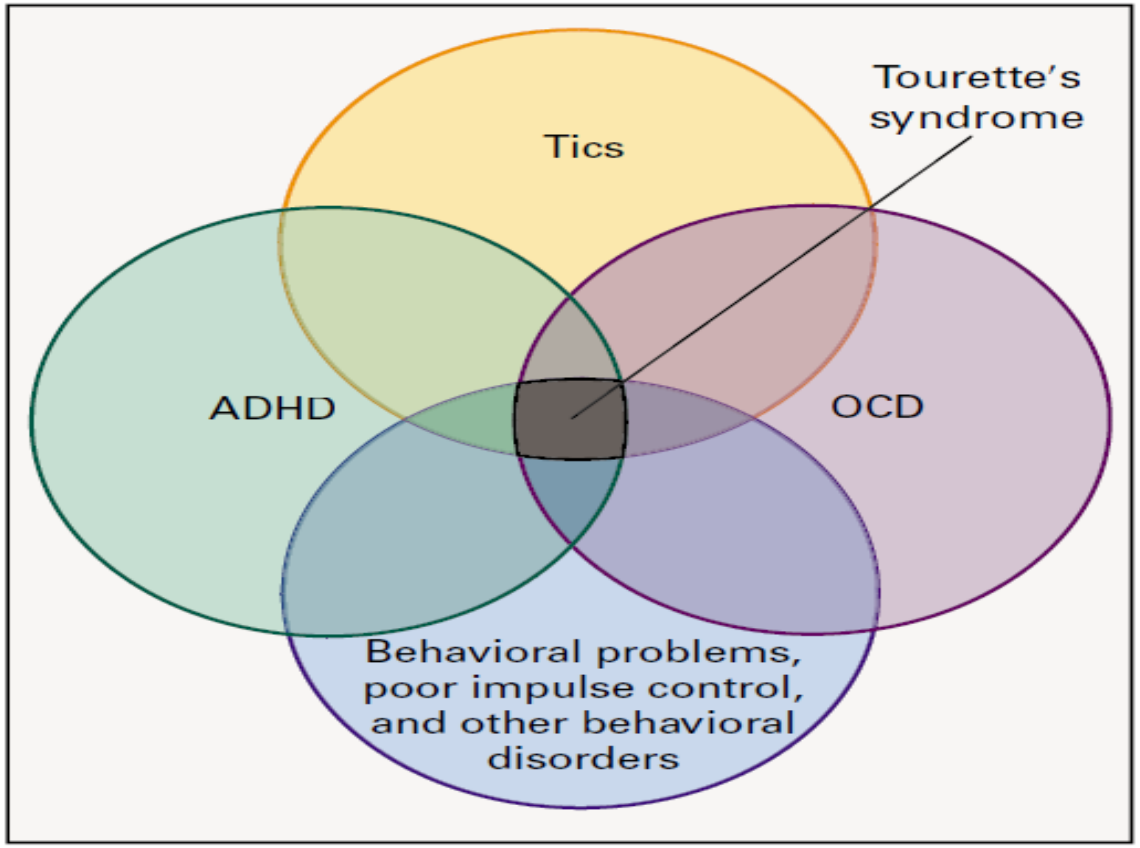

Figure 1. Clinical Hallmarks of Tourette's Syndrome.
The diagnosis is based on the occurrence of tics along with behavioral disorders, including attention-deficit–hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD). Other behavioral disorders include anxiety and mood disorders, learning disorders, sleep disorders, conduct and oppositional behavior, and self-injurious behavior.

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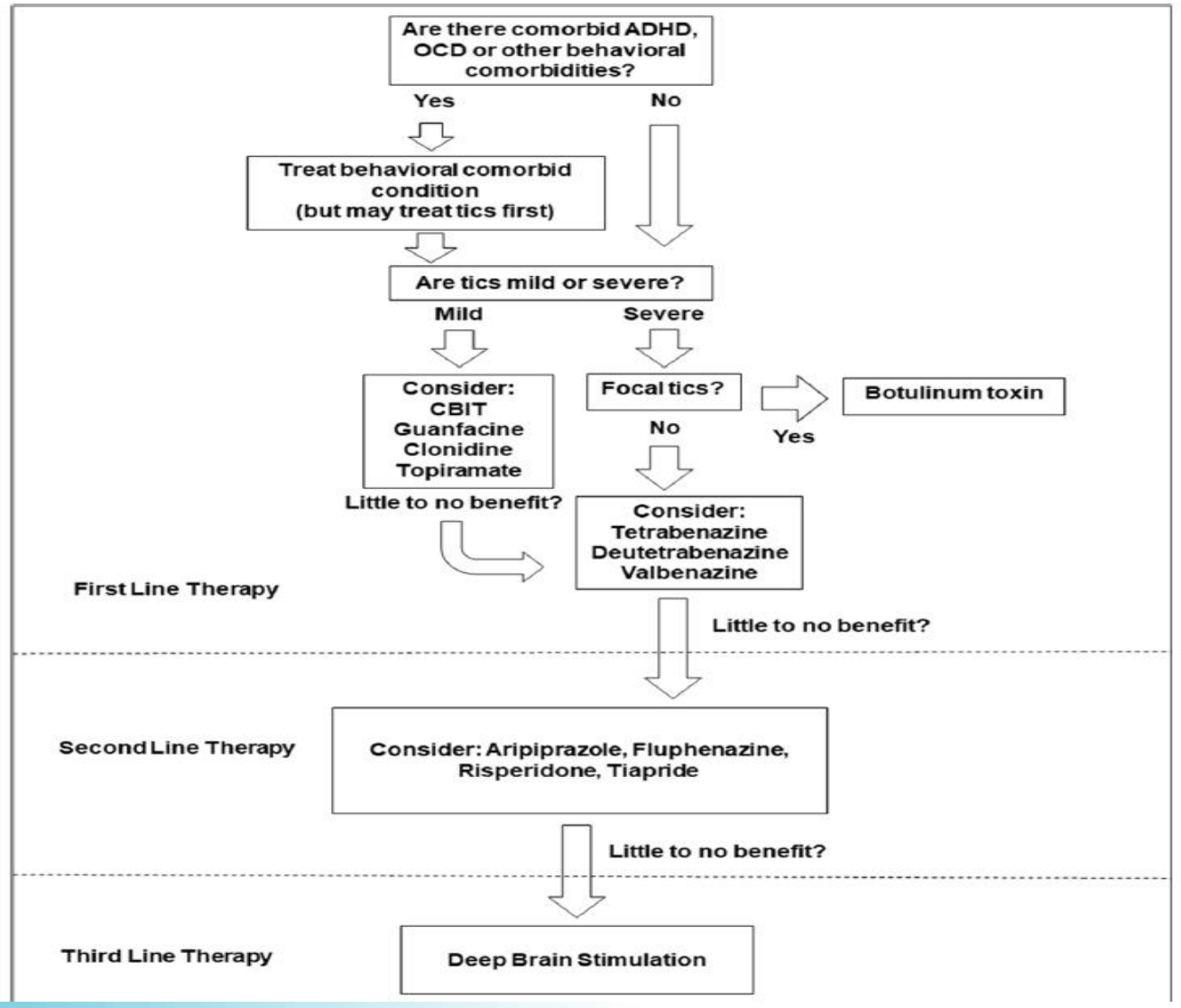
Jankovic J.NEJM; 2001.

Fig. 1 Suggested treatment algorithm for the management of tics associated with Tourette syndrome



Billnitzer, A., & Jankovic, J. (2020). Current Management of Tics and Tourette Syndrome: Behavioral, Pharmacologic, and Surgical Treatments. *Neurotherapeutics: Journal American Soc for Experimental NeuroTherapeutics*, *17*(4), 1681–1693. https://doi.org/10.1007/s13311-020-00914-6

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

Billnitzer, A., & Jankovic, J. (2020). Current Management of Tics and Tourette Syndrome: Behavioral, Pharmacologic, and Surgical Treatments. *Neurotherapeutics: Journal American Soc for Experimental NeuroTherapeutics*, *17*(4), 1681–1693. https://doi.org/10.1007/s13311-020-00914-6

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

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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.

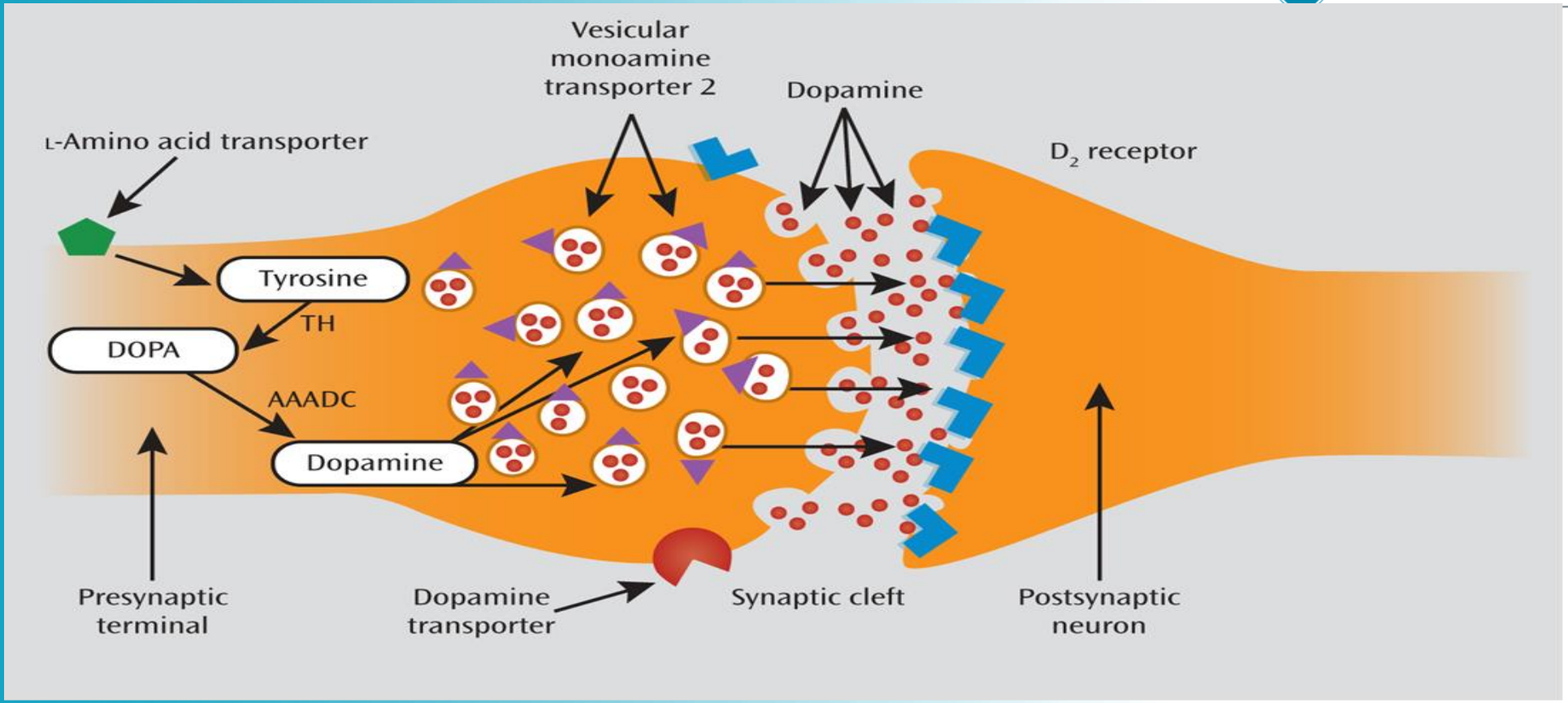
Comprehensive Behavioral Intervention for Tics (CBIT): lack of trained therapists; duration of treatment

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

Canada Day

TUESDAY
JULY 1

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.

	DTBZ (N=59)	Placebo (N=60)	Total (N=119)
Age, y, mean (±SD)	11.5 (±2.52)	11.5 (±2.59)	11.5 (±2.54)
Age group, n (%)			
6-11 y	30 (50.8%)	31 (51.7%)	61 (51.3%)
12-16 y	29 (49.2%)	29 (48.3%)	58 (48.7%)
Gender, n (%)			
Male	53 (89.8%)	51 (85.0%)	104 (87.4%)
Female	6 (10.2%)	9 (15.0%)	15 (12.6%)
Race, n (%)			
White	49 (83.1%)	53 (88.3%)	102 (85.7%)
Non-White	10 (16.9%)	7 (11.7%)	17 (14.3%)
Region, n (%)			
North America	44 (74.6%)	43 (71.7%)	87 (73.1%)
Eurasia	15 (25.4%)	17 (28.3%)	32 (26.9%)

DTBZ, deutetrabenazine; ITT, intention-to-treat; SD, standard deviation.

Tourette's Disorder (ARTSTS1) 1: Demographic and Baseline Characteristics (ITT Analysis Set)

ARTISTS 1: YGTSS-TTS Change From Baseline by Visit

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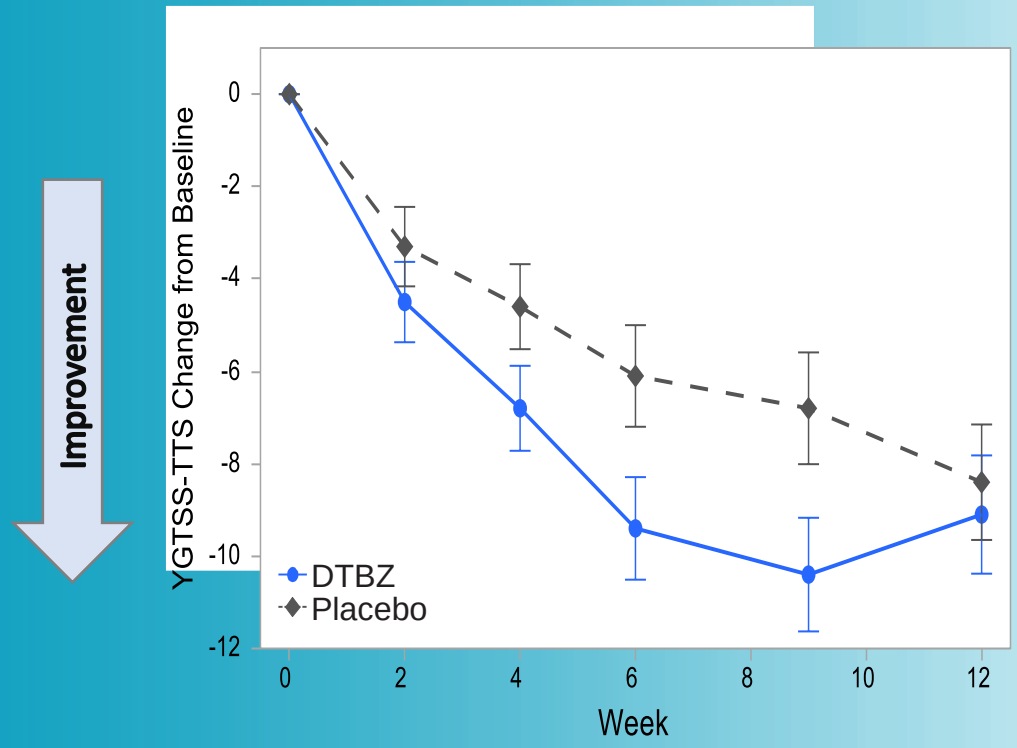
- Although a favorable trend during titration was noted, the primary endpoint was not met



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.

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

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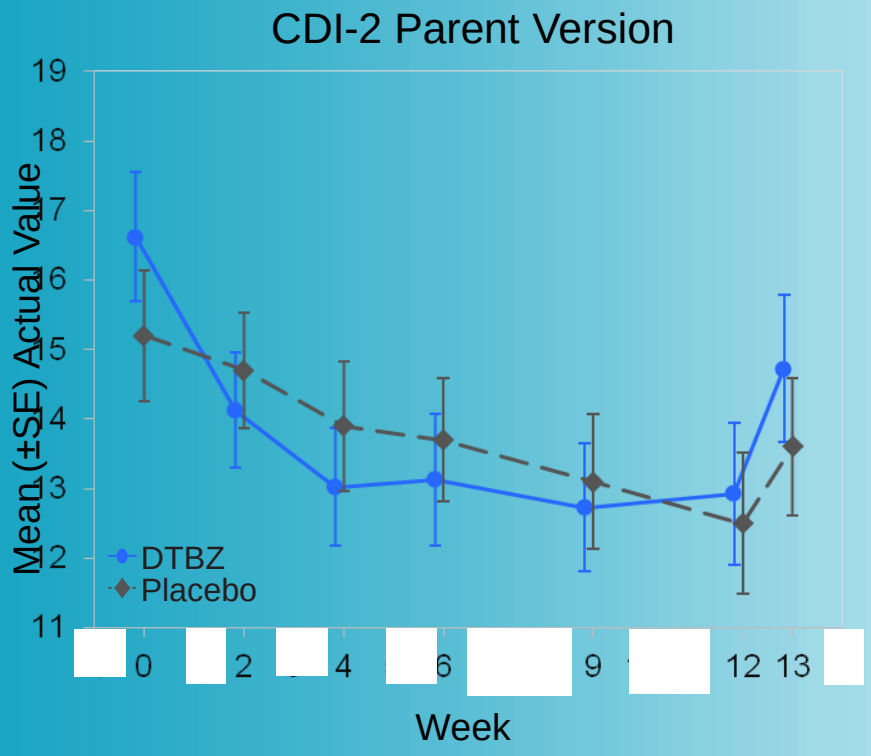
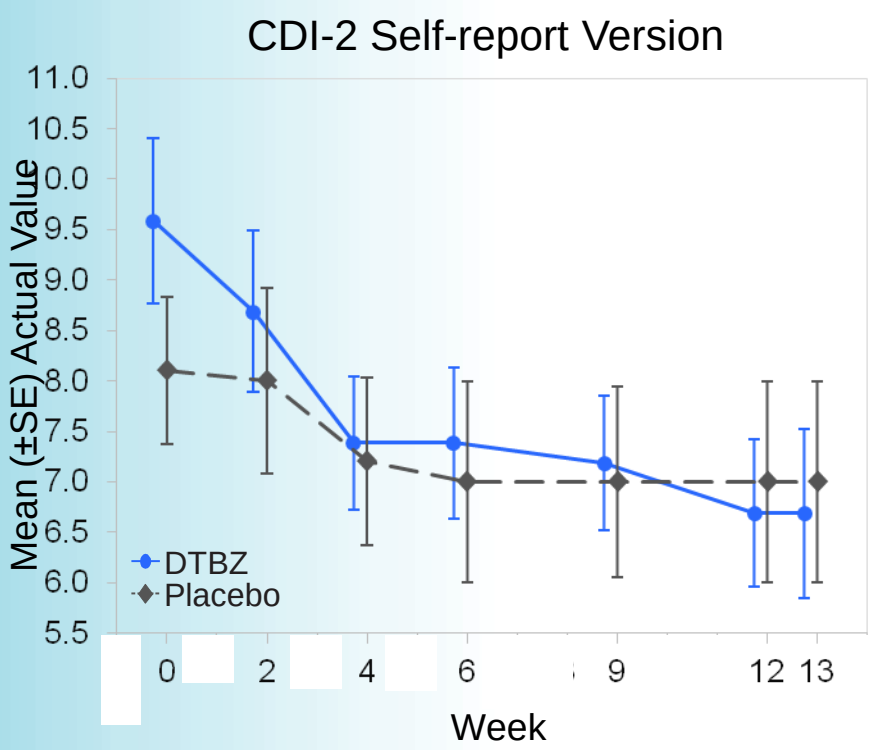
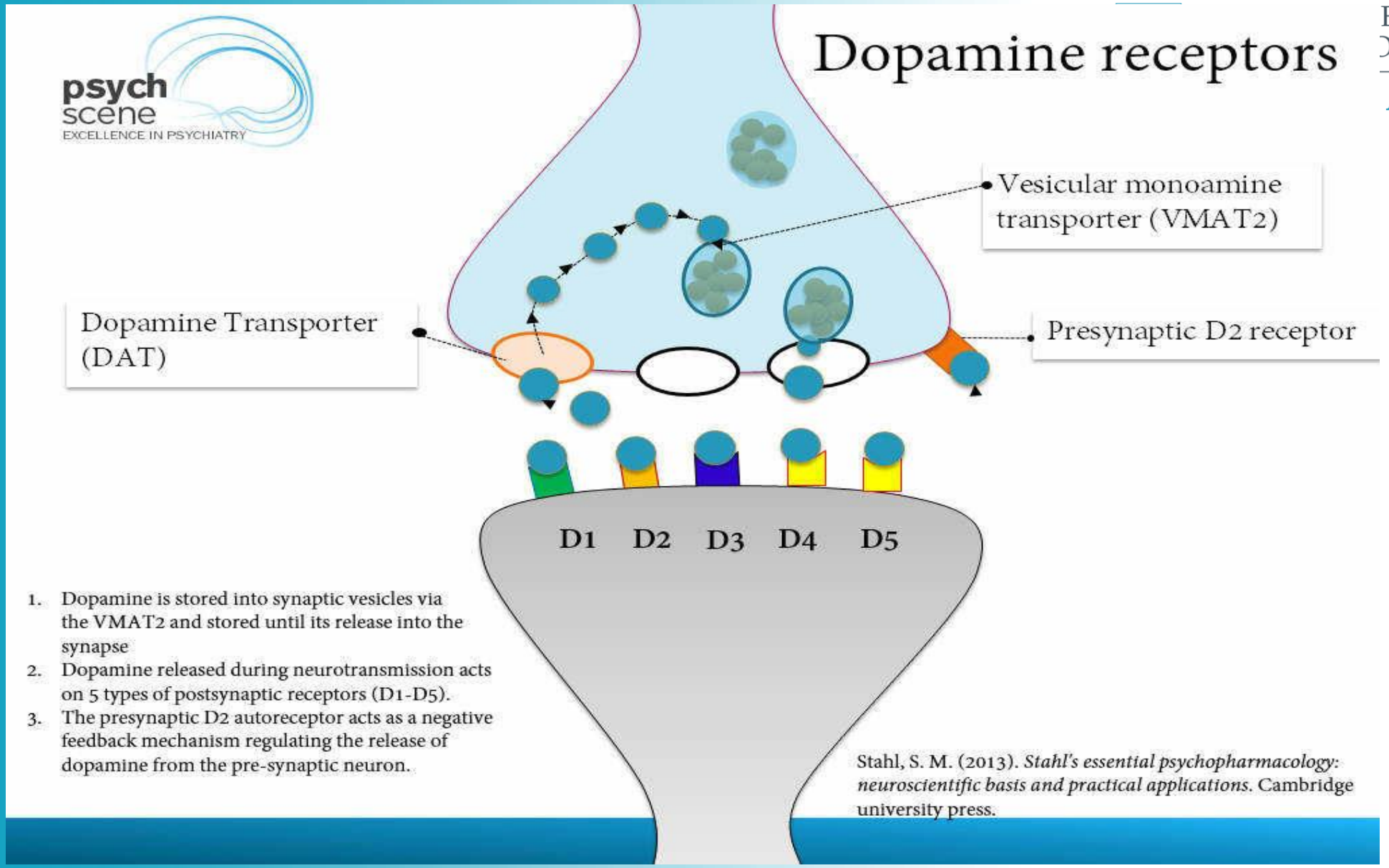




- CDI, Children's Depression Inventory; SE, standard error.

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.

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, age 7 to 17, with TS and YGTSS– total tic score (TTS) of ≥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.

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

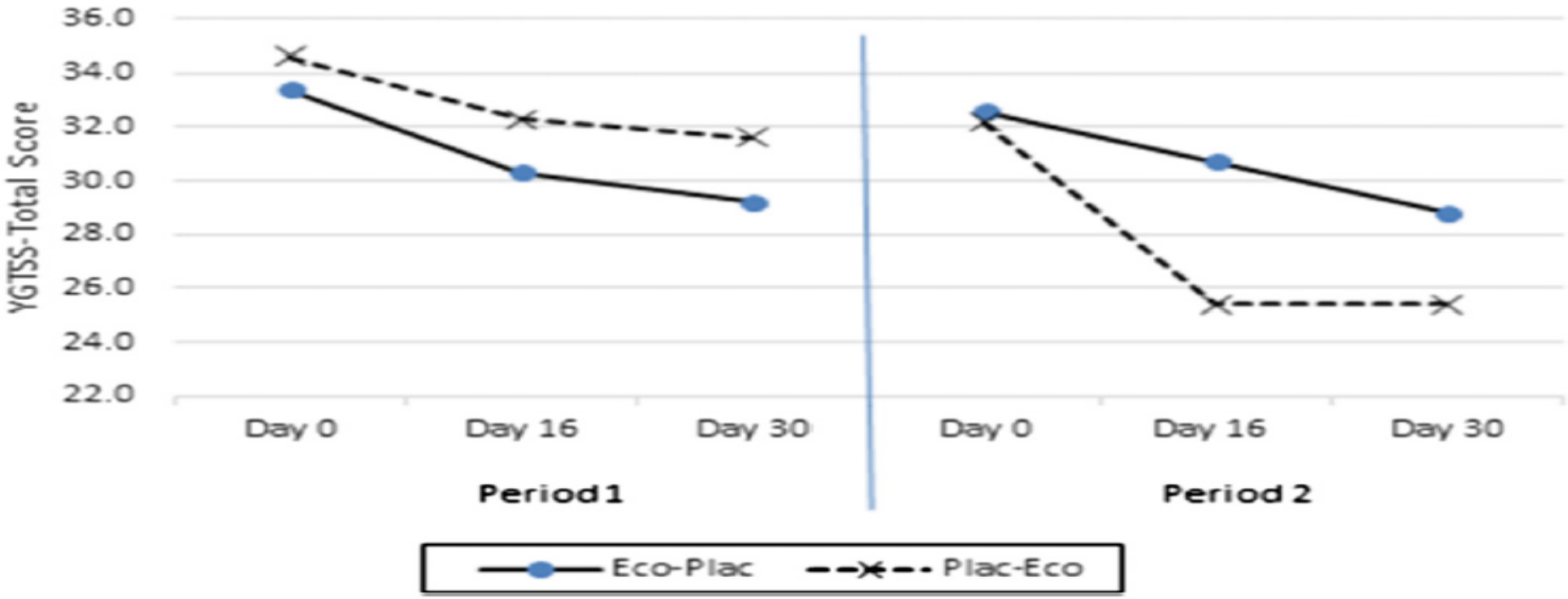


FIG. 2. Treatment effects by period. YGTSS, Yale Global Tic Severity Scale; YGTSS-total score, motor and phonic tic scores, the primary outcome for the trial; Eco-Plac, ecopipam in period 1, followed by placebo in period 2; Plac-Eco, placebo in period 1, followed by ecopipam in period 2. Means are from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

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Endocannabinoids and Tourette Syndrome?

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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.

A Double-Blind, Randomized, Controlled Crossover Trial of Cannabis in Adults with Tourette Syndrome

Elia Abi-Jaoude at al.

(Cannabis and cannabinoid research 10.1089/can.2022.0091. Advance online publication. https://doi.org/10.1089/can.2022.0091)

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Background: Effective evidence-based treatment options for patients with Tourette syndrome (TS) are limited. Emerging evidence shows cannabinoids as promising for the treatment of tics.

Objectives: To compare the efficacy and tolerability of single doses of three vaporized medical cannabis products and placebo in reducing tics in adults with TS.

Methods: In a randomized, double-blind, crossover design, each participant received a vaporized single 0.25 g dose of D9-tetrahydrocannabinol (THC) 10%, THC/cannabidiol (CBD) 9%/9%, CBD 13%, and placebo at 2-week intervals. Our primary outcome was the Modified Rush Video-Based Tic Rating Scale (MRVTRS), taken at baseline and at 0.5, 1, 2, 3, and 5 h after dose administration. Secondary measures included the Premonitory Urge for Tics Scale (PUTS), Subjective Units of Distress Scale (SUDS), and Clinical Global Impression–Improvement (CGI-I). Correlations between outcomes and cannabinoid plasma levels were calculated. Tolerability measures included open-ended and specific questions about adverse events (AEs).

Results: Twelve adult patients with TS were randomized, with nine completing the study. There was no statistically significant effect of product on the MRVTRS. However, there was a significant effect of THC 10%, and to lesser extent THC/CBD 9%9%, versus placebo on the PUTS, SUDS, and CGI-I. As well, there were significant correlations between plasma levels of THC and its metabolites, but not CBD, with MRVTRS, PUTS, and SUDS measures. There were more AEs from all cannabis products relative to placebo, and more AEs from THC 10% versus other cannabis products, particularly cognitive and psychomotor effects. Most participants correctly identified whether they had received cannabis or placebo.

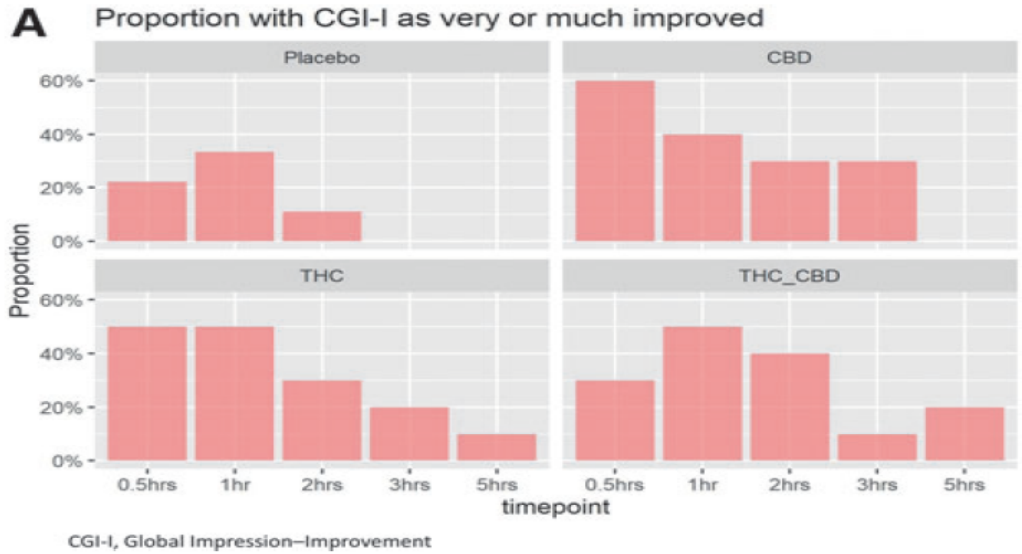
Conclusions: In this pilot randomized controlled trial of cannabis for tics in TS, there was no statistically significantdifference on the MRVTRS for any of the cannabis products, although the THC 10% product was significantly better than placebo on the secondary outcome measures. Also, THC and metabolite plasma levels correlated with improvement on all measures. The THC 10% product resulted in the most AEs. ClinicalTrials.gov ID: NCT03247244.

Table 1. Demographic and Clinical Characteristics of the 12 Study Participants

Age, years/ Gender	Comorbidities	Concurrent medications	Previous cannabis use	YGTSS-TTS
47/M	OCD, ADHD, depression	Methylphenidate extended release, lurasidone, bupropion, clonazepam, benztropine	Yes	44
35/M	None	None	No	30
49/M	None	Diltiazem	No	25
36/M	ADHD	None	No	18
38/F	ADHD, OCD, PTSD, depression	Aripiprazole, fluoxetine, venlafaxine, clonazepam, benztropine, gabapentin	No	37
23/M	OCD, ADHD, anxiety	Methylphenidate, sertraline	No	25
37/M	None	None	No	25
34/M	OCD	None	No	27
22/M	OCD, ADHD, anxiety	Sertraline	Yes	28
54/M	OCD, ASD, anxiety, depression	Clonazepam, budesonide intranasal spray, bismuth subsalicylate	No	27
31/M	OCD, ADHD	Aripiprazole	No	43
50/M	None	None	Yes	15

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; F, female; M, male; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; YGTSS-TTS, Yale Global Tic Severity Scale Total Tic Score.

Abi-Jaoude, E., Bhikram, T., Parveen, F., Levenbach, J., Lafreniere-Roula, M., & Sandor, P. (2022). A Double-Blind, Randomized, Controlled Crossover Trial of Cannabis in Adults with Tourette Syndrome. Cannabis and cannabinoid research, 10.1089/can.2022.0091. Advance online publication. https://doi.org/10.1089/can.2022.0091



B

Contrast	OR [95% CI]	P-value
CBD / Placebo	5.114 [0.967,27.038]	0.057
THC / Placebo	7.221 [1.288,40.487]	0.017
THC-CBD / Placebo	4.936 [0.958,25.447]	0.06

FIG. 2. **(A)** Proportion of participants rated as "very much improved" or "much improved" on the CGI-I over the course of 5 h after administration of cannabis or placebo product. **(B)** Odds ratio estimates [95% CI] for pairwise contrasts with *p*-values adjusted with the Tukey's method. 95% CI, 95% confidence interval; CGI-I, Clinical Global Impression–Improvement.

Abi-Jaoude, E., Bhikram, T., Parveen, F., Levenbach, J., Lafreniere-Roula, M., & Sandor, P. (2022). A Double-Blind, Randomized, Controlled Crossover Trial of Cannabis in Adults with Tourette Syndrome. Cannabis and cannabinoid research, 10.1089/can.2022.0091. Advance online publication. https://doi.org/10.1089/can.2022.0091

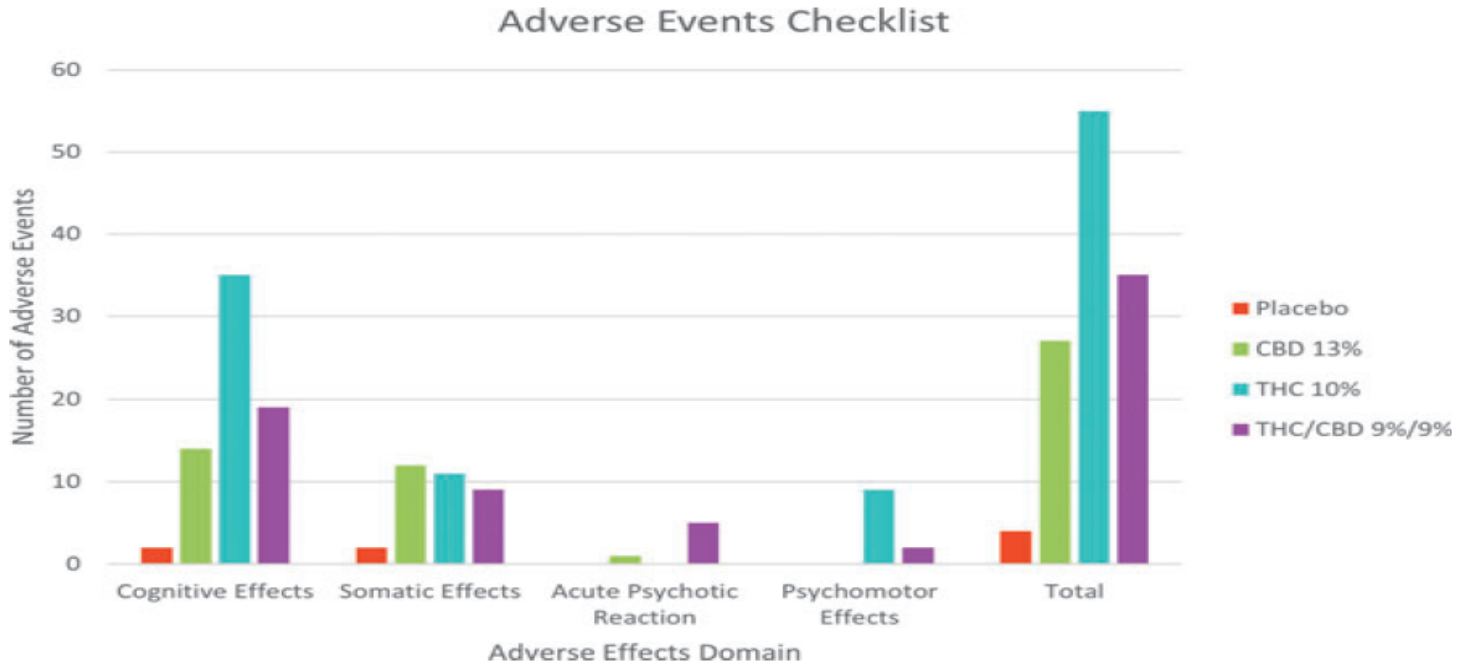


FIG. 5. Number of adverse events reported for each of the cannabis and placebo products based on the adverse events checklist.

Abi-Jaoude, E., Bhikram, T., Parveen, F., Levenbach, J., Lafreniere-Roula, M., & Sandor, P. (2022). A Double-Blind, Randomized, Controlled Crossover Trial of Cannabis in Adults with Tourette Syndrome. Cannabis and cannabinoid research, 10.1089/can.2022.0091. Advance online publication. https://doi.org/10.1089/can.2022.0091

A Phase-2 Pilot Study of a Therapeutic Combination of D9-Tetrahydracannabinol and Palmitoylethanolamide for Adults With Tourette's Syndrome

Michael H. Bloch et al. Journal of neuropsychiatry and clinical neurosciences, 33(4), 328–336. https://doi.org/10.1176/appi.neuropsych.19080178

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- **Objective:** The investigators conducted a small, uncontrolled trial to examine the safety, tolerability, and dosing of THX-110, a combination of D9-tetrahydracannabinol (D9-THC) and palmitoylethanolamide (PEA), in Tourette's syndrome.
- **Methods:** 2-week uncontrolled trial of THX-110 (maximum daily D9-THC dose, 10 mg, and a constant 800-mg dose of PEA) in 16 adults with Tourette's syndrome was conducted. The primary outcome was improvement on the Yale Global Tic Severity Scale (YGTSS) total tic score. Secondary outcomes included measures of comorbid conditions and the number of participants who elected to continue treatment in the 24-week extension phase.
- **Results:** Tic symptoms significantly improved over time with THX-110 treatment. Improvement in tic symptoms was statistically significant within 1 week of starting treatment compared with baseline. THX-110 treatment led to an average improvement in tic symptoms of more than 20%, or a 7-point decrease in the YGTSS score.
- Twelve of the 16 participants elected to continue to the extension phase, and only two participants dropped out early. Side effects were common but were generally managed by decreasing D9-THC dosing, slowing the dosing titration, and shifting dosing to nighttime.
- **Conclusions:** Although the initial data from this trial in adults with refractory Tourette's syndrome are promising, future randomized double-blind placebo-controlled trials are necessary to demonstrate efficacy of THX-110 treatment. The challenges raised by the difficulty in blinding trials due to the psychoactive properties of many cannabis-derived compounds need to be further appreciated in these trial designs.

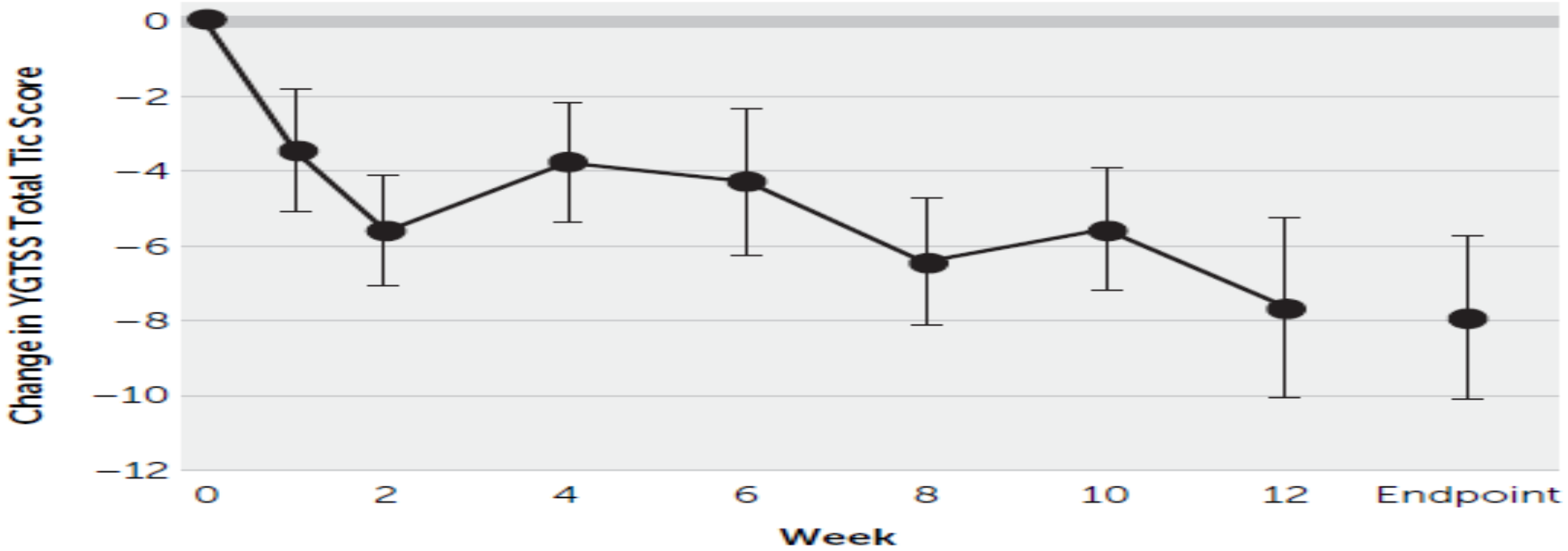
TABLE 1. Demographic and clinical characteristics of 16 adults with Tourette's syndrome[a]

Study subject	Age (years)	Gender	Age at onset (years)	Illness duration (years)	YGTSS Total Tic score		Comorbid condition
					Current baseline	Worst ever	
1	18	Male	12	6	38	42	ADHD, anxiety disorder, MDD
2	56	Male	6	50	42	50	OCD
3	43	Male	17	26	48	48	OCD, panic disorder, MDD
4	56	Male	7	49	38	50	Cocaine dependence in remission, OCD, ADHD
5	40	Female	9	31	43	50	OCD, GAD
6	29	Female	18	11	33	36	OCD
7	26	Male	6	20	37	37	OCD, ASD
8	23	Male	7	16	35	42	OCD
9	24	Male	6	18	44	50	OCD, ADHD, GAD, MDD, PD
10	29	Male	6	23	48	50	OCD
11	31	Male	6	25	26	38	OCD
12	49	Female	12	37	50	50	OCD, MDD
13	55	Female	6	49	45	50	MDD
14	32	Male	6	26	26	37	NA
15	21	Female	5	16	32	44	OCD, MDD, anxiety
16	28	Female	5	23	43	48	ASD, OCD

[a] ADHD=attention deficit hyperactivity disorder; ASD=autism spectrum disorder; GAD=generalized anxiety disorder; OCD=obsessive-compulsive disorder; MDD=major depressive disorder; NA=not applicable; PD=Parkinson's disease; VMAT=vesicular monoamine transporter; YGTSS=Yale Global Tic Severity Scale.

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

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



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Summary: Tourette's Disorder and Tics

- There are **3 FDA approved medications** in US and all have significant adverse effects.
- **Off label** agents (alpha 2 agonists, anticonvulsants) are recommended as first line pharmacotherapy.
- N**ovel agents** may hold promise as pharmacotherapy for tics and Tourette's Disorder.
- **VMAT2 inhibitors** are better tolerated than tetrabenazine.
- **Ecopipam:** D1 receptor antagonist is first in class with specific development program for TS. Phase 2 results were promising. Phase 3 study is currently underway in US.
- **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. Controlled studies of different compounds with adults are the first step.
- Tune in next year!!!