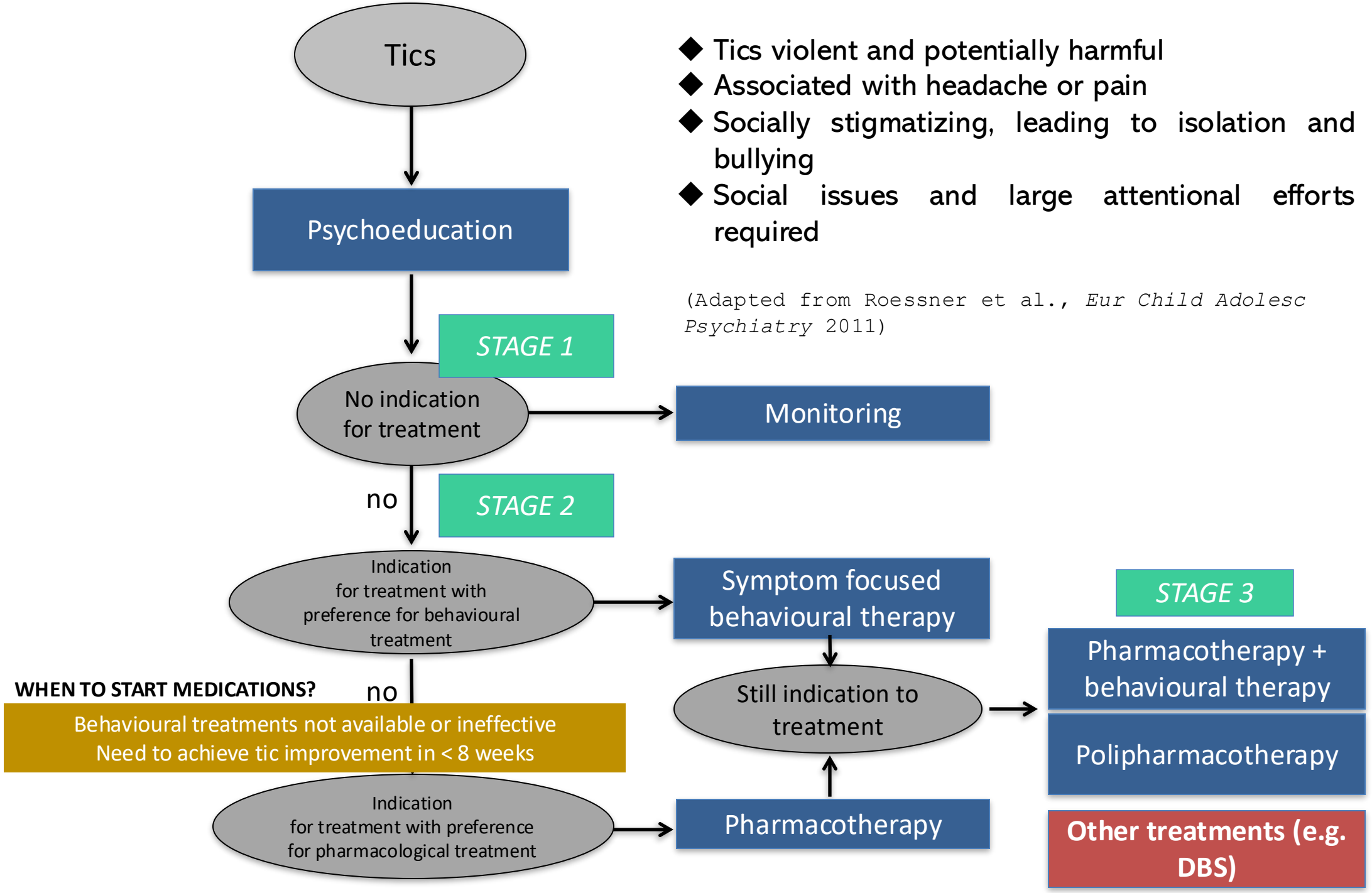
Pharmacotherapy for tics: a primer for non-prescribers

Davide Martino, MD, PhD

Professor of Neurology – University of Calgary, Canada

Co-Lead, Calgary Parkinson's Research Initiative (CaPRI),

Hotchkiss Brain Institute & Department of Clinical Neuroscience



- Tics violent and potentially harmful
- Associated with headache or pain
- Socially stigmatizing, leading to isolation and bullying
- Social issues and large attentional efforts required

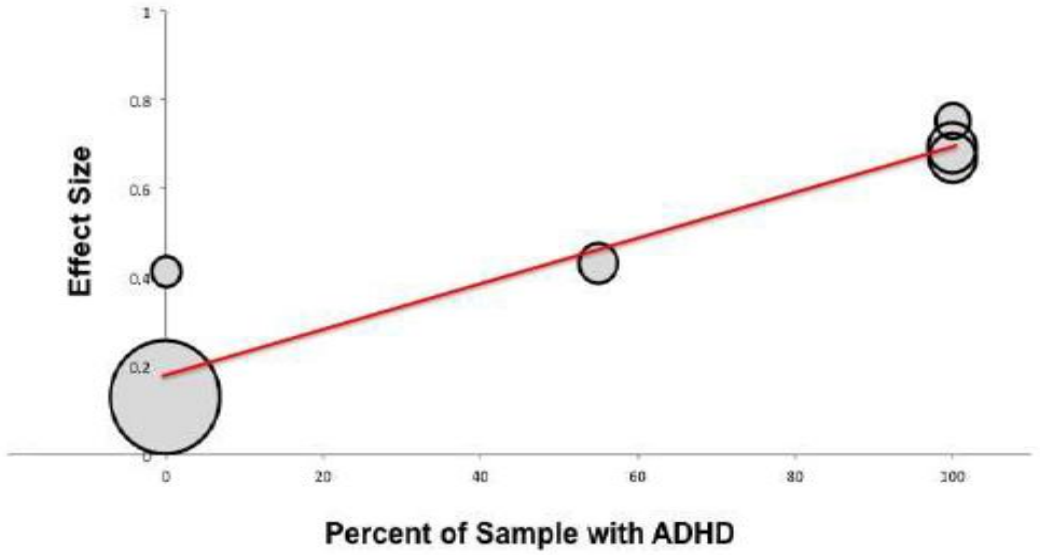
(Adapted from Roessner et al., *Eur Child Adolesc Psychiatry* 2011)

α_{2A}-agonists

- ✓ Moderate confidence of efficacy for Clonidine; low confidence of efficacy for Guanfacine (Extended Release) [1-4 mg]
- ✓ Sedation (Clonidine) – Drowsiness (Guanfacine)
- ✓ Monitor HR and BP with both
- ✓ Monitor QTc in pts with cardiac hx, family hx of long QT and on other QT prolonging agents
- ✓ Gradual taper to avoid rebound hypertension

Larger effect size of **Clonidine** in RCTs ***for <u>TS children/adolescents with comorbid ADHD</u>***
[Weisman et al., 2013]

→ SMD from 0.45 (all) to 0.72 (those with comorbid ADHD)



Dopamine receptor blockers supported by RCTs

DRUG	EFFICACY	CONFIDENCE in efficacy Modified from the GRADE system	TOXICITY
Aripiprazole (partial agonist)	SMD 0.64 (0.31-0.97)	1 Class I, 1 Class II Moderate confidence	**Weight gain**, BMI and WC increase, sedation, somnolence
Risperidone	SMD 0.79 (0.31-1.27)	2 Class II Moderate confidence	**Weight gain**, parkinsonism, fatigue, somnolence
Tiapride	SMD 0.62 (0.36-0.88)	1 Class I Moderate confidence	**Fatigue,** **sleep disturbances**
Haloperidol	SMD 0.59 (0.11-1.06)	2 Class II Moderate confidence	Movement disorders, hyperprolactinemia
Pimozide	SMD 0.66 (0.06-1.25)	3 Class II Low confidence	**Movement disorders,** QTc prolong, hyperprolactinemia
Ziprasidone	SMD 1.14 (0.32-1.97)	1 Class II Low confidence	QTc prolong, hyperprolactinemia
Metoclopramide	SMD 1.14 (0.33-1.95)	1 Class II Low confidence	Movement disorders, hyperprolactinemia

Dopamine receptor blockers supported by RCTs

Ecopipam for Tourette Syndrome: A Randomized Trial

Pediatrics 2023

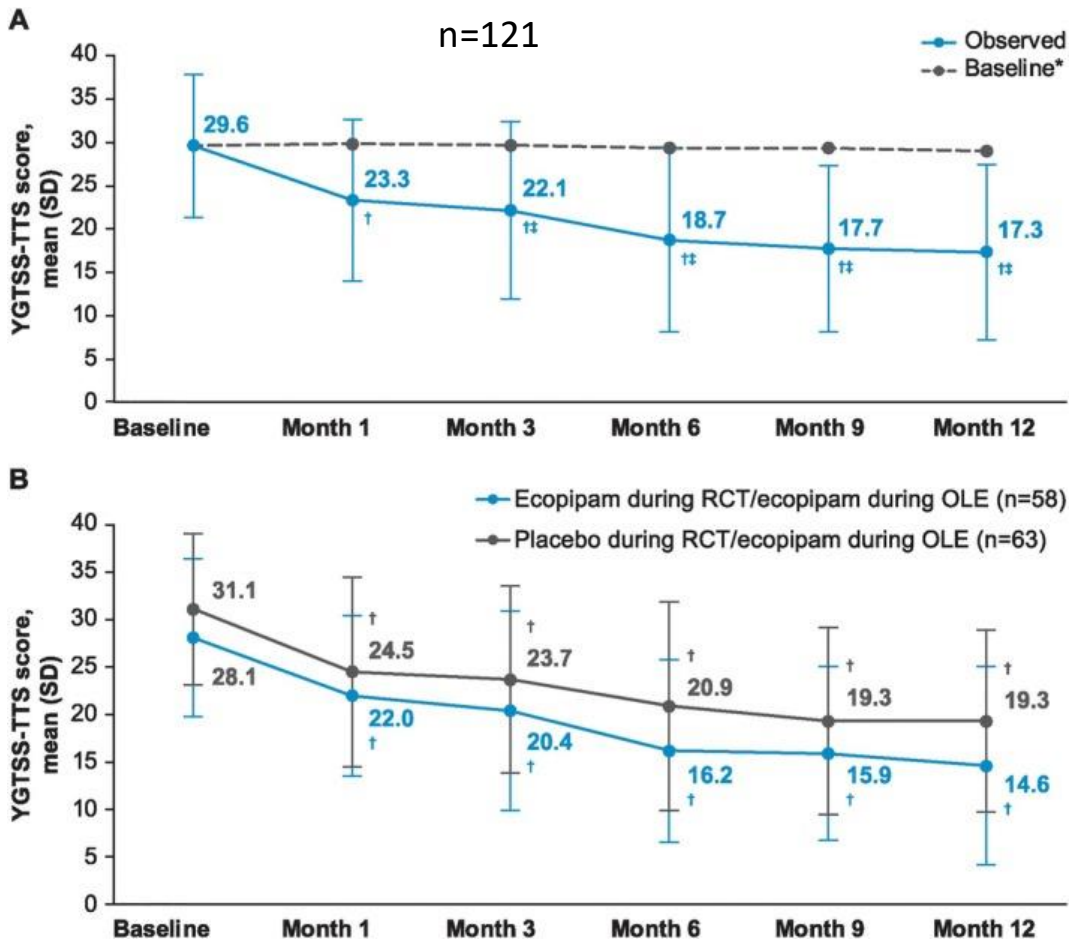
Donald L. Gilbert, MD, MS,[a,b] Jordan S. Dubow, MD,[c] Timothy M. Cunniff, PharmD,[d] Stephen P. Wanaski, PhD,[d] Sarah D. Atkinson, MD,[e] Atul R. Mahableshwarkar, MD[f]

- Phase 2b double-blind, randomized, placebo-controlled crossover study
- N=153, age 6-17 years
  - Change of approximately 4 points on the Yale Global Tic Severity Scale compared to placebo
  - Good tolerability

12-month OLE
1.8 mg/kg/day

[Gilbert et al., *Mov Disord Clin Pract* 2025]

n=121



- No significant metabolic or motor changes
- Sustained significant improvements on YGTSS-TTS and GTS-QoL for Children & Adolescents

Fluphenazine

- 1 single blind RCT
  - Comparison of fluphenazine, haloperidol, trifluoperazine and placebo
  - 10 patients, aged 12-43 years
  - Dosage 8-24 mg/day
  - All drugs produced significant improvement in tics compared to placebo
  - Fluphenazine least likely to produce side effects
- 1 open label study
  - 21 patients, aged 7-47 years, all previously intolerant of haloperidol
  - Dosage 2-15 mg/day
  - 16/21 reported fewer side effects than haloperidol, and greater or similar improvement in tics
- AAN Guidelines: option for severe, treatment-resistant TS, acting as a second-line pharmacotherapy

Topiramate

- 1 single blind RCT
  - Comparison with placebo
  - 29 patients, children and adults
  - Low confidence of efficacy
- In patients who are not obtaining a satisfactory response or experience adverse effects from other medical treatments, topiramate may be a useful alternative
- Adverse effects include cognitive and language problems, somnolence, weight loss, and it may increase the risk of renal stones

Botulinum neurotoxins

Neglected by research, but huge treatment resource in older teens and adults, especially for motor tics

- Moderate confidence in the evidence – 1 Class II study (Marras et al., 2001)
  - → SMD 1.27 [95% CI 0.51-2.03]
- Doses similar to those used for dystonia (lower for larynx → 0.625-1.5 MU abo-BoNT bilaterally)
- Weakness and hypophonia – Premonitory sensations and urges also improve
- Do we need better education (atlases, courses) for this?

Movement Disorders
CLINICAL PRACTICE
BRIEF REPORT

Toxin for Tics: Practical Guidance for Clinicians from a Registry-Based Naturalistic Study

Tamara Pringsheim, MD* and Davide Martino, MD, PhD

Tic type	Muscle	Number of participants	Mean dose (in units) per side (range)
Eye blinking	Orbicularis oculi	12	12.9 (5–22.5)
	Corrugator	4	7.5 (5–10)
Head turn	Splenius capitis	10	31 (5–70)
	Sternocleidomastoid	5	22 (5–30)
	Trapezius	1	50
Shoulder raising	Trapezius	10	63.5 (15–125)
	Levator scapulae	2	50
Eyebrow depression	Corrugator	7	6.8 (5–10)
	Procerus	7	7.1 (2.5–10)
Jaw clenching	Temporalis	5	7 (5–10)
	Masseter	3	9.2 (5–15)
Eyebrow raising	Frontalis	6	13.3 (5–20)
Head flexion/extension	Semispinalis	5	30 (20–50)
	Trapezius	1	25
Lowering of midfacial muscles and jaw	Platysma	4	15 (10–20)
Nose wrinkling	Nasalis	2	4.5 (4–5)
Mouth movement	Depressor labii inferioris	1	2
Wink	Orbicularis oculi	1	5

- Out of 95 participants, 32 (33.7%) received botulinum toxin → the most common medication for tics in this cohort
- Participants receiving botulinum toxin: older and lower vocal and total tic severity
- Average duration of treatment: 40.4 months, with 19 participants continuing injections every three months
- Mean total dose: 10-250 units
- Concurrent oral medications used by 34% of participants, with topiramate and aripiprazole being the most common

Exogenous cannabinoids

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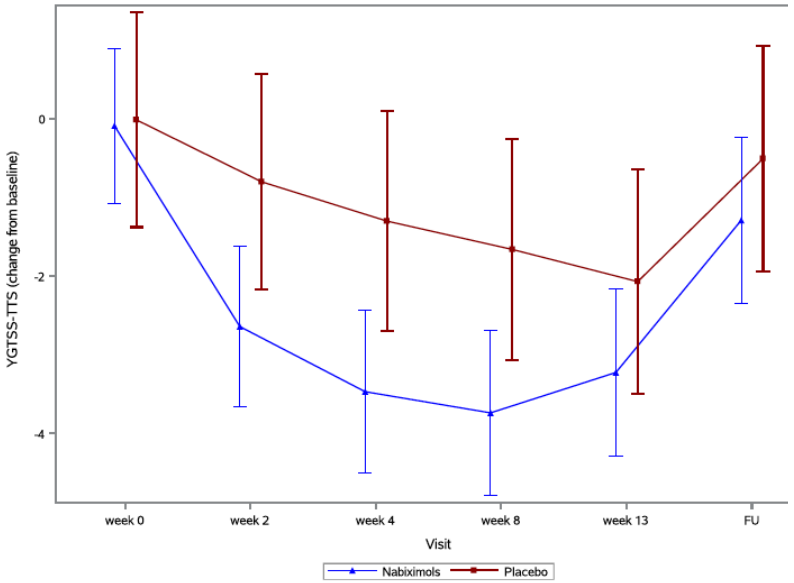
CANNA-TICS: Efficacy and safety of oral treatment with nabiximols in adults with chronic tic disorders – Results of a prospective, multicenter, randomized, double-blind, placebo controlled, phase IIIb superiority study

Kirsten R. Müller-Vahl [a], Anna Pisarenko [a], Natalia Szejko [b,c], Marti
Ewgeni Jakubovski [a], Richard Musil [d], Alexander Münchau [e], Irene
Ludger Tebartz van Elst [k], Christoph Schröder [l], Rieke Ringlstetter [n]
Beate Jenz [m], Anika Großhennig [m,*]

[a] Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany
[b] Department of Neurology, Medical University of Warsaw, Poland
[c] Department of Bioethics, Medical University of Warsaw, Poland
[d] Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Munich, Germany
[e] Institute of Systems Motor Science, University of Lübeck, Lübeck, Germany
[f] Departments of Psychiatry, Psychotherapy, and Psychosomatics, School of Medicine, RWTH Aachen University, Aac
[g] Institute of Neuroscience and Medicine (INM-4), Forschungszentrum Jülich, Jülich, Germany
[h] JARA-BRAIN - Translational Medicine, Aachen, Germany
[i] Department of Psychiatry and Psychotherapy, University of Cologne, Faculty of Medicine and University Hospital Cc
[j] Department of Psychiatry and Psychotherapy III, LVR Hospital Bonn, Bonn, Germany
[k] Department of Psychiatry and Psychotherapy, Medical Center-University of Freiburg, Faculty of Medicine, Universit
[l] Institute of Clinical Pharmacology, Hannover Medical School, Hannover, Germany
[m] Institute of Biostatistics, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover 30625, Germany



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ABSTRACT

Preliminary data suggest that cannabis-based medicines might be a promising new treatment for patients with Tourette syndrome (TS)/chronic tic disorders (CTD) resulting in an improvement of tics, comorbidities, and quality of life. This randomized, multicenter, placebo-controlled, phase IIIb 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). The primary efficacy endpoint was defined as a tic reduction of ≥ 25% according to the Total Tic Score of the Yale Global Tic Severity Scale after 13 weeks of treatment. Although a much larger number of patients in the nabiximols compared to the placebo group (14/64 (21.9%) vs. 3/33 (9.1%)) met the responder criterion, superiority of nabiximols could formally not be demonstrated. In secondary analyses, substantial trends for improvements of tics, depression, and quality of life were observed. Additionally exploratory subgroup analyses revealed an improvement of tics in particular in males, patients with more severe tics, and patients with comorbid attention deficit/hyperactivity disorder suggesting that these subgroups may benefit better from treatment with cannabis-based medication. There were no relevant safety issues. Our data further support the role of cannabinoids in the treatment of patients with chronic tic disorders.

Randomized Controlled Trial Cannabis Cannabinoid Res. 2023 Oct;8(5):835-845.
doi: 10.1089/can.2022.0091. Epub 2022 Aug 30.

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

Elia Abi-Jaoude [1 2], Tracy Bhikram [2], Ferdous Parveen [2], Jody Levenbach [2],
Myriam Lafreniere-Roula [2], Paul Sandor [2 3]

Affiliations
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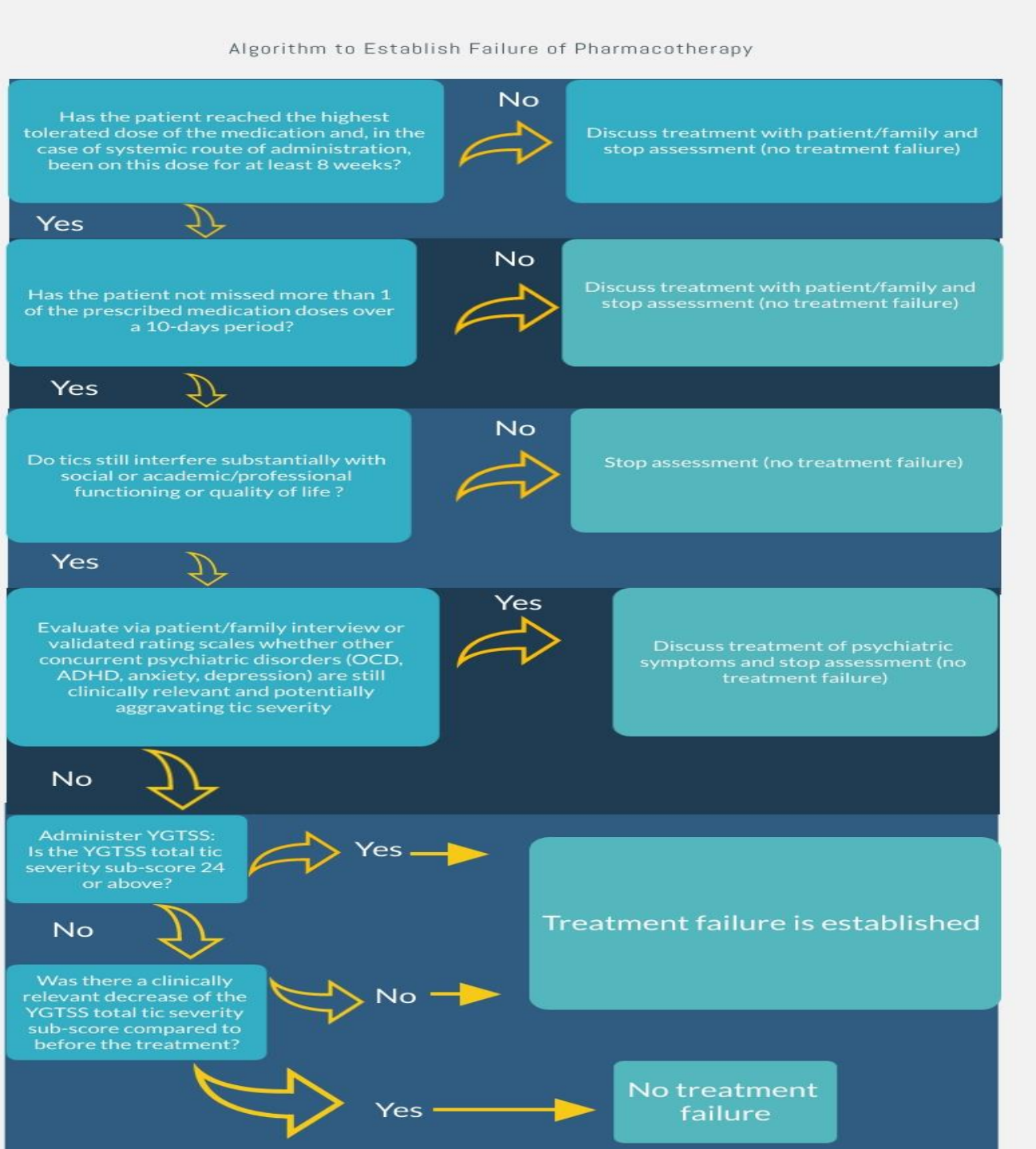
Abstract

Background: The number of effective evidence-based treatment options for patients with Tourette syndrome (TS) is 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 Δ^9-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 a 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 significant difference 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.

2019 AAN recommendations on cannabinoids

- 12a: Due to the risk associated with cannabis use and widespread self-medication with cannabis for tics, where regional legislation allows, physicians must offer to direct patients to appropriate medical supervision when cannabis is used as self-medication for tics (A). Appropriate medical supervision would entail education and monitoring for efficacy and adverse effects.
- 12b: Where regional legislation allows, physicians may consider treatment with cannabis-based medication in otherwise treatment resistant adult patients with TS suffering from clinically relevant tics (C).
- 12c: Where regional legislation allows, physicians may consider treatment with cannabis-based medication in adult patients with TS who already use cannabis efficiently as a self-medication in order to better control and improve quality of treatment (C).
- 12d: Where regional legislation allows, physicians prescribing cannabis-based medication must prescribe the lowest effective dose to decrease the risk of adverse effects (A).
- 12e: Physicians prescribing cannabis-based medication must inform patients that medication may impair driving ability (A).
- 12f: Physicians prescribing cannabis-based medication to patients with TS must periodically re-evaluate the need for on-going treatment



International Parkinson and Movement Disorder Society

Tic Disorders and Tourette Syndrome Study Group

[Martino…Ganos, *Eur Child Adolesc Psychiatry* 2021]

CASE #1

✓ 10-year-old girl who has completed grade 5

Medications: Lisdexamfetamine 20 mg once in the morning per day and fluticasone furoate 27.5 mcg per actuation nasal spray, one spray in both nostrils daily; also on magnesium, multivitamin, and omega-3 fish oil supplementation

Tic onset age of 6 during the pandemic time

First ever tics, quite complex → whole body movements in extension of the trunk. Since then, relatively broad repertoire of both motor and phonic tics in the past 4 years:

eye winking, eye rolling movements, head jerks, and some finger tapping movements mostly when writing or playing the piano

whole upper body startle-like movements involving the trunk and both shoulders and the neck and often coupled to a hiccup-resembling phonic tic; skin picking thumbs

pausing, especially when reading loud, at the middle of a sentence or a word, giving a robotic pattern to the enunciation

Yale Global Tic Severity Scale: total tic severity subscore of 25, to which an impairment score of 30 is added to lead to a global tic severity score of 65.

CASE #1

- Difficulties in verbalizing premonitory urges
- Denies being significantly bothered by the tics in her daily life; does not feel that the tics are having a negative role on her social interactions and are usually not commented upon by her peers
- Takes a **longer time to complete her school assignments** when they are written as well as an impact on piano playing, for which she has reached grade 3.

COMORBIDITIES

- **ADHD, inattentive subtype**, in the past few months and has been on stimulants, for a couple of months with good response
- Some **obsessional** behavior, mostly excessive focus on keeping the same position of the seats during meals and a general perfectionistic attitude
- Sometimes put off by unexpected changes from routines and sporadic emotional tantrum with crying and yelling (emotional dysregulation but overall manageable for her family)
- Misophonia

✓ Premature labor at 26 weeks of pregnancy; developmental milestones in time and regularly.
✓ Unremarkable past medical history (adenoidectomy and tonsillectomy)
✓ Home schooled over the past 2 years and has just finished grade 5; family soon to relocate to the US for study leave
✓ Father diagnosed with ADHD inattentive subtype and improved on Vyvanse
✓ Unremarkable physical exam

CASE #1: what shall we do?

- ❖ Care navigation through the TS-OCD Alberta Network
- ❖ Education
- ❖ Consideration for active treatment:
  - difficult access to behavioral therapy
  - start an alpha-agonist (guanfacine) → hear preference from family and child

CASE #4

✓ 17-year-old girl, Grade 10

Tic onset age 4 (diagnosis of TS age 8)

First ever tics → rubbing her nose

blinking, eye movements, nasal movements, facial grimacing, head jerks, shoulder shrugging, touching, evening up, leg stretching (a bit painful)

grunting, burping, coughing, throat clearing, sniffing, whistling, squeaking, 'hiccups', forceful exhalation, repetition of random phrases when alone, adding the letter "J" in front of words

Moderate intensity and frequency, mild interference

Moderate impairment (impact on self esteem and no sense of agency or volitional control)

Typical fluctuating course, no consistent trigger of typical exacerbations; tics worsen when excited and can improve when painting or listening to music

CASE #4

COMORBIDITIES

No ADHD features

OCS/OCB: miscellaneous obsessions (mainly intrusive words) and compulsions, e.g., walking back and forth repeatedly and forced touching or evening up; mild and not impairing

MASC: T-score of 75 for Obsessions/Compulsions, otherwise normal

No depression

No sleep issues

Born at term, natural delivery, normal achievement of developmental milestones

Family history: ADHD in several family members on her maternal side; maternal cousin with ASD, depression in maternal aunt and grandmother

In Grade 10, average academic performance, very social, enjoys theatre, painting, reading, drawing, arts and movies

CASE #4: what shall we do?

- Is the patient in need of active treatment of tics?

- Does the presence of obsessive-compulsive behaviors influence our management decision, and how?

- Consideration for active treatment:
  - access to behavioral therapy and/or start an alpha-agonist (guanfacine)

- 6 months later: tics have worsened in terms of frequency and overall impairment; difficult access to therapists using HRT or ERP and moderate dose of guanfacine not helpful; tics very tiring and bad meltdowns at home in terms of tic intensity and emotional control → WHAT NOW?
  - start aripiprazole 2 mg, good adherence and tolerability → 3 months later 25-30% decrease in tic frequency and impairment / new bird sound-like vocal tic → increase aripiprazole to 4 mg → 3 months control improved with sporadic persistence of head jerks and shoulder/hand movements → back to 2 mg → 4 months later new worsening of tics, back to 4 mg but not enough → increase to 6 mg but expedited clinical follow-up