17th International Conference on Tourette Syndrome & Tic Disorders

TS school

Athens

TS-school Athens | Tuesday, 20th May 2025, Eugenides Foundation

Pharmacological treatment, psychological intervention, deep brain stimulation

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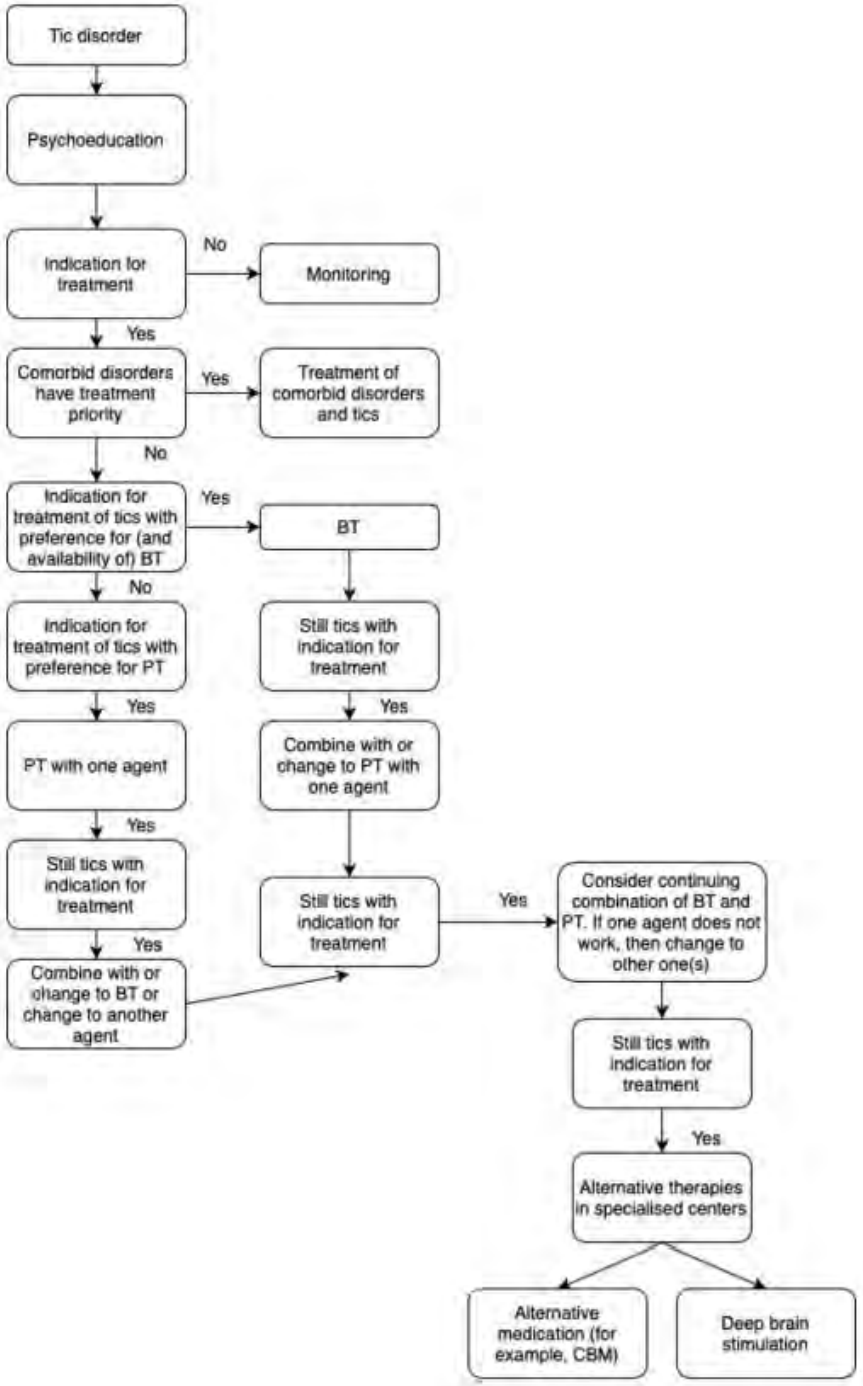

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European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-021-01832-4

REVIEW

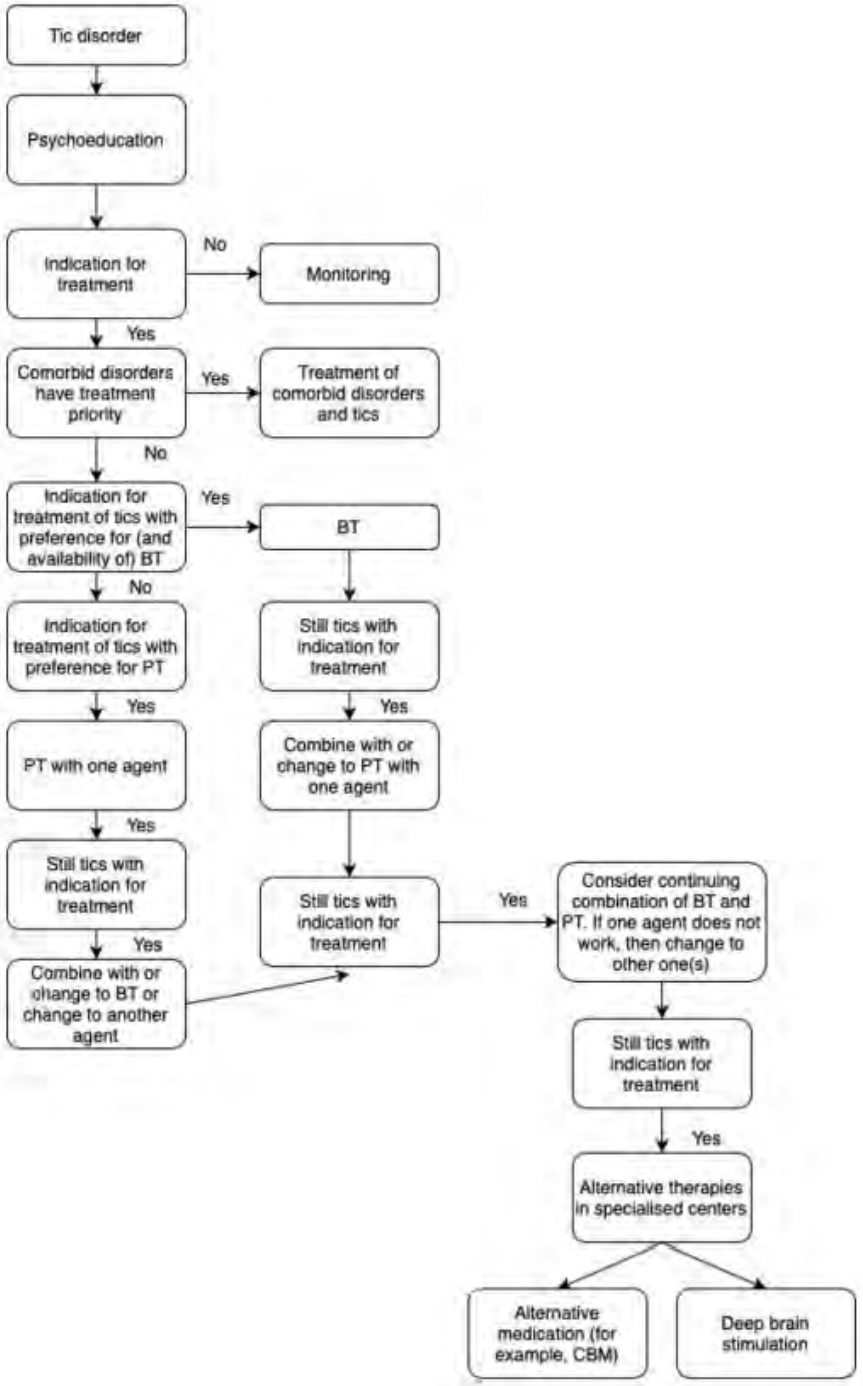
European clinical guidelines for Tourette syndrome and other tic disorders: summary statement

Kirsten R. Müller-Vahl[1] · Natalia Szejko[2,3,4] · Cara Verdellen[5,11] · Veit Roessner[6] · Pieter J. Hoekstra[7] · Andreas Hartmann[8] · Danielle C. Cath[9,10]

Received: 8 March 2021 / Accepted: 19 June 2021

Part I: Assessment
Part II: Psychological interventions
Part III: Pharmacological treatment
Part IV: Deep brain stimulation

Summary statement
Patients' perspectives
Editorial



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Treatment of Tics

- Motor and vocal tics
- Simple and complex tics
- Children and adults
- Duration of tics

- Primary and secondary tics (not functional „tic-like“ behaviors)
- Self-injurious behavior

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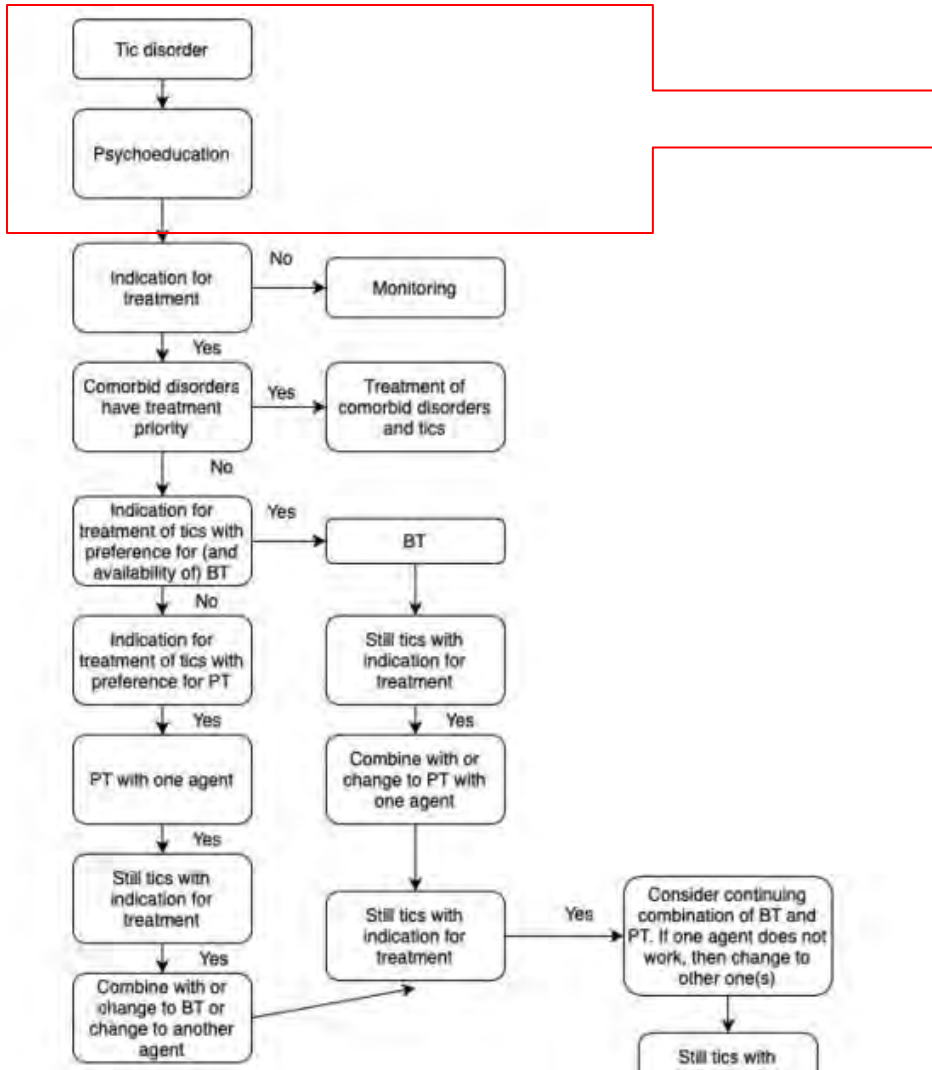

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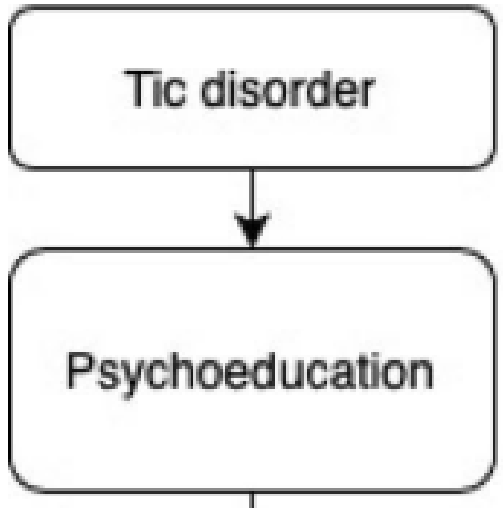
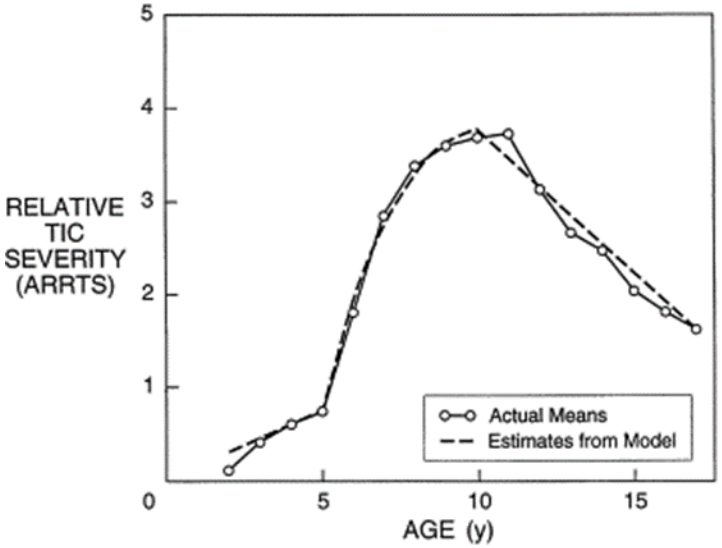


Course of Tics

- Age dependency
- Age at onset: 5-7 years
- Maximum: 10. -12. (-14.) years
- In most cases improvement of tics in adolescents and adulthood



Leckman JF, King RA, Bloch MH. Clinical Features of Tourette Syndrome and Tic Disorders. J Obsessive Compuls Relat Disord. 2014 Oct;3(4):372-379.

Review

Why Tic Severity Changes from Then to Now and from Here to There

Ann M. Iverson [1] and **Kevin J. Black** [2,*]

Citation: Iverson, A.M.; Black, K.J. Why Tic Severity Changes from Then to Now and from Here to There. *J. Clin. Med.* **2022**, *11*, 5930. https://doi.org/10.3390/jcm11195930

Table 1. Summary of factors that impact tics.

Improves Tics	Mixed Effects	Worsens Tics	Unclear Effects
Rewards for tic suppression	Stress	Fatigue	Social media
Musical performance	Distraction	Anxiety	Some foods
Exercise	Observation by others	Thinking about tics	Dietary supplements
		Attention to tics	
		Social conflict	

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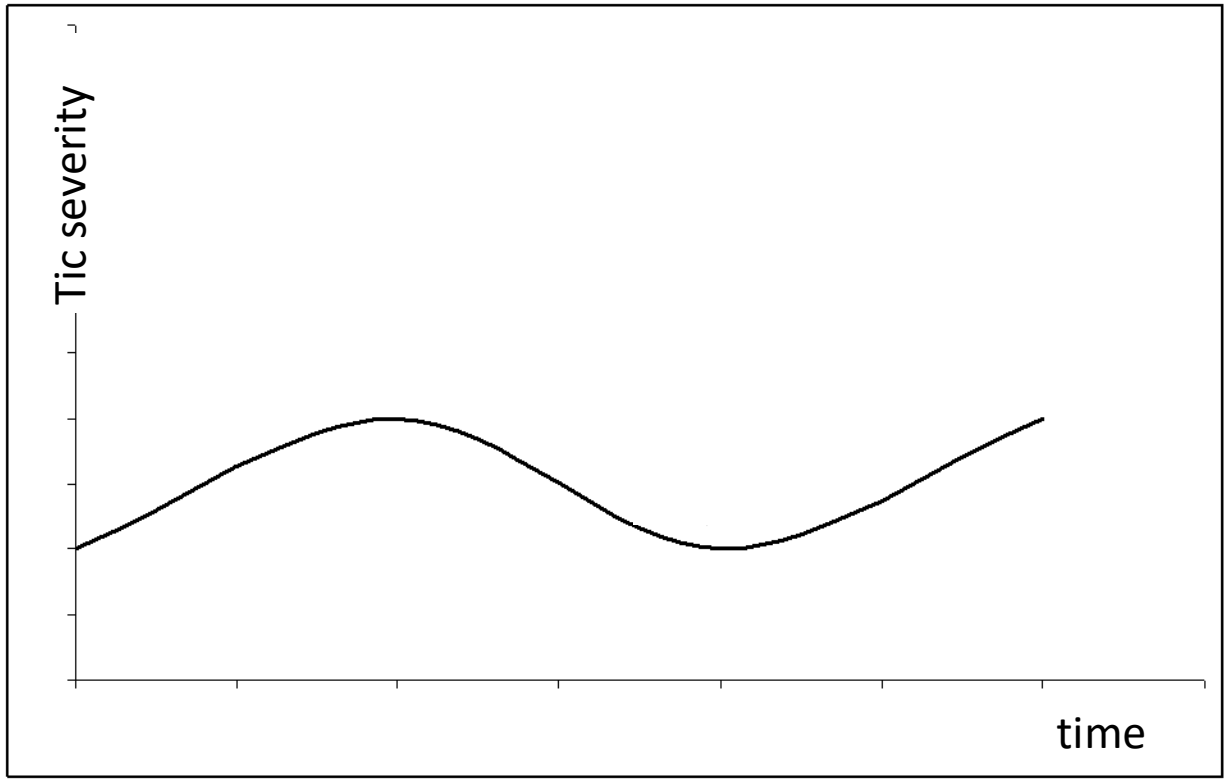
Worsens tics: stress, emotional stress
anger, anxiousness, excitement
conversation about tics

Improves tics: concentration
relaxation

Waxing and waning



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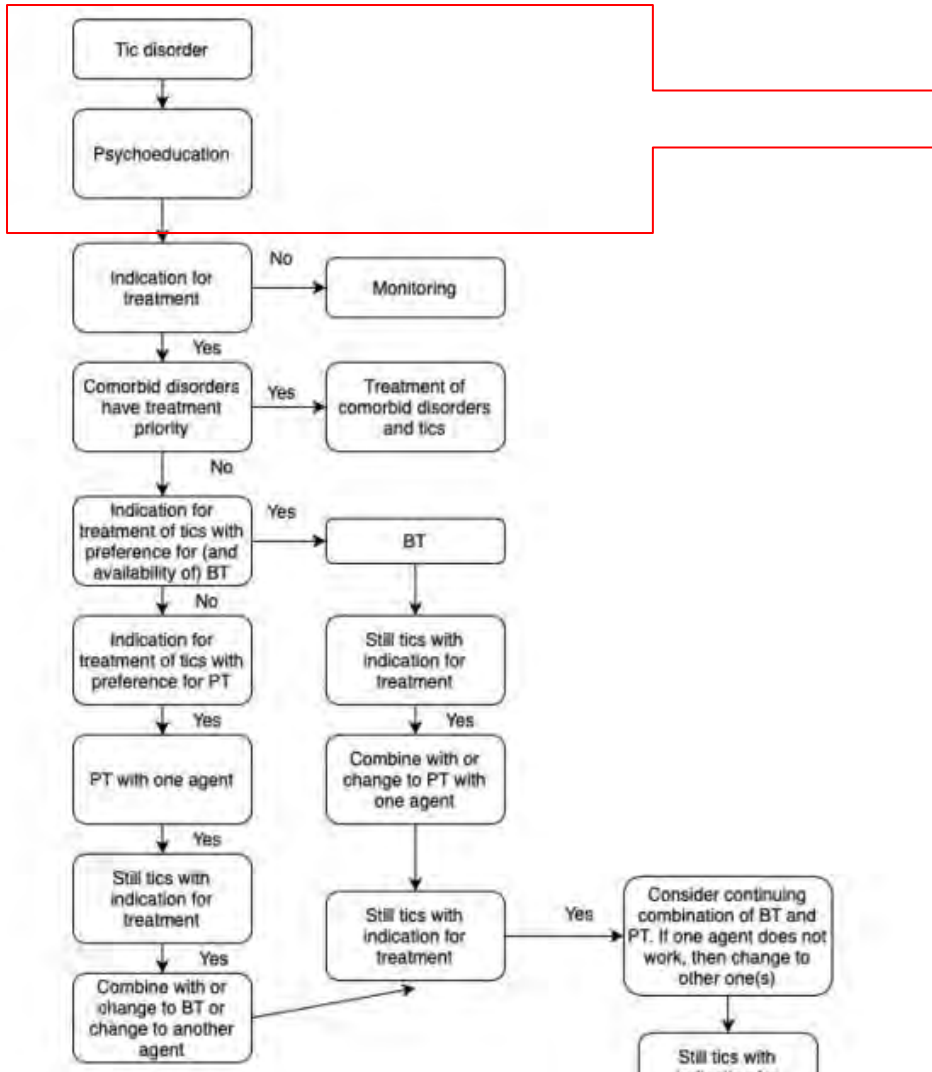

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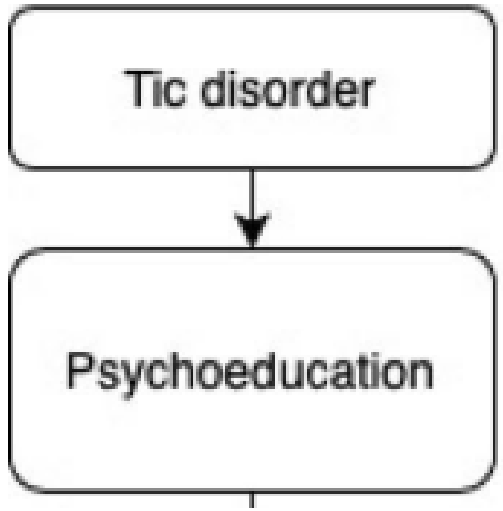

- Typical course of tics
- Prognosis
- Comorbidities
- Treatment options
- Presentation in TV/social media
- Advocacy groups
- Information for school/work

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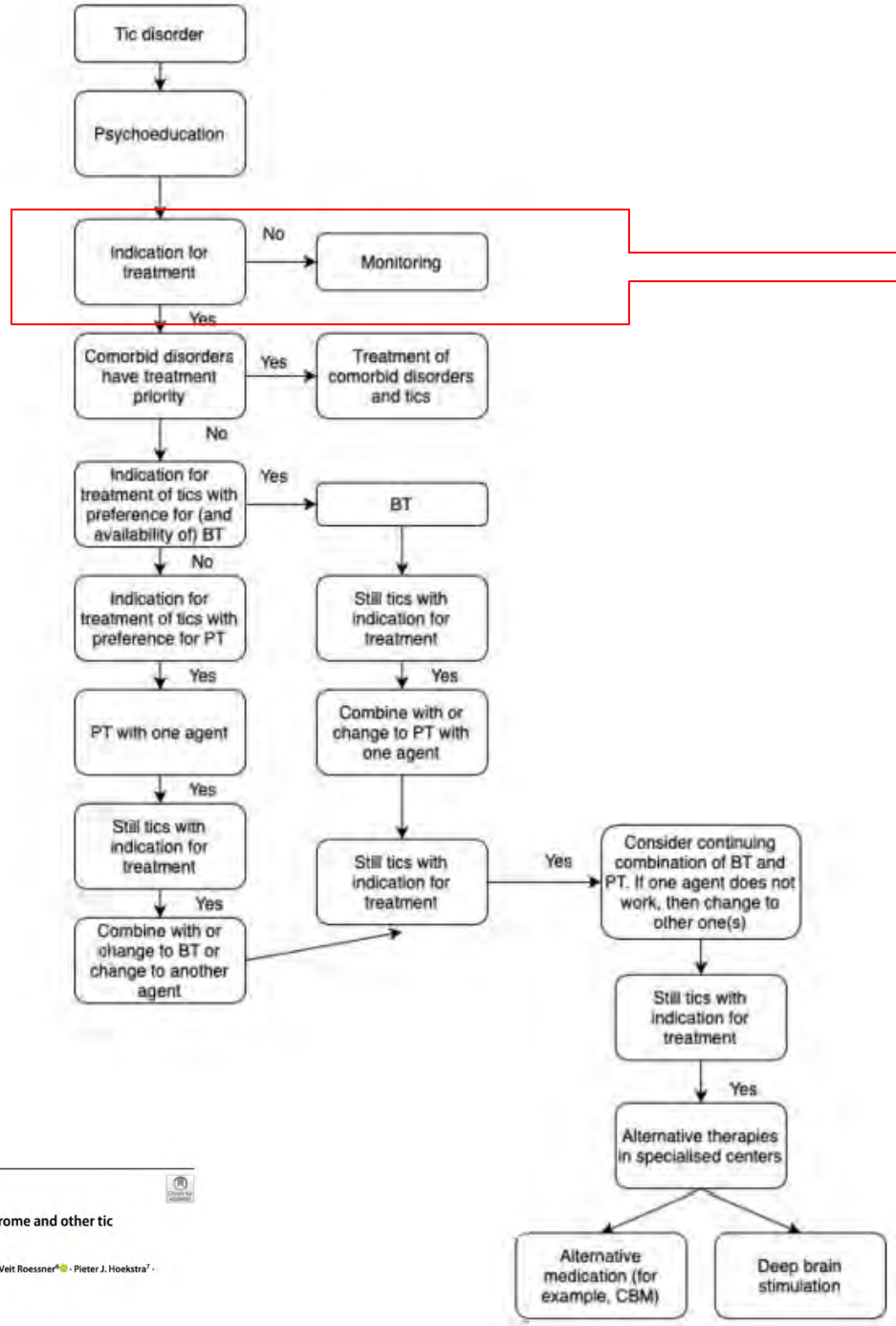

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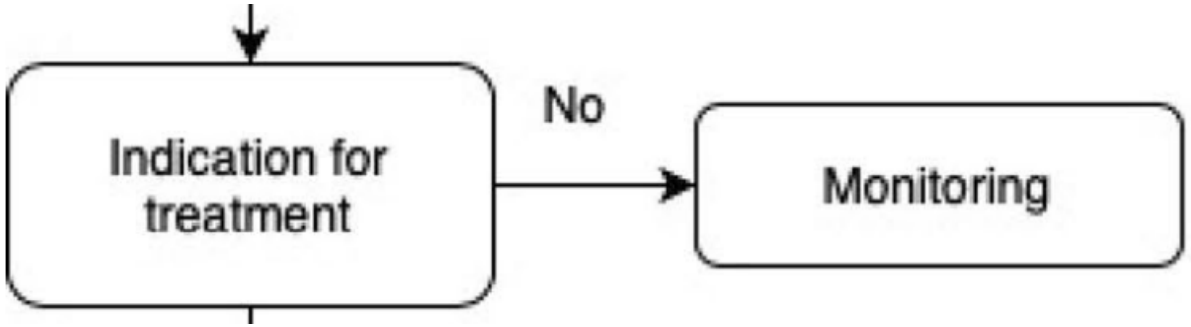
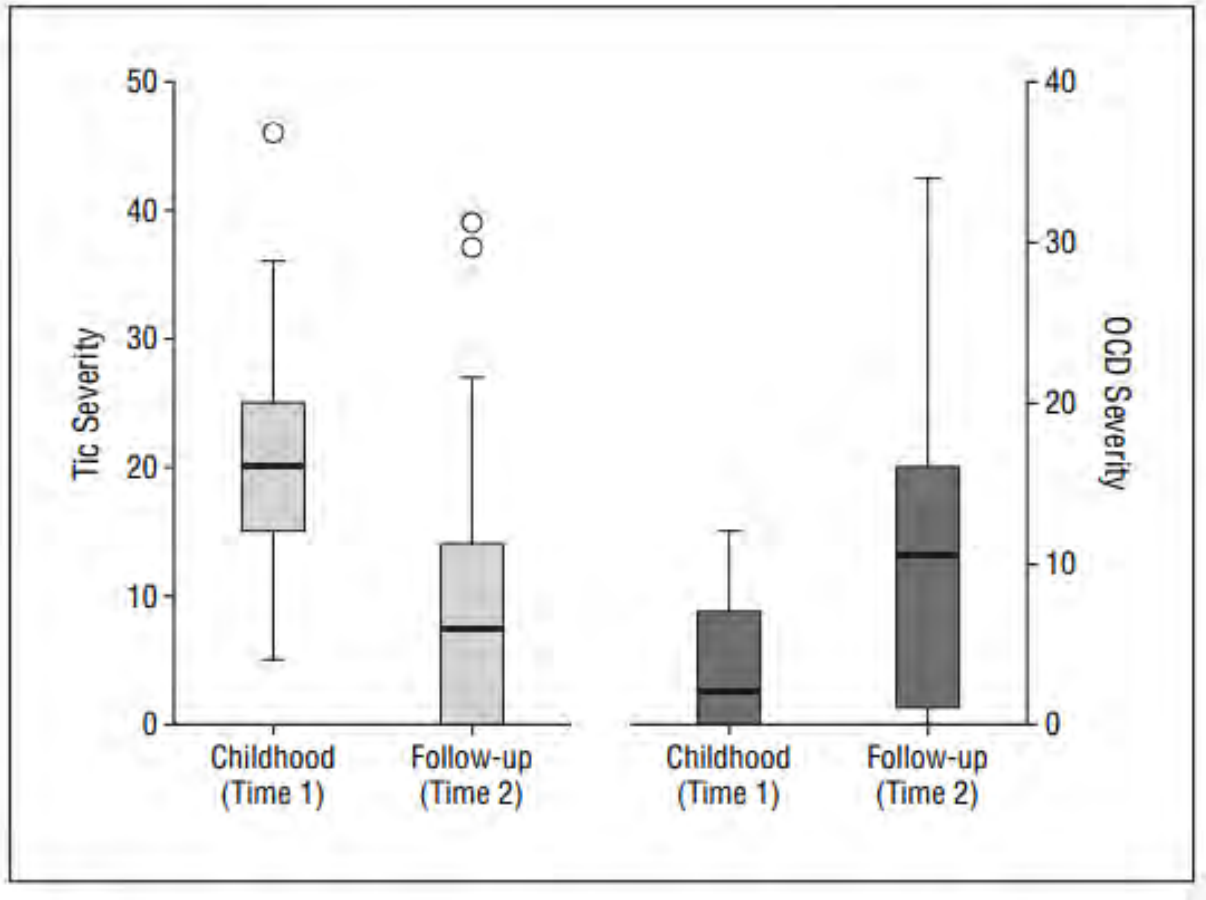


Course of Tourette Syndrome



Adulthood Outcome of Tic and Obsessive-Compulsive Symptom Severity in Children With Tourette Syndrome

Michael H. Bloch, BA; Bradley S. Peterson, MD; Lawrence Scahill, MSN, PhD; Jessica Otka, BA; Lily Katsovich, MS; Heping Zhang, PhD; James F. Leckman, MD

Arch Pediatr Adolesc Med. 2006;160:65-69

Figure 1. Box plots comparing tic and obsessive-compulsive disorder (OCD) symptom severity at the time of initial assessment in childhood (time 1) and follow-up in early adulthood (time 2). Tic symptom severity scores were measured by the Yale Global Tic Severity Scale[7] and are reported for all 46 subjects with Tourette syndrome. The OCD symptom severity scores were measured using the Children's Yale-Brown Obsessive Compulsive Scale[8] (CY-BOCS) and are reported for those 19 patients with Tourette syndrome with lifetime worst-ever OCD symptom severity scores that were at least in the moderate-severity range (CY-BOCS score, ≥10) as assessed at time 2.

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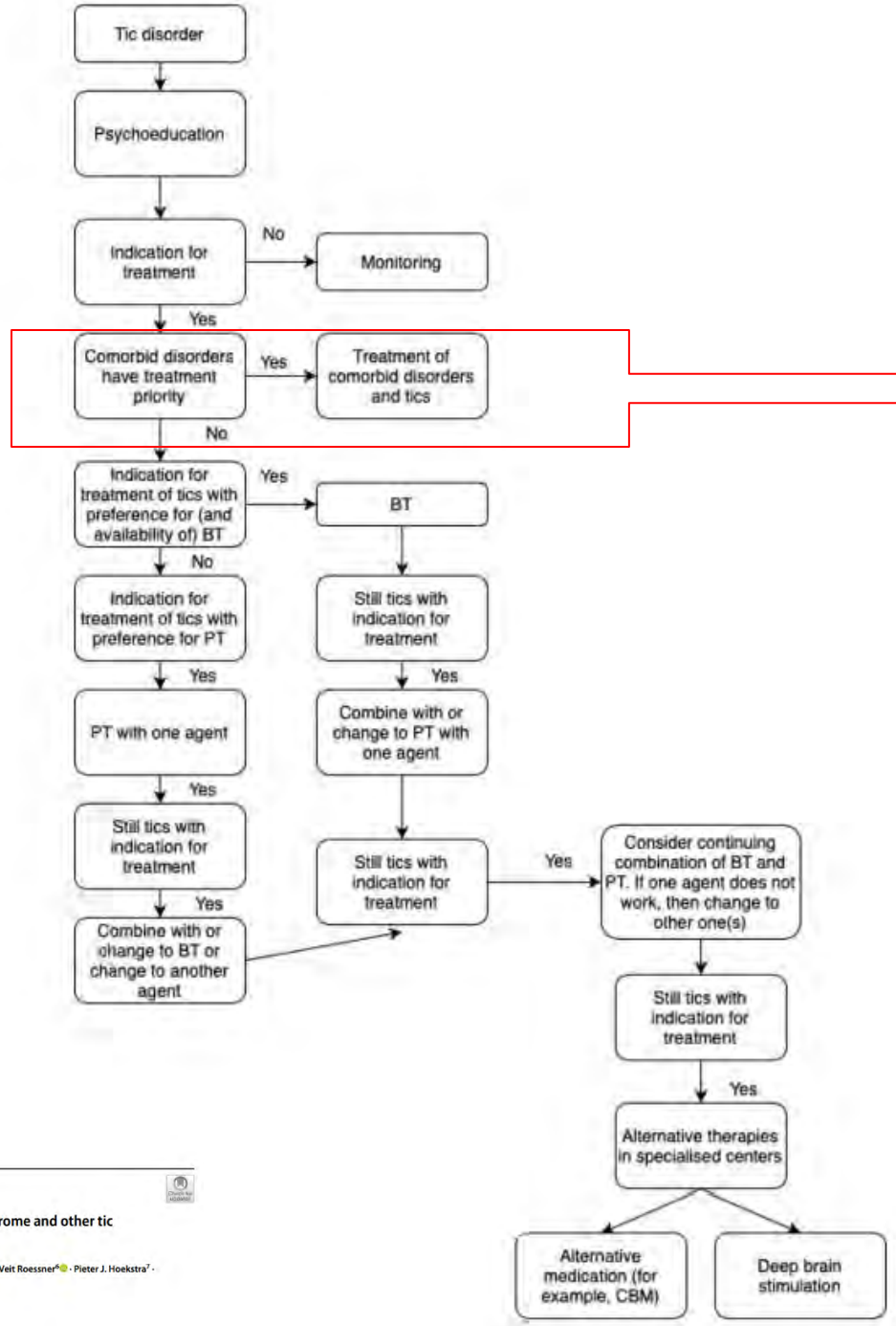

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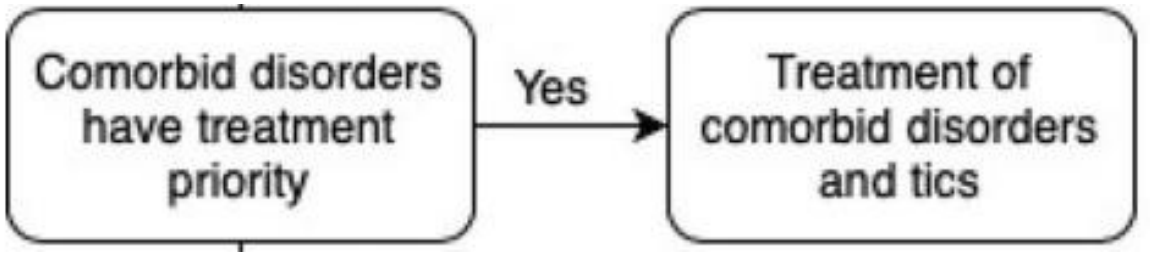

The Effects of Comorbid Obsessive-Compulsive Disorder and Attention-Deficit Hyperactivity Disorder on Quality of Life in Tourette Syndrome

Clare M. Eddy, Ph.D.
Andrea E. Cavanna, M.D., Ph.D.
Mariangela Gulisano, M.D., Ph.D.
Paola Calì, M.D.
Mary M. Robertson, MBChB, M.D., D.Sc.(Med.), DPM, FRCPCH, FRCP(UK), FRCPsych
Renata Rizzo, M.D., Ph.D.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2012; 24:458–462)

Tourette syndrome (TS) is a complex neuropsychiatric disorder affecting patients' quality of life (QoL). The authors compared QoL measures in young patients with "pure" TS (without comorbid conditions) versus those with TS+OCD (obsessive-compulsive disorder), TS+ADHD (attention-deficit hyperactivity disorder), or TS +OCD+ADHD. Age and scores on scales assessing tic severity, depression, anxiety, and behavioral problems were included as covariates. Young patients with both comorbidities exhibited significantly lower Total and Relationship Domain QoL scores, versus patients with pure TS. Across the whole sample, high ADHD-symptom scores were related to poorer QoL within the Self and Relationship domains, whereas high OCD symptom scores were associated with more widespread difficulties across the Self, Relationship, Environment, and General domains. Significant differences in QoL may be most likely when both comorbidities are present, and features of OCD and ADHD may have different impacts on QoL across individual domains.

Effects of comorbidity on Tourette's tic severity and quality of life

Acta Neurol Scand. 2019;140:390–398.

Hilde M. Huisman-van Dijk[1,2] | Suzy J. M. A. Matthijssen[1,2] | Ruben T. S. Stockmann[1] | Anne V. Fritz[1] | Danielle C. Cath[3,4,5]

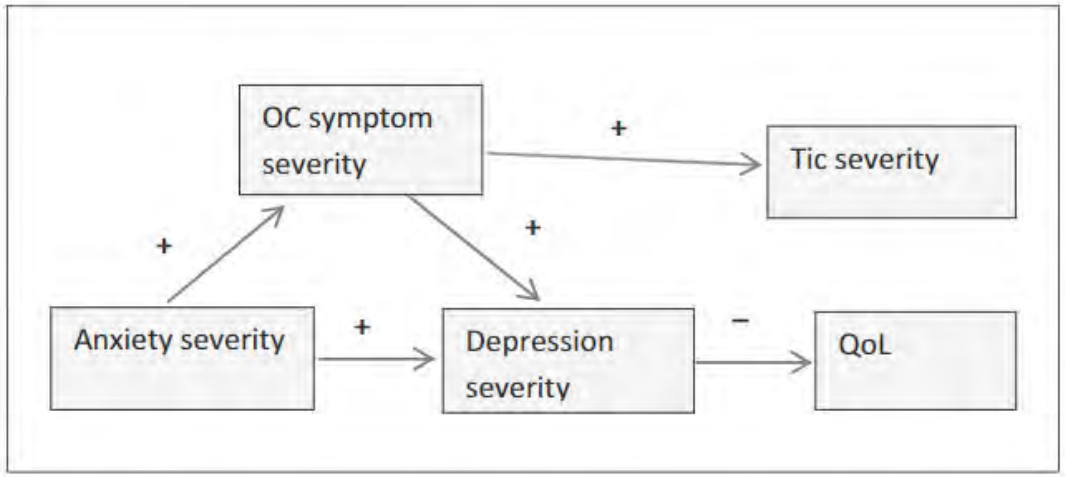

FIGURE 3 Graphic representation of a potential model combining the results of our study. +, Positive effect; −, Negative effect

Conclusion: In line with and extending previous studies, these findings indicate that OC symptom severity directly influences tic symptom severity whereas depression severity directly influences QoL in TD. Results imply that to improve QoL in TD patients, treatment should primarily focus on diminishing OC and depressive symptom severity rather than focusing on tic reduction.

frontiers in Neuroscience

ORIGINAL RESEARCH
published: 12 September 2016
doi: 10.3389/fnins.2016.00415

New Insights into Clinical Characteristics of Gilles de la Tourette Syndrome: Findings in 1032 Patients from a Single German Center

Tanvi Sambrani[1,2]*, Ewgeni Jakubovski[2] and Kirsten R. Müller-Vahl[2]

TABLE 3 | Association between number of comorbidities (=comorbidity score) and mean tic severity*.

Number of comorbidities	*N*	Mean tic severity	*SD*	Std. Error	95% Confidence Interval for Mean	
					Lower bound	Upper bound
0	82	2.11	0.817	0.09	1.93	2.29
1	179	2.38	1.006	0.075	2.23	2.53
2	206	2.71	1.083	0.075	2.56	2.86
3	217	2.82	1.147	0.078	2.67	2.97
4	170	3.02	1.186	0.091	2.84	3.20
5	107	3.38	1.264	0.122	3.14	3.63
6	36	3.69	1.091	0.182	3.33	4.06

**comorbidity score including OCD, anxiety, depression, SIB, rage attacks, and ADHD, mean tic severity (according to SPSS-GSR; missing data: n = 35).*

OCD, obsessive-compulsive disorder; OCB, obsessive-compulsive behavior; ADHD, attention-deficit hyperactivity disorder; SIB, self-injurious behavior; STSS-GSR, Global Severity Rating of the Shapiro Tourette-Syndrome Severity Scale; N, number of cases; SD, standard deviation; Std., Standard.

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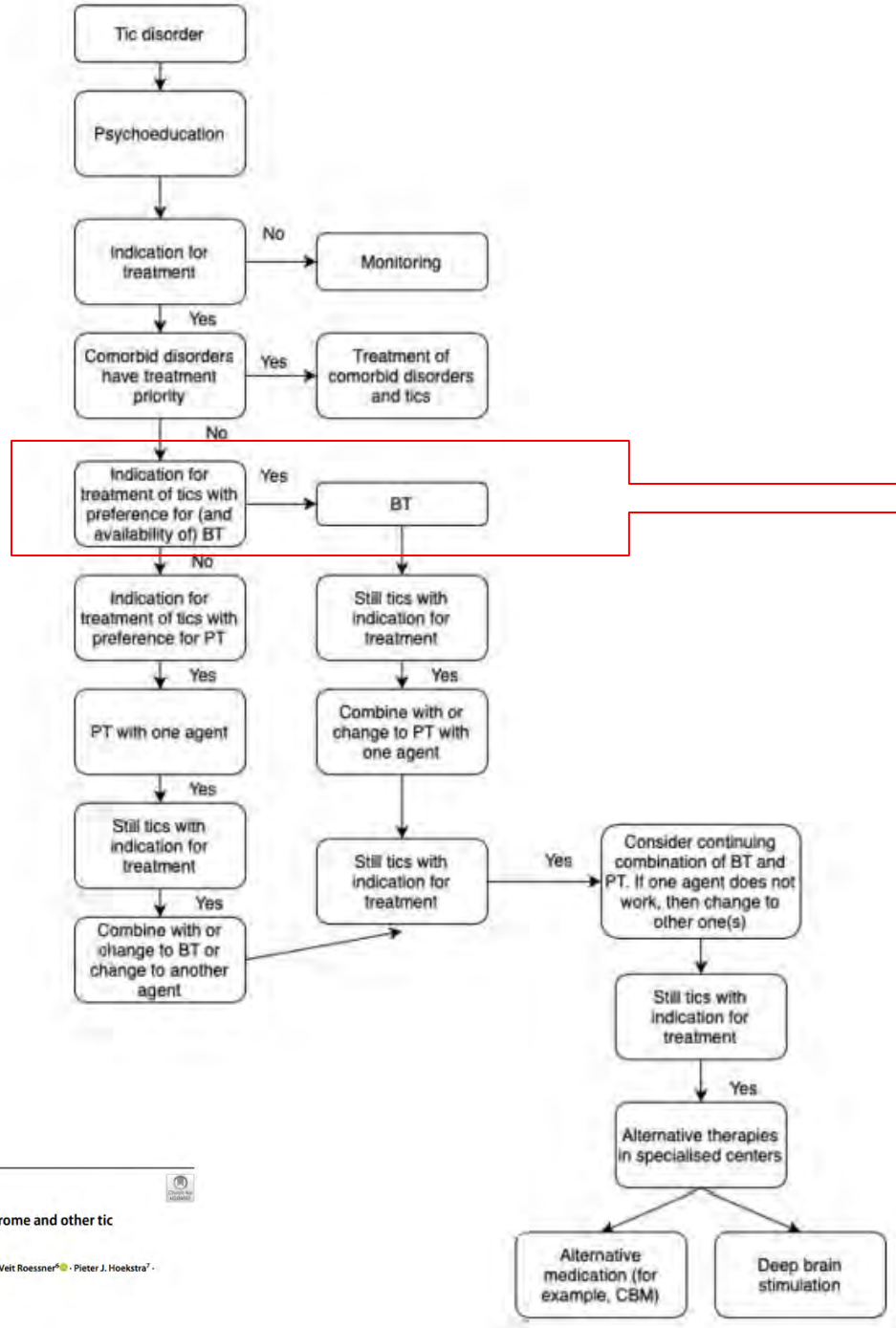

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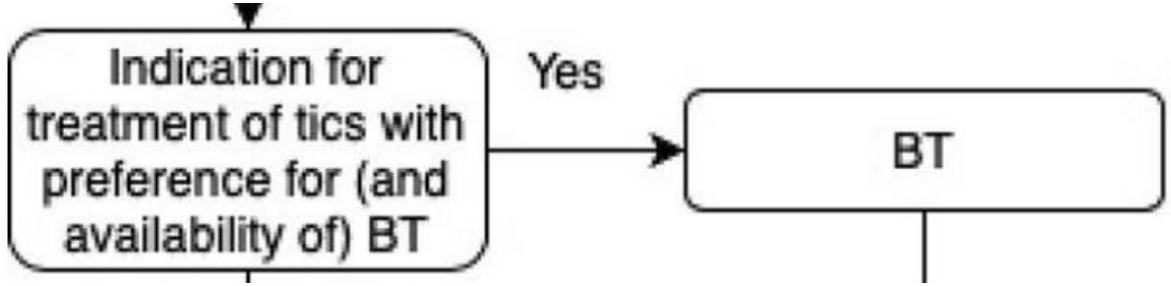


BT=Behavioral Therapy

Behavioral Therapy

- Comprehensive Behavioral Intervention for Tics (CBIT)
  - Habit Reversal Training (HRT)

- Exposure and response prevention (ERP)

Behavioral Therapy

- Comprehensive Behavioral Intervention for Tics (CBIT)
  - Habit Reversal Training (HRT)
    - Self-awareness training
    - Establishing a tic hierarchy, selecting a target tic and reverse engineering it
    - Formulating a competing response to the target tic using habit reversal techniques
  - Psychoeducation
  - Relaxation training
  - Social support

Behavioral Therapy

- Comprehensive Behavioral Intervention for Tics (CBIT)
  - Habit Reversal Training (HRT)
    - Self-awareness training
    - Establishing a tic hierarchy, selecting a target tic and reverse engineering it
    - Formulating a **competing response** to the target tic using habit reversal techniques
  - Psychoeducation
  - Relaxation training
  - Social support

CBIT/HRT: Competing Response

- Initiation of a purposeful movement when the urge to tic appears
- Response/movement physically incompatible with the targeted tic
- To be used at each occurrence of the urge
- To be hold until the urge passes, but at least 1 minute

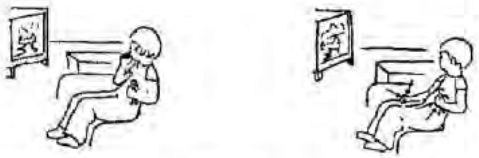
Nervöse Verhaltens-gewohnheit oder Tic		Competing Response
Zucken der Schulter		Herabziehen der Schultern
Zucken der Schulter und Hochziehen des Ellenbogens		Herabziehen der Schultern, Pressen der Ellebogen an den Körper , Hände an die Beine
Drehen des Kopfes		Isometrische Anspannung der Nackenmuskulatur, leichtes Herabziehen des Kinns, geradeaus schauen
Schütteln des Kopfes		Langsame Anspannung der Nackenmuskulatur, geradeaus schauen
Zupfen der Augenbrauen		Festhalten von Objekten
Nägelkauen		Festhalten von Objekten
Daumenlutschen		Hände zu Fäusten ballen

Abb. 43.3. Bildliche Darstellung der von Azrin und Nunn vorgeschlagenen, mit der Verhaltensgewohnheit inkompatiblen Competing Response bei einigen nervösen Verhaltensgewohnheiten und Tics. (Nach Azrin u. Nunn 1973)

Behavior Therapy: CBIT / HRT

Behavior Therapy for Children With Tourette Disorder
A Randomized Controlled Trial

John Piacentini, PhD
Douglas W. Woods, PhD
Lawrence Scahill, PhD, MSN
Sabine Wilhelm, PhD
Alan L. Peterson, PhD
Susanna Chang, PhD
Golda S. Ginsburg, PhD
Thilo Deckersbach, PhD
James Dziura, PhD
Sue Levi-Pearl, MA
John T. Walkup, MD

Context Tourette disorder is a chronic and typically impairing childhood-onset neurologic condition. Antipsychotic medications, the first-line treatments for moderate to severe tics, are often associated with adverse effects. Behavioral interventions, although promising, have not been evaluated in large-scale controlled trials.

Objective To determine the efficacy of a comprehensive behavioral intervention for reducing tic severity in children and adolescents.

Design, Setting, and Participants Randomized, observer-blind, controlled trial of 126 children recruited from December 2004 through May 2007 and aged 9 through 17 years, with impairing Tourette or chronic tic disorder as a primary diagnosis, randomly assigned to 8 sessions during 10 weeks of behavior therapy (n=61) or a control treatment consisting of supportive therapy and education (n=65). Responders received 3 monthly booster treatment sessions and were reassessed at 3 and 6 months following treatment.

Intervention Comprehensive behavioral intervention.

Main Outcome Measures Yale Global Tic Severity Scale (range 0-50, score >15 indicating clinically significant tics) and Clinical Global Impressions–Improvement Scale (range 1 [very much improved] to 8 [very much worse]).

Results Behavioral intervention led to a significantly greater decrease on the Yale Global Tic Severity Scale (24.7 [95% confidence interval (CI), 23.1-26.3] to 17.1 [95% CI, 15.1-19.1]) from baseline to end point compared with the control treatment (24.6 [95% CI, 23.2-26.0] to 21.1 [95% CI, 19.2-23.0]) ($P<.001$; difference between groups, 4.1; 95% CI, 2.0-6.2) (effect size=0.68). Significantly more children receiving behavioral intervention compared with those in the control group were rated as being very much improved or much improved on the Clinical Global Impressions–Improvement scale (52.5% vs 18.5%, respectively; $P<.001$; number needed to treat=3). Attrition was low (12/126, or 9.5%); tic worsening was reported by 4% of children (5/126). Treatment gains were durable, with 87% of available responders to behavior therapy exhibiting continued benefit 6 months following treatment.

Conclusion A comprehensive behavioral intervention, compared with supportive therapy and education, resulted in greater improvement in symptom severity among children with Tourette and chronic tic disorder.

Trial Registration clinicaltrials.gov Identifier: NCT00218777

JAMA. 2010;303(19):1929-1937 www.jama.com

TOURETTE DISORDER IS A CHRONIC neurologic disorder characterized by motor and vocal tics. Prevalence estimates in school-aged children range from 1 to 10 per 1000, with a rate of 6 per 1000 replicated in several countries.[1,2] Tics are usually brief, rapid movements (eg, blinking, facial grimacing) or vocalizations (eg, throat clearing, grunting) but can include more complex movements and vocalizations. Tics begin in childhood; severity peaks in early adolescence and often declines in young adulthood.[3] Epidemiologic and clinical data indicate that Tourette disorder can be associated with considerable impairment[2] and social isolation[4] in school-aged children. Tics are

ORIGINAL ARTICLE

Randomized Trial of Behavior Therapy for Adults With Tourette Syndrome

Sabine Wilhelm, PhD; Alan L. Peterson, PhD; John Piacentini, PhD; Douglas W. Woods, PhD; Thilo Deckersbach, PhD; Denis G. Sukhodolsky, PhD; Susanna Chang, PhD; Haibei Liu, MPH; James Dziura, PhD; John T. Walkup, MD; Lawrence Scahill, MSN, PhD

Context: Tics in Tourette syndrome begin in childhood, peak in early adolescence, and often decrease by early adulthood. However, some adult patients continue to have impairing tics. Medications for tics are often effective but can cause adverse effects. Behavior therapy may offer an alternative but has not been examined in a large-scale controlled trial in adults.

Objective: To test the efficacy of a comprehensive behavioral intervention for tics in adults with Tourette syndrome of at least moderate severity.

Design: A randomized controlled trial with posttreatment evaluations at 3 and 6 months for positive responders.

Setting: Three outpatient research clinics.

Patients: Patients (N=122; 78 males; age range, 16-69 years) with Tourette syndrome or chronic tic disorder were recruited between December 27, 2005, and May 21, 2009.

Interventions: Patients received 8 sessions of comprehensive behavioral intervention for tics or 8 sessions of supportive treatment for 10 weeks. Patients with a positive response were given 3 monthly booster sessions.

Main Outcome Measures: Total tic score on the Yale Global Tic Severity Scale and the Clinical Global Impression–Improvement scale rated by a clinician masked to treatment assignment.

Results: Behavior therapy was associated with a significantly greater mean (SD) decrease on the Yale Global Tic Severity Scale (24.0 [6.47] to 17.8 [7.32]) from baseline to end point compared with the control treatment (21.8 [6.59] to 19.3 [7.40]) ($P<.001$; effect size=0.57). Twenty-four of 63 patients (38.1%) were rated as much improved or very much improved on the Clinical Global Impression–Improvement scale compared with 4 of 63 (6.4%) in the control group ($P<.001$). Attrition was 13.9%, with no difference across groups. Patients receiving behavior therapy who were available for assessment at 6 months after treatment showed continued benefit.

Conclusion: Comprehensive behavior therapy is a safe and effective intervention for adults with Tourette syndrome.

Trial Registration: clinicaltrials.gov Identifier: NCT00231985

Arch Gen Psychiatry. 2012;69(8):795-803

HRT in TS: Results

Table III - Difference in tic severity before and after habit reversal therapy and control treatment in the randomized controlled trials.

Study	Treatment group	YGTSS		
		Pre-treatment	Post-treatment	% change
Wilhelm et al. 2003	Habit reversal	30.5	19.8	-35.1
	Supportive psychotherapy	26.6	26.9	1.1
Verdellen et al. 2004	Habit reversal	24.1	19.7	-18.3
	Exposure with response prevention	26.2	17.6	-32.8
Deckersbach et al. 2006	Habit reversal	29.3	18.3	-37.5
	Supportive psychotherapy	27.7	26.8	-3.2
Piacentini et al. 2010	Habit reversal	24.7	17.1	-30.8
	Supportive psychotherapy	24.6	21.1	-14.2
Wilhelm et al. 2012	Habit reversal	24.0	17.8	-25.8
	Supportive psychotherapy	21.8	19.3	-11.5

Abbreviations: YGTSS=Yale Global Tic Severity Scale.

Neeladri Dutta[a,b]
Andrea E. Cavanna, MD, PhD[a,b,c]

The effectiveness of habit reversal therapy in the treatment of Tourette syndrome and other chronic tic disorders: a systematic review

Functional Neurology 2013; 28(1): 7-12

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

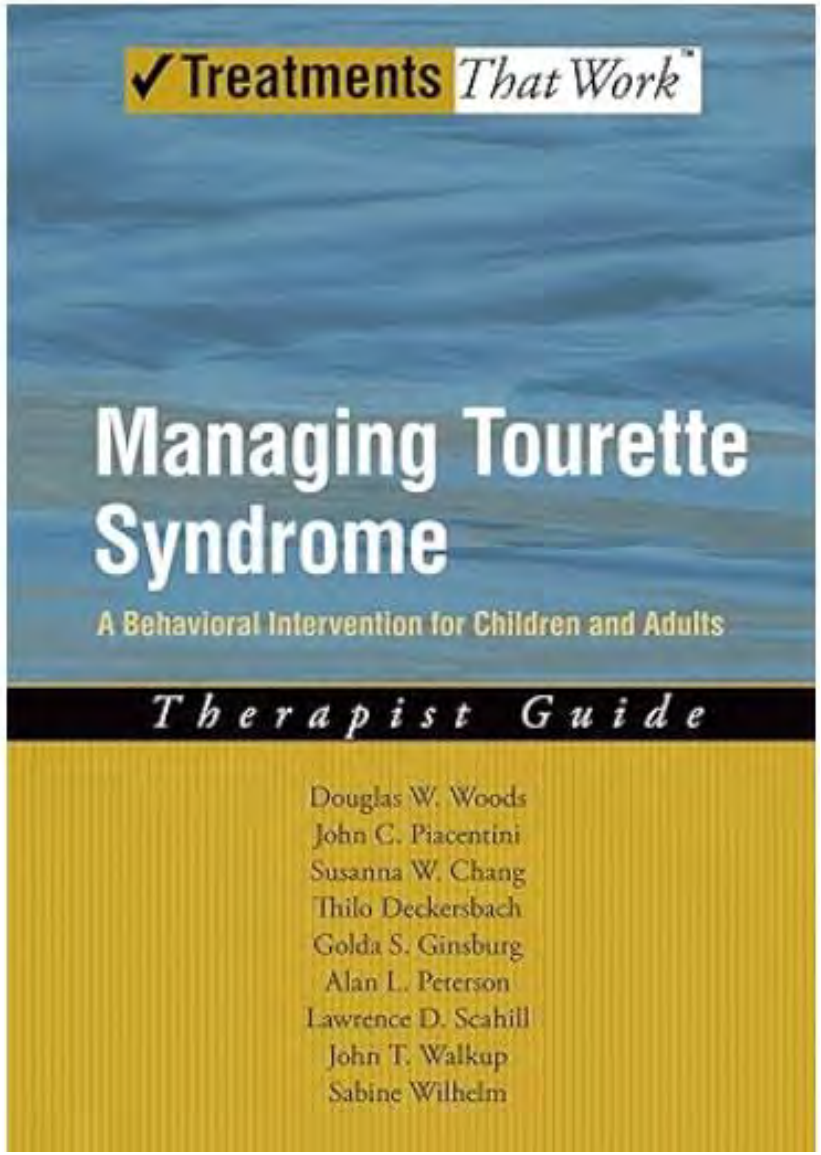
Tamara Pringsheim, MD, MSc, Yolanda Holler-Managan, MD, Michael S. Okun, MD, Joseph Jankovic, MD, John Piacentini, PhD, Andrea E. Cavanna, MD, PhD, Davide Martino, MD, PhD, Kirsten Müller-Vahl, MD, Douglas W. Woods, PhD, Michael Robinson, Elizabeth Jarvie, MSW, LCSW, Veit Roessner, MD, and Maryam Oskoui, MD, MSc

Correspondence
American Academy of Neurology
guidelines@aan.com

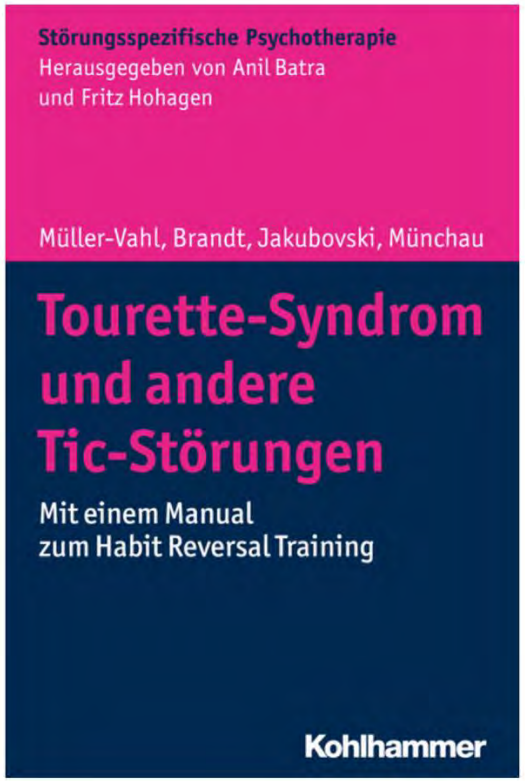
Neurology® 2019;92:907-915. doi:10.1212/WNL.0000000000007467

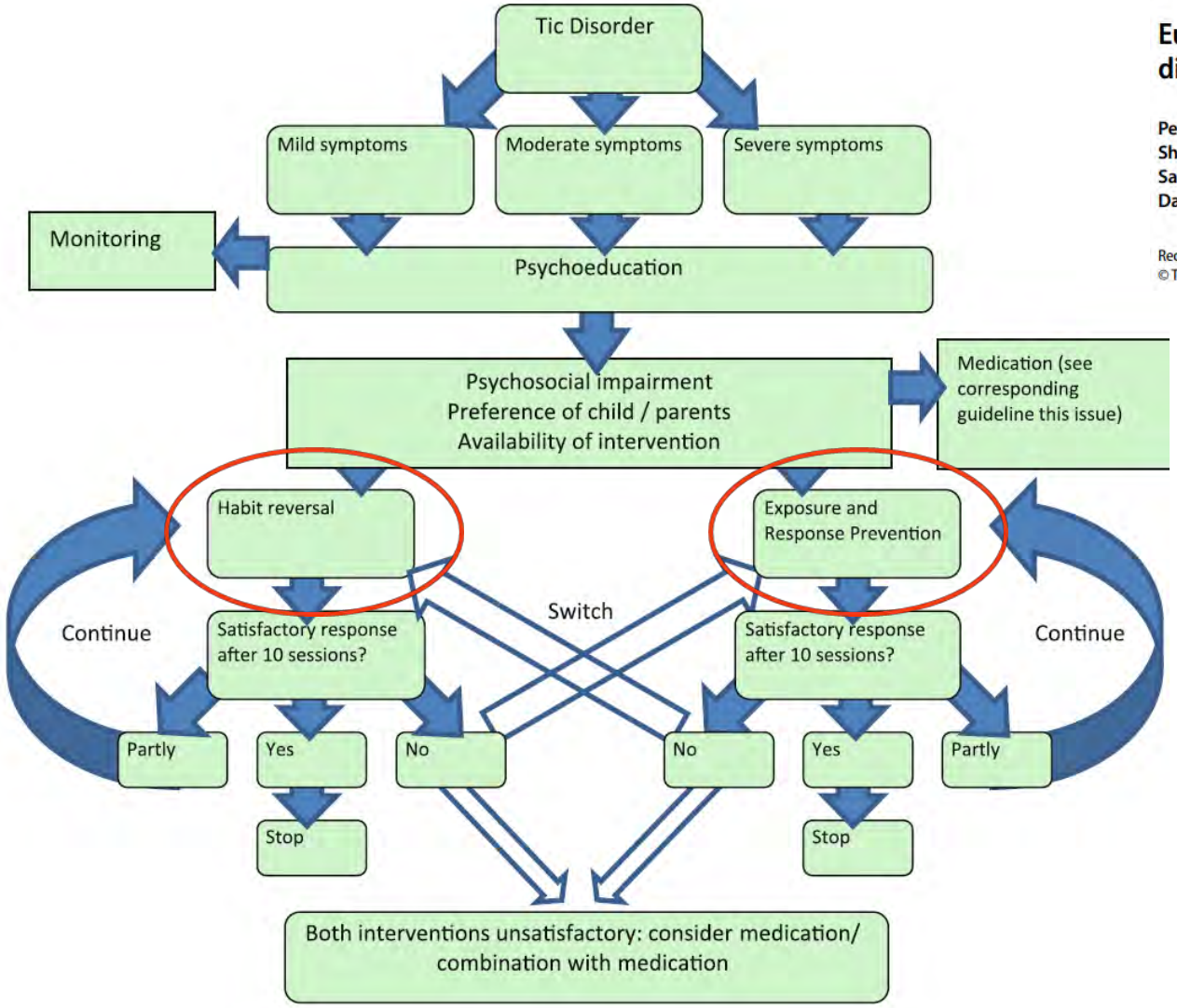
Results

There was high confidence that the Comprehensive Behavioral Intervention for Tics was more likely than psychoeducation and supportive therapy to reduce tics. There was moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, onabotulinumtoxinA injections, 5-ling granule, Ningdong granule, and deep brain stimulation of the globus pallidus were probably more likely than placebo to reduce tics. There was low confidence that pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinol were possibly more likely than placebo to reduce tics. Evidence of harm associated with various treatments was also demonstrated, including weight gain, drug-induced movement disorders, elevated prolactin levels, sedation, and effects on heart rate, blood pressure, and ECGs.


✓Treatments That Work™
Managing Tourette Syndrome
A Behavioral Intervention for Children and Adults
Therapist Guide
Douglas W. Woods
John C. Piacentini
Susanna W. Chang
Thilo Deckersbach
Golda S. Ginsburg
Alan L. Peterson
Lawrence D. Scahill
John T. Walkup
Sabine Wilhelm


Katrin Woitecki · Manfred Döpfner
Therapieprogramm
für Kinder und Jugendliche
mit Tic-Störungen (THICS)
mit CD-ROM
HOGREFE


Störungsspezifische Psychotherapie
Herausgegeben von Anil Batra
und Fritz Hohagen
Müller-Vahl, Brandt, Jakubovski, Münchau
Tourette-Syndrom
und andere
Tic-Störungen
Mit einem Manual
zum Habit Reversal Training
Kohlhammer



European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-021-01845-z

REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part II: psychological interventions

Per Andrén[1] · Ewgeni Jakubovski[2] · Tara L. Murphy[3] · Katrin Woitecki[4] · Zsanett Tarnok[5] · Sharon Zimmerman-Brenner[6] · Jolande van de Griendt[7] · Nanette Mol Debes[8] · Paula Viefhaus[4] · Sally Robinson[9] · Veit Roessner[10] · Christos Ganos[11] · Natalia Szejko[12,13,14] · Kirsten R. Müller-Vahl[2] · Danielle Cath[15] · Andreas Hartmann[16] · Cara Verdellen[17]

Received: 9 March 2021 / Accepted: 7 July 2021

ELSEVIER

Brain & Development 38 (2016) 233–241

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

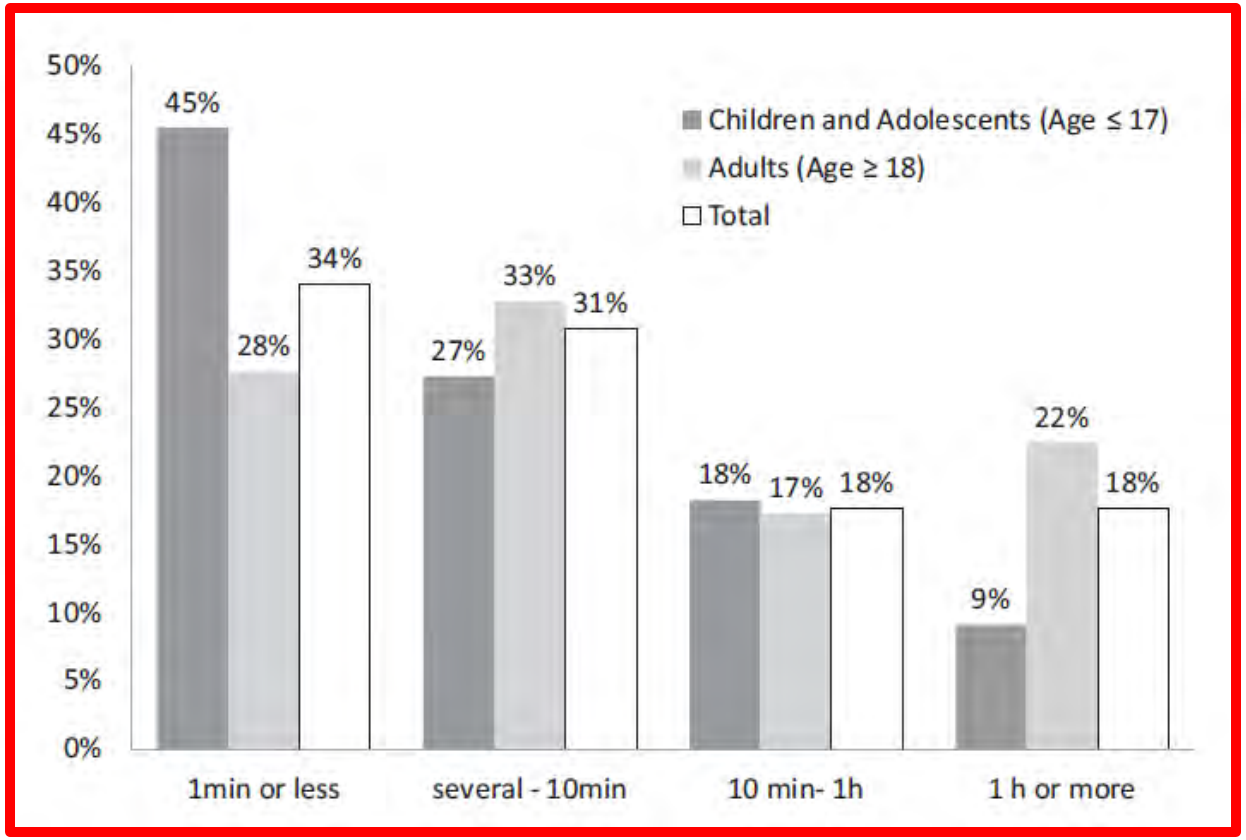
www.elsevier.com/locate/braindev

Original article

Self-initiated coping with Tourette's syndrome: Effect of tic suppression on QOL

Natsumi Matsuda[a], Toshiaki Kono[b], Maiko Nonaka[a], Miyuki Fujio[a,c], Yukiko Kano[a,d,*]

Maximal duration of tic suppression (patient self-report)



Exposure and response prevention (ERP)

- Tic suppression for prolonged periods of time (response prevention)
- Gradually increased exposure to premonitory urges and environmental factors (e.g. situations and activities) likely to induce tics
- Aiming to increase urge tolerance
- Resulting in tic reduction

→ Suppression of all tics at the same time

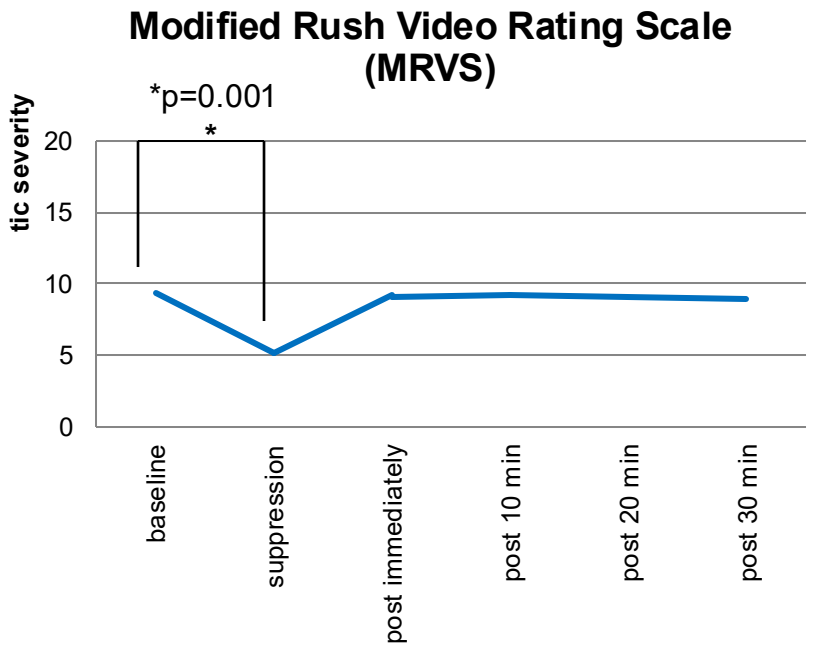
Contents lists available at ScienceDirect

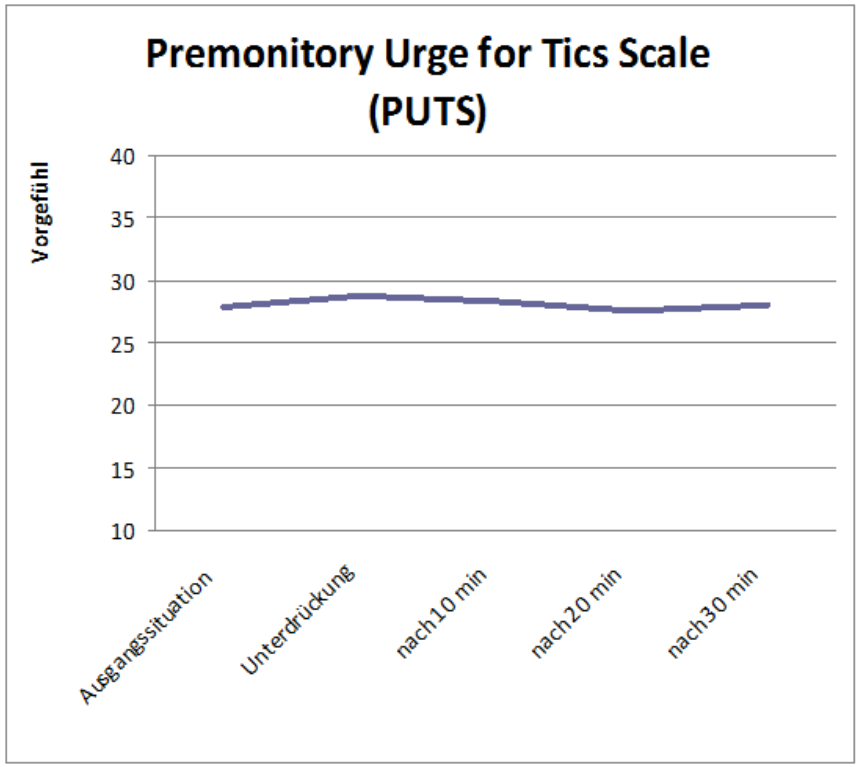
Journal of Psychosomatic Research

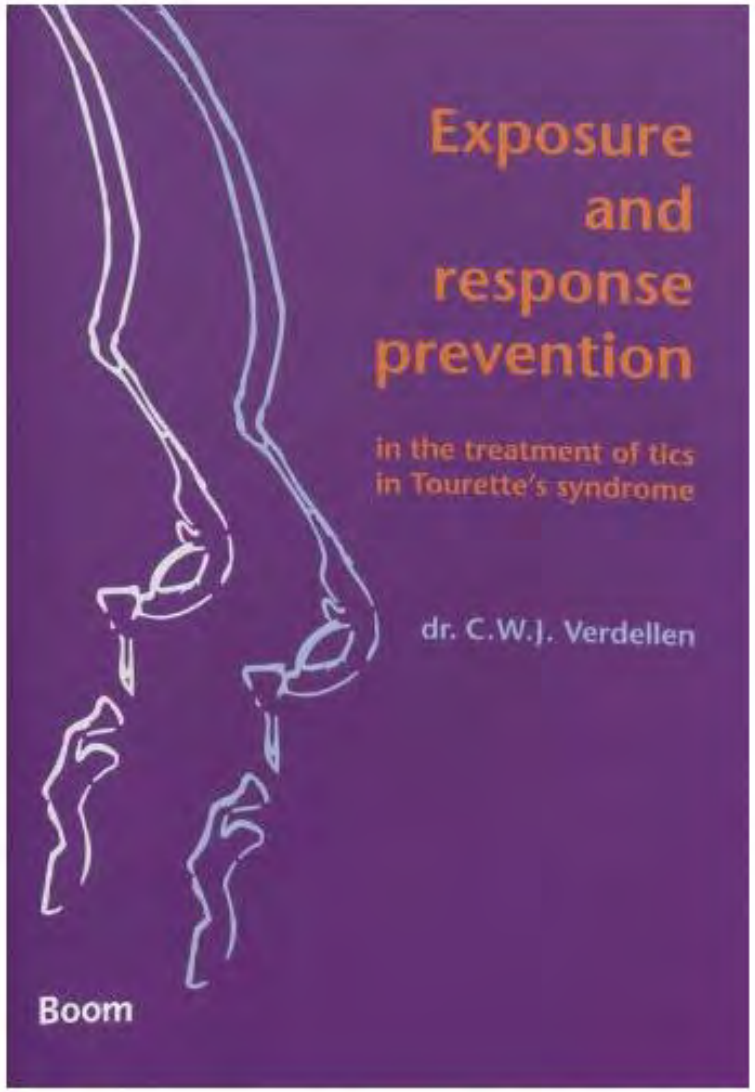
Tourette patients' misbelief of a tic rebound is due to overall difficulties in reliable tic rating

Kirsten R Müller-Vahl *, Laura Riemann, Stefanie Bokemeyer

Clinic of Psychiatry, Socialpsychiatry and Psychotherapy, Hannover Medical School, Germany






Exposure and response prevention
in the treatment of tics in Tourette's syndrome
dr. C.W.J. Verdellen
Boom

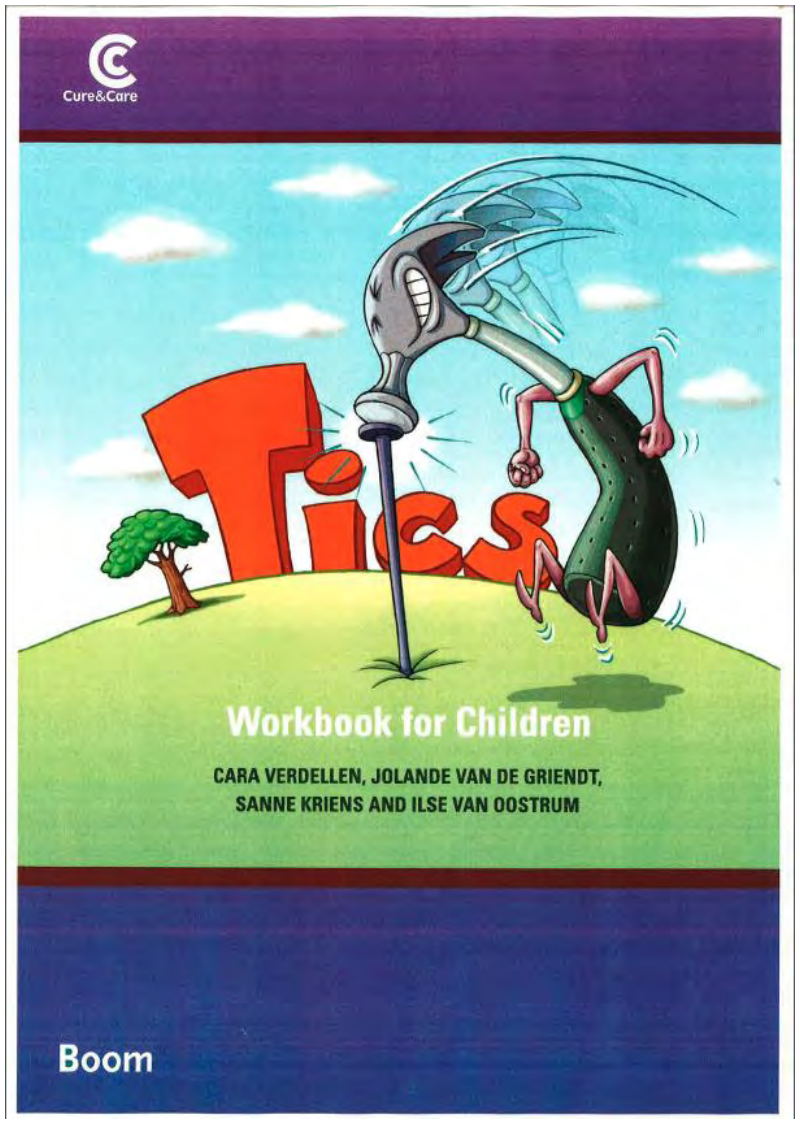
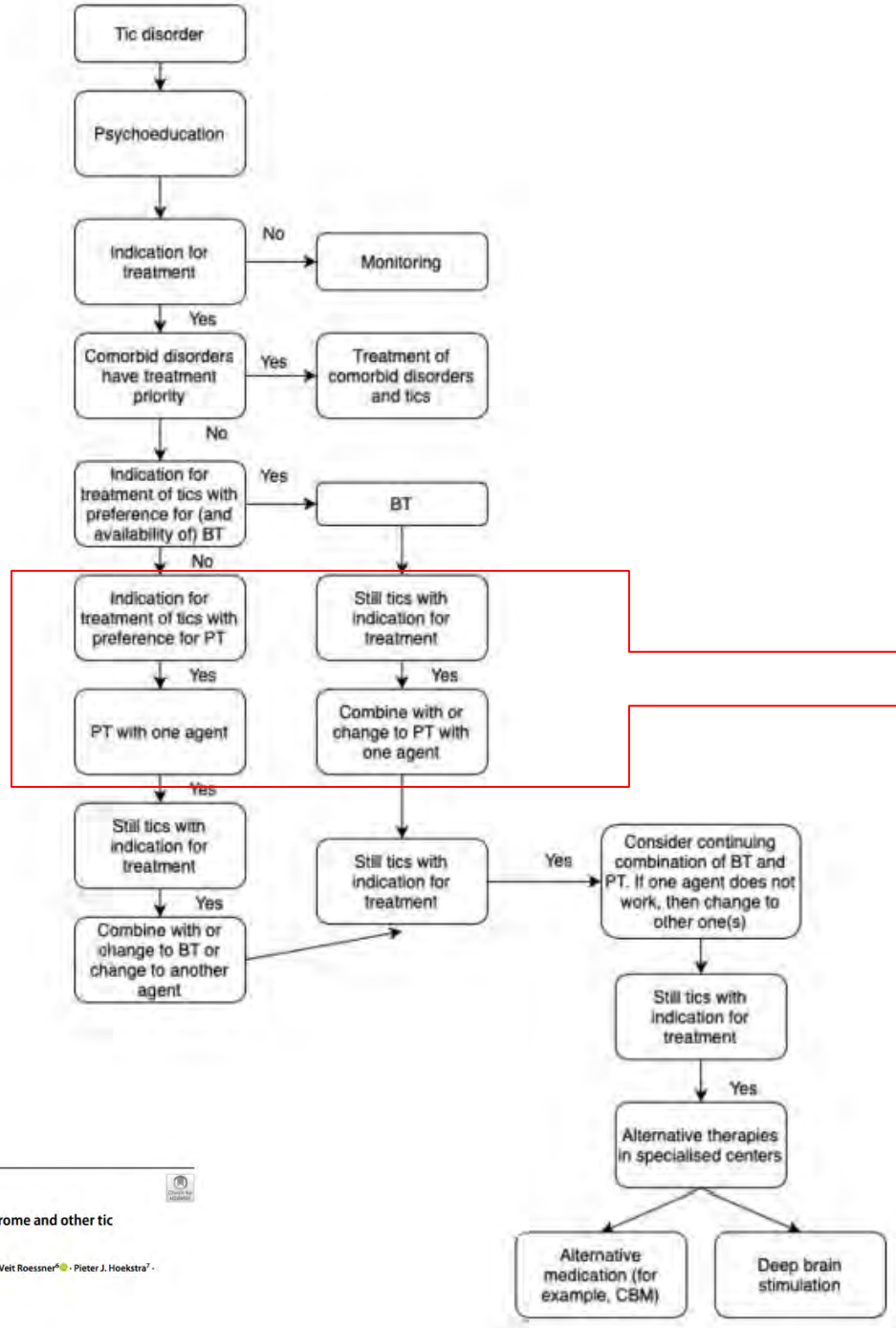

Cure&Care
Tics
Workbook for Children
CARA VERDELLEN, JOLANDE VAN DE GRIENDT, SANNE KRIENS AND ILSE VAN OOSTRUM
Boom

Fig. 1 Algorithm for the treatment of patients with TS based on shared clinician patient decision making (adapted with permission from [14], Springer). *TS* Tourette syndrome, *PT* pharmacotherapy, *BT* behaviour therapy, *CBM* cannabis-based medicine



European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-021-01832-4

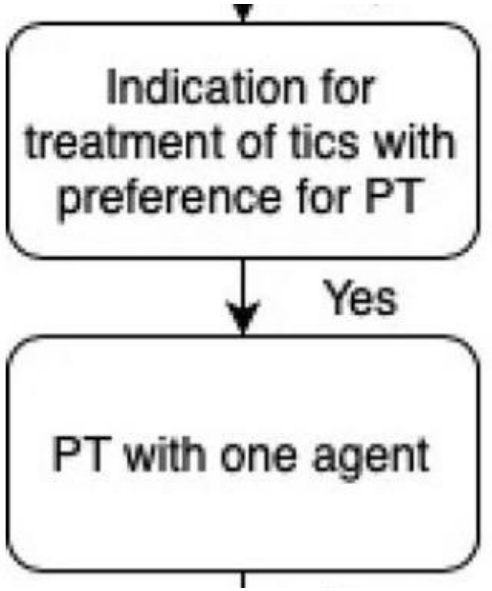
REVIEW

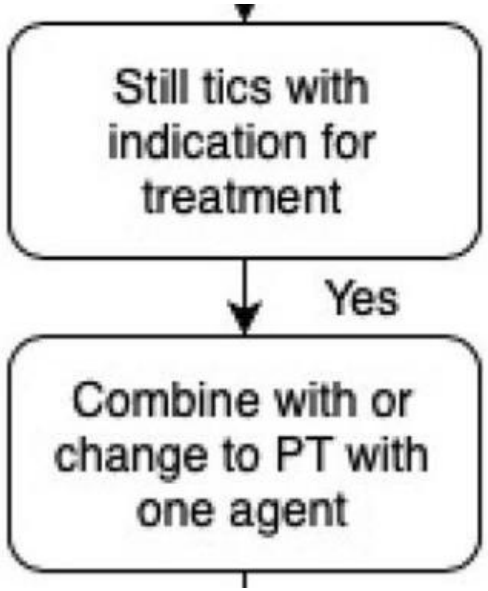
European clinical guidelines for Tourette syndrome and other tic disorders: summary statement

Kirsten R. Müller-Vahl[1] · Natalia Szejko[2,3,4] · Cara Verdellen[5,11] · Veit Roessner[6] · Pieter J. Hoekstra[7] · Andreas Hartmann[8] · Danielle C. Cath[9,10]

Received: 8 March 2021 / Accepted: 19 June 2021

STS





Licensed for Treatment of Tics/Tourette Syndrome

- US:
  - haloperidol
  - pimozide
  - aripiprazole
- Europe
  - haloperidol

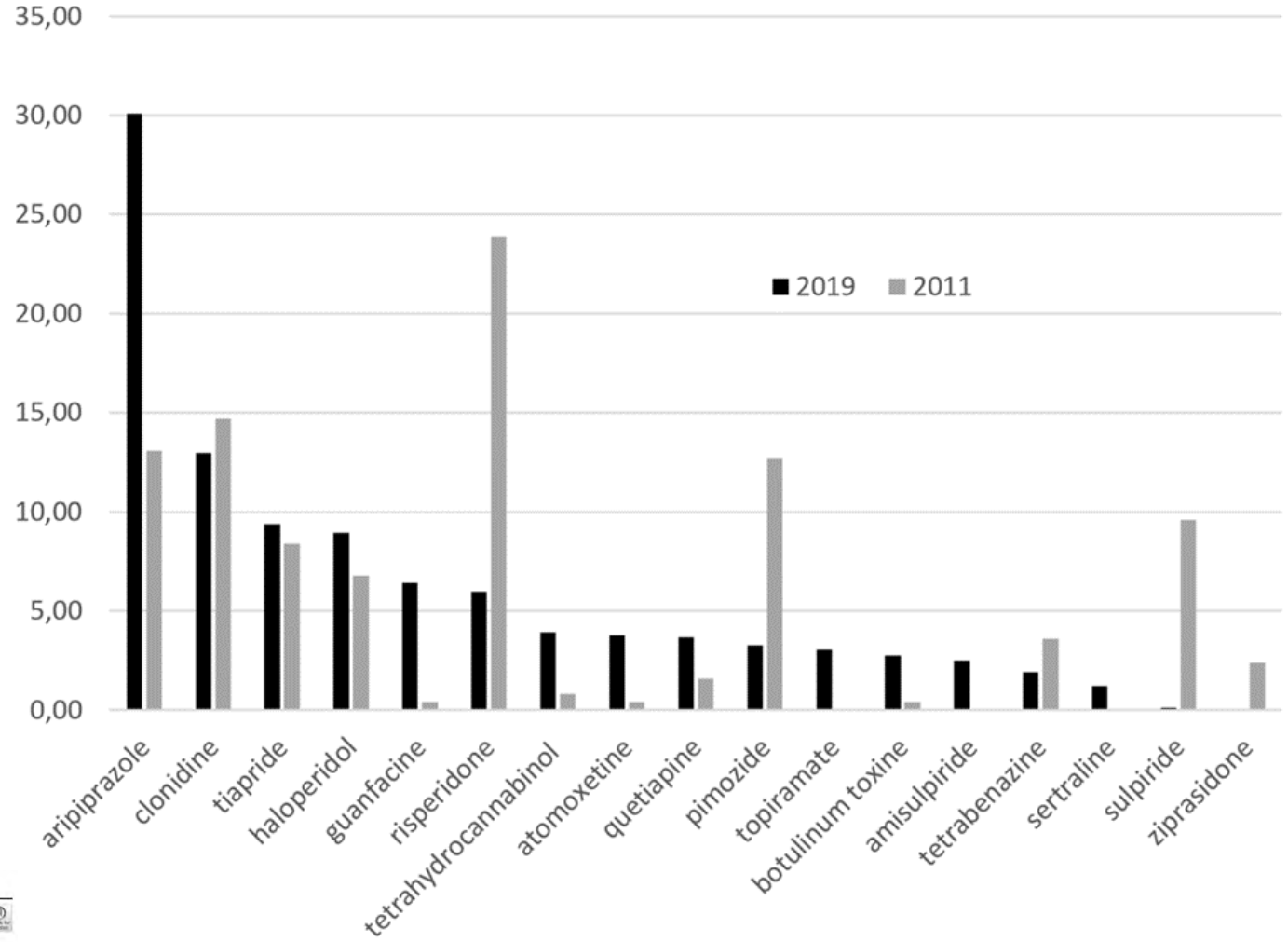
Comparative efficacy, tolerability, and acceptability of pharmacological interventions for the treatment of children, adolescents, and young adults with Tourette's syndrome: a systematic review and network meta-analysis

Luis C Farhat, Emily Behling, Angeli Landeros-Weisenberger, Jessica L S Levine, Pedro Macul Ferreira de Barros, Ziyu Wang, Michael H Bloch

www.thelancet.com/child-adolescent **Published online December 14, 2022** **https://doi.org/10.1016/S2352-4642(22)00316-9**

Interpretation Our analyses show that antipsychotic drugs are the most efficacious intervention for Tourette's syndrome, while α-2 agonists are also more efficacious than placebo and could be chosen by those who elect not to take antipsychotic drugs. Shared decision making about the degree of tic-related severity and distress or impairment, the trade-offs of efficacy and safety between antipsychotic drugs and α-2 agonists, and other highly relevant individual factors that could not be addressed in the present analysis, should guide the choice of medication for children and young people with Tourette's syndrome.

ESSTS Survey: clinical practice: 2011 vs. 2019



European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-021-01899-z

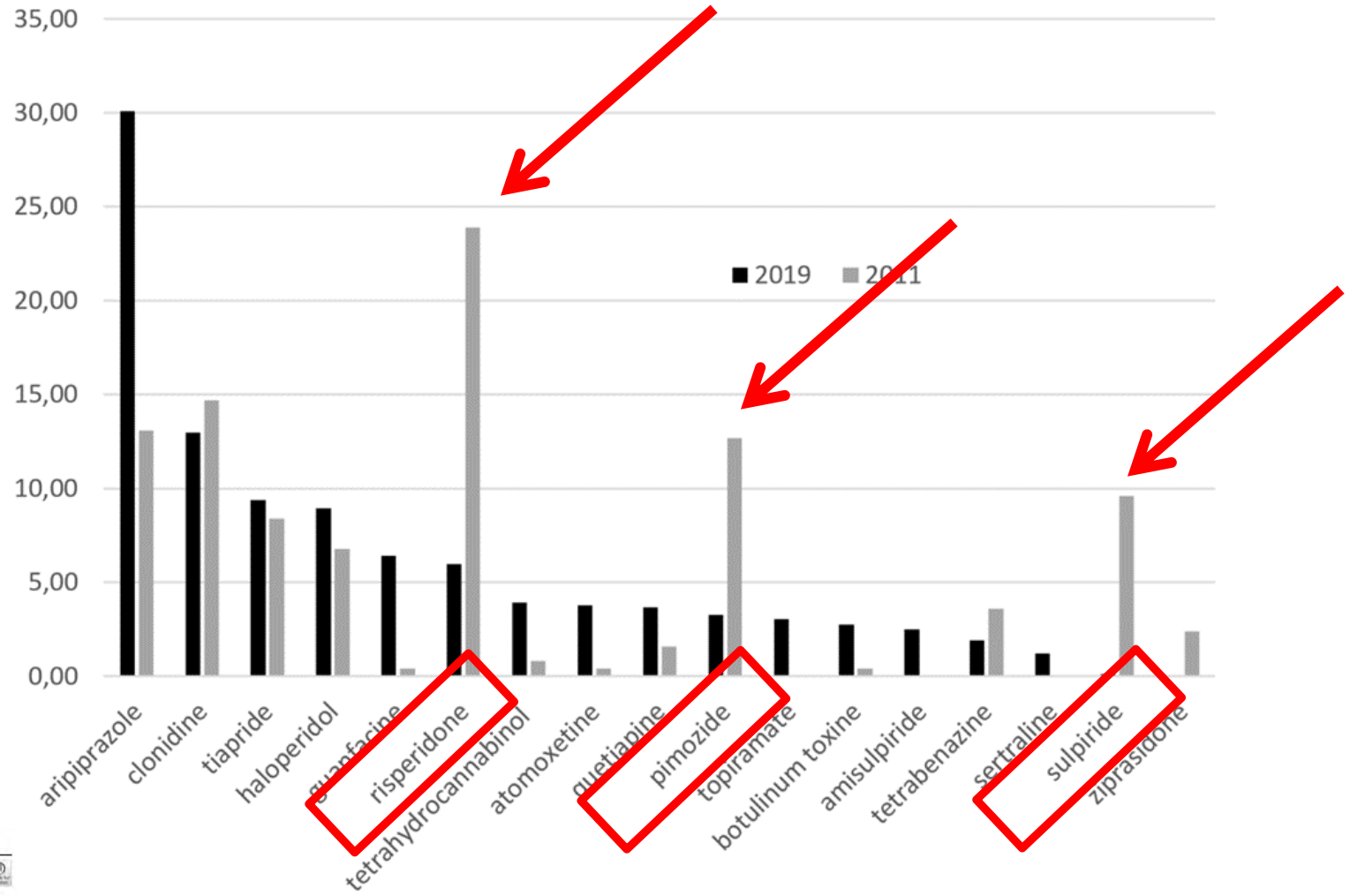
REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part III: pharmacological treatment

Veit Roessner[1] · Heike Eichele[2,3] · Jeremy S. Stern[4] · Liselotte Skov[5] · Renata Rizzo[6] · Nanette Mol Debes[5] · Péter Nagy[7] · Andrea E. Cavanna[8] · Cristiano Termine[9] · Christos Ganos[10] · Alexander Münchau[11] · Natalia Szejko[12,13,14] · Danielle Cath[15] · Kirsten R. Müller-Vahl[16] · Cara Verdellen[17,18] · Andreas Hartmann[19,20] · Aribert Rothenberger[21] · Pieter J. Hoekstra[22] · Kerstin J. Plessen[23,24]

Received: 28 March 2021 / Accepted: 24 October 2021

ESSTS Survey: clinical practice: 2011 vs. 2019



European Child & Adolescent Psychiatry
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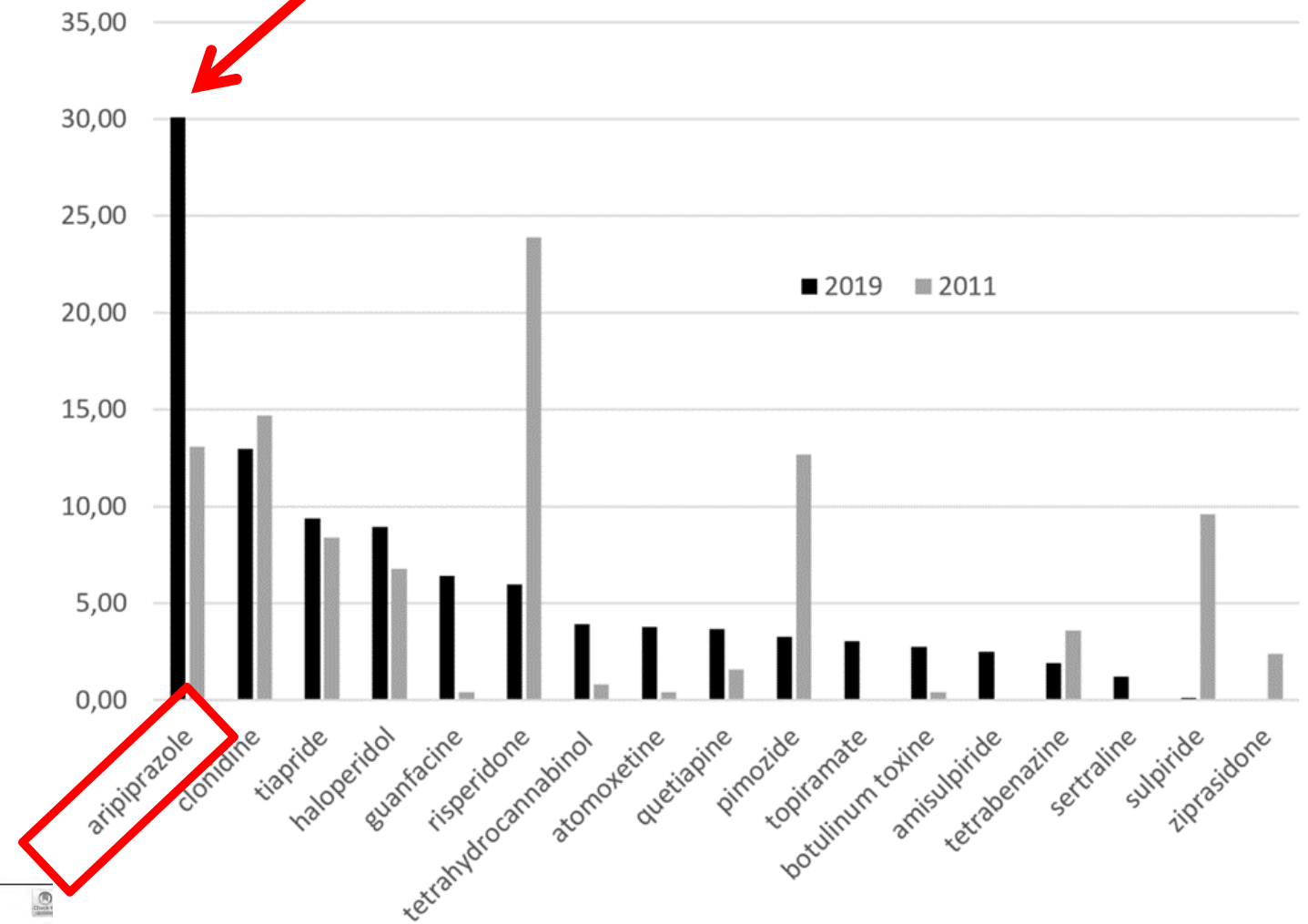

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experts. The first preference should be given to psychoeducation and to behavioral approaches, as it strengthens the patients' self-regulatory control and thus his/her autonomy. Because behavioral approaches are not effective, available, or feasible in all patients, in a substantial number of patients pharmacological treatment is indicated, alone or in combination with behavioral therapy. The largest amount of evidence supports the use of dopamine blocking agents, preferably aripiprazole because of a more favorable profile of adverse events than first- and second-generation antipsychotics. Other agents that can be considered include tiapride, risperidone, and especially in case of co-existing attention deficit hyperactivity disorder (ADHD), clonidine and guanfacine. This view is supported by the results of our survey on medication preference among members of ESSTS, in which aripiprazole was indicated as the drug of first choice both in children and adults. In treatment resistant cases, treatment with agents with either a limited evidence base or risk of extrapyramidal adverse effects might be considered, including pimozide, haloperidol, topiramate, cannabis-based agents, and botulinum toxin injections. Overall, treatment of TS should be individualized, and decisions based on the patient's needs and preferences, presence of co-existing conditions, latest scientific findings as well as on the physician's preferences, experience, and local regulatory requirements.

European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-021-01899-z

REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part III: pharmacological treatment

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Received: 28 March 2021 / Accepted: 24 October 2021

Until 2011, the use of aripiprazole was only reported in case studies, retrospective observational studies, and open-label trials [51]. Thereafter, aripiprazole has become the main focus in research on the pharmacological treatment of tics: seven systematic reviews including five meta-analyses or combinations of the two [6, 8, 66, 68, 69, 71, 72] and two placebo controlled RCTs [136, 137] have been published since 2011. All publications consistently documented the effectiveness of aripiprazole in reducing tics, with similar effect sizes as compared to other dopamine-modulating agents, such as haloperidol and risperidone [6, 127, 138]. The most recent meta-analysis (including also Chinese-language RCTs) pointed to a standardized mean difference of aripiprazole compared with placebo of 4.74 (95% CI [1.06–8.67]) [6]. Moreover, there is some evidence from an

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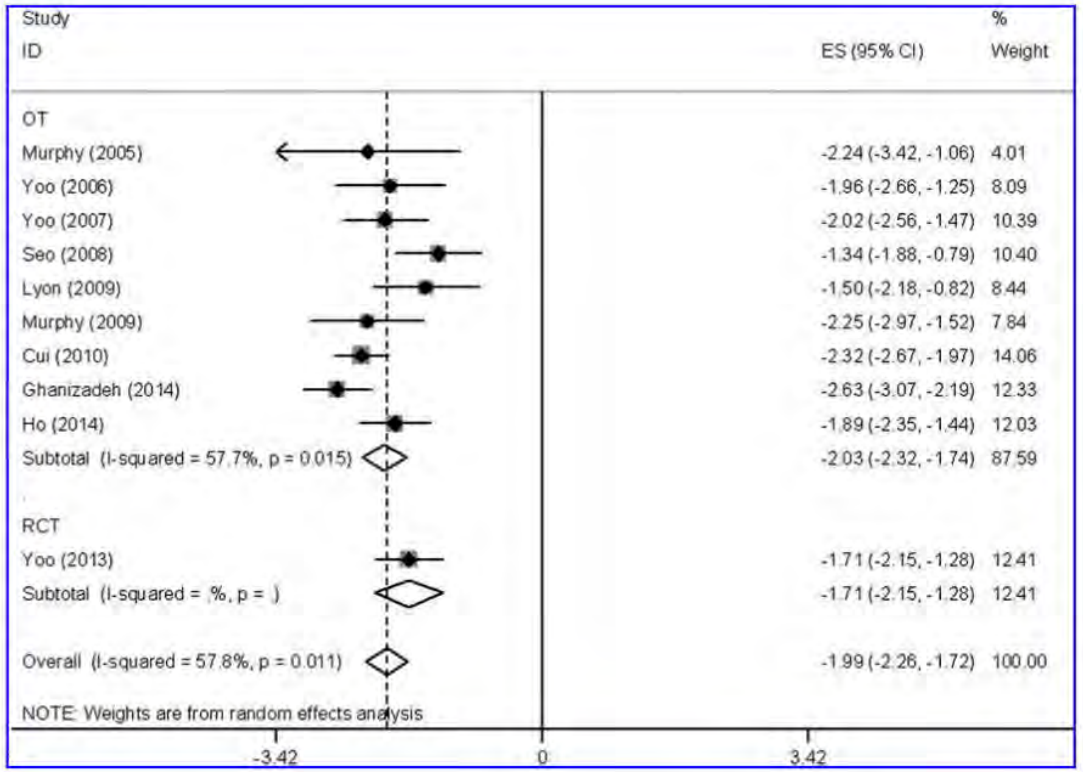
Volume X, Number x, 2016

Pp. 1–6
DOI: 10.1089/cap.2015.0125

Original Article

Effectiveness and Tolerability of Aripiprazole in Children and Adolescents with Tourette's Disorder: A Meta-Analysis

Yueying Liu, MD,[1] Hong Ni, MD,[2] Chunhong Wang, MD,[1] Lili Li, MD,[2] Zaohuo Cheng, MD,[3] and Zhen Weng, PhD[4]



Methods: We searched for clinical trials that investigated the effect of aripiprazole in children and adolescents with TD in PubMed and Web of Science. The outcomes of interest comprised the Yale Global Tic Severity Score (YGTSS) total tic scores and the Clinical Global Impressions Scale for Tic Severity (CGI-S) scores. The pooled effect size (ES) and 95% confidence interval (CI) were calculated to assess the effectiveness of aripiprazole in children and adolescents with TD.

Results: Ten studies were retrieved from 122 citations for the analysis, and in total, 302 patients (mean age, 11.6 years; median follow-up, 9 weeks) were included in the analysis. After synthesis of the data, the meta-analysis showed significantly greater improvement in the mean change in the YGTSS total tic scores (ES = −1.99, 95% CI = [−2.26]–[−1.72]; p = 0.001) and the mean CGI-S scores (ES = −2.34, 95% CI = [−2.96]–[−1.73]; $p = 0.001$) from pretreatment to posttreatment. Adverse events were reported in nine trials. Drowsiness (28.5%), nausea (20.2%), and headache (13.8%) were common adverse events.

Conclusions: The use of aripiprazole is safe, and shows therapeutic effectiveness in children and adolescents with TD.

Medicine (2019) 98:22(e15816)

Systematic Review and Meta-Analysis

Medicine

OPEN

Safety of aripiprazole for tics in children and adolescents

A systematic review and meta-analysis

Chunsong Yang, MPH[a,b], Qiusha Yi, BS[a,b,c], Lingli Zhang, MD[a,b,*], Hao Cui, MPH[d,e], Jianping Mao, BS[c]

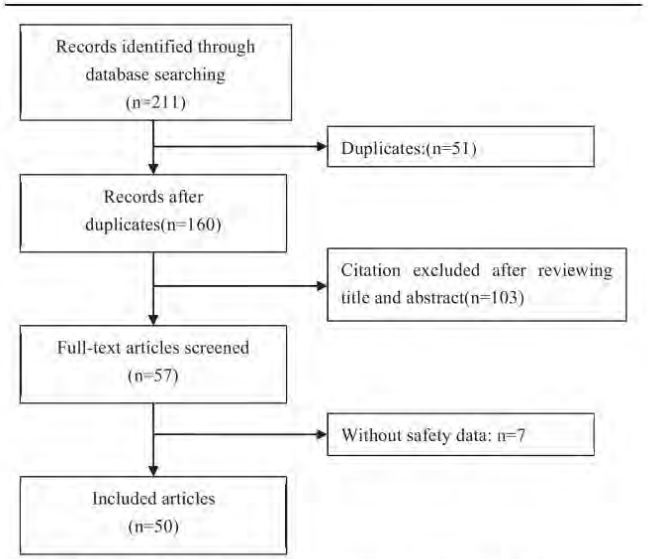


Figure 1. Flow chart of literature screening and the selection process.

Results: A total 50 studies involving 2604 children met the inclusion criteria. The result of meta-analysis of randomized controlled trials showed that there was a significant difference between aripiprazole and haloperidol with respect to rate of somnolence (RR = 0.596, 95% CI: 0.394, 0.901), extrapyramidal symptoms (RR = 0.236, 95% CI: 0.111, 0.505), tremor (RR = 0.255, 95% CI: 0.114, 0.571), constipation (RR = 0.148, 95% CI: 0.040, 0.553), and dry mouth (RR = 0.141, 95% CI: 0.046, 0.425). There was a significant difference between aripiprazole and placebo in the incidence rate of adverse events (AEs) for somnolence (RR = 6.565, 95% CI: 1.270, 33.945). The meta-analysis of incidence of AEs related to aripiprazole for case series studies revealed that the incidence of sedation was 26.9% (95% CI: 16.3%, 44.4%), irritability 25% (95% CI: 9.4%, 66.6%), restlessness 31.3% (95% CI: 13%, 75.1%), nausea and vomiting 28.9% (95% CI: 21.1%, 39.5%), and weight gain 31.3% (95% CI: 10.7%, 91.3%).

Treatment with Antipsychotics: what to expect?

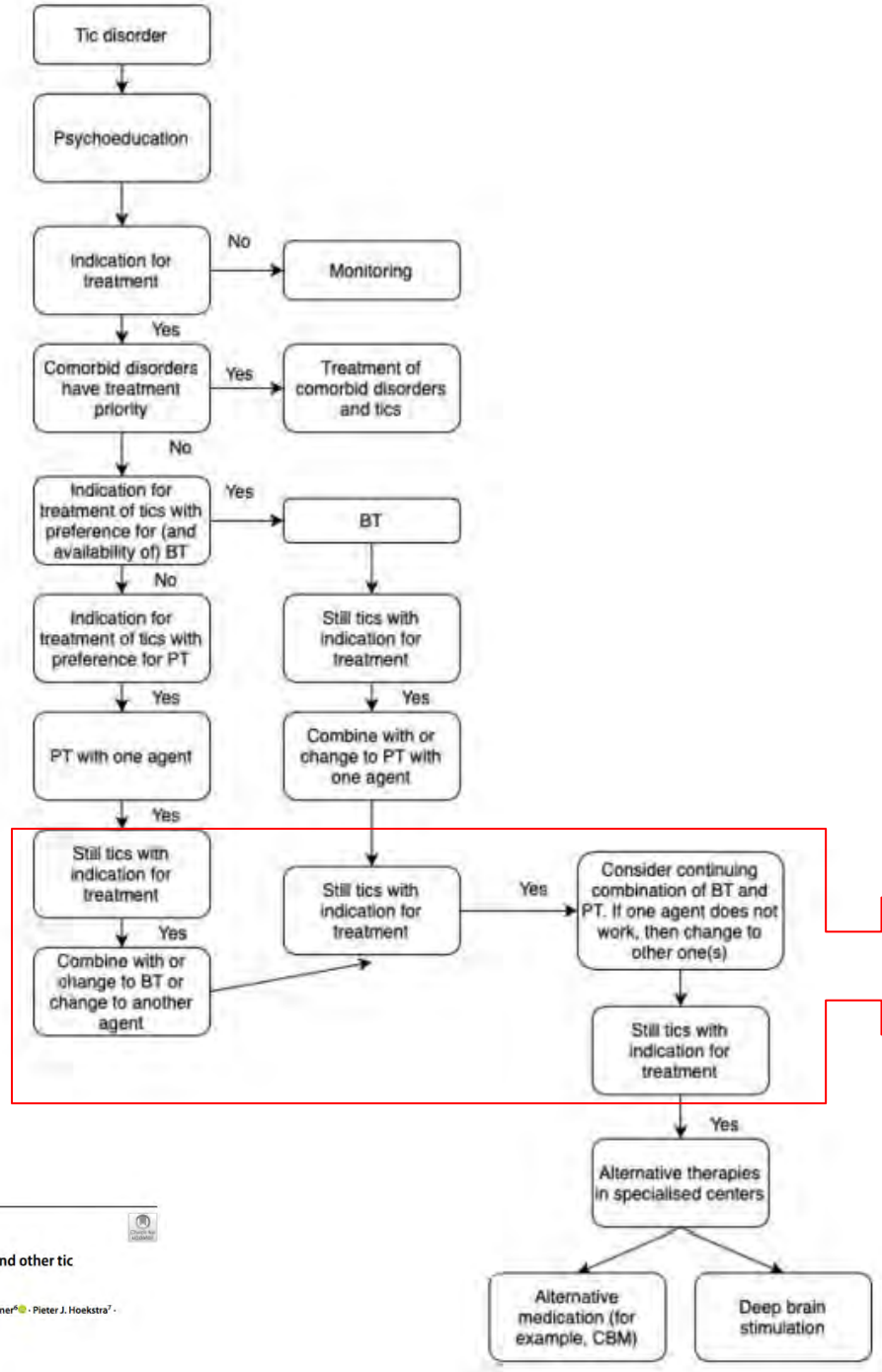
Antipsychotics

- are effective in about 90% of patients
- on average reduce tics by about 50% (with a wide range)
- do not improve comorbidities in most cases
- may cause side effects

Treatment with Antipsychotics: how to do?

- Start low
- Go slow
- Increase dosage until tics decrease or intolerable side effects occur
- Find the individually optimal dose together with the patient/parents
- Adapt the dose depending on kind and severity of tics (according to waxing and waning of tics)

Fig. 1 Algorithm for the treatment of patients with TS based on shared clinician patient decision making (adapted with permission from [14], Springer). *TS* Tourette syndrome, *PT* pharmacotherapy, *BT* behaviour therapy, *CBM* cannabis-based medicine



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REVIEW

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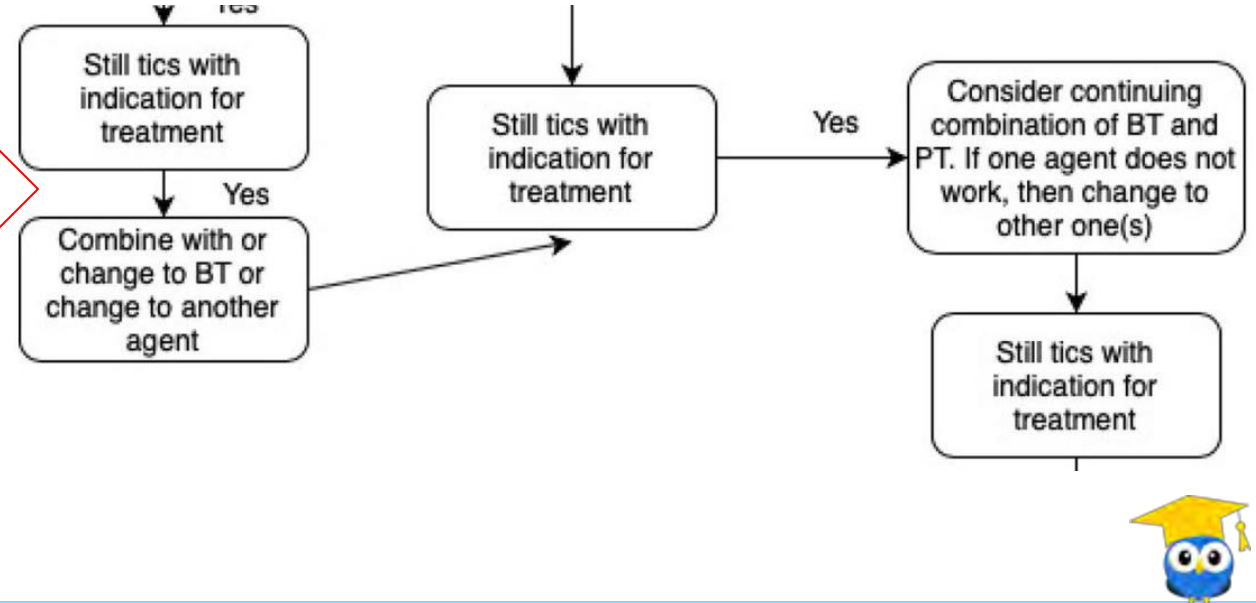
Kirsten R. Müller-Vahl[1] · Natalia Szejko[2,3,4] · Cara Verdellen[5,11] · Veit Roessner[6] · Pieter J. Hoekstra[7] · Andreas Hartmann[8] · Danielle C. Cath[9,10]

Received: 8 March 2021 / Accepted: 19 June 2021



ESSTS survey 2019 (n=50)

Children & adolescents (n=15 different agents were given)		
Points	*Percentage*	
141	29.2	aripiprazole
82	17.0	clonidine
81	16.8	tiapride
49	10.1	guanfacine
25	5.2	atomoxetine
20	4.1	risperidone
18	3.7	topiramate
18	3.7	cannabinoids
15	3.1	pimozide
11	2.3	amisulpiride
8	1.7	tetrabenazine
5	1.0	quetiapine
4	0.8	haloperidol
3	0.6	botulinum toxin
2	0.4	sertraline
1	0.2	sulpiride
483	100	

Adults (n=14 different agents were given)		
Points	*Percentage*	
127	31.0	aripiprazole
70	17.1	haloperidol
37	9.0	clonidine
32	7.8	risperidone
26	6.3	quetiapine
20	4.9	botulinum toxin
17	4.1	cannabinoids
14	3.4	pimozide
11	2.7	guanfacine
11	2.7	amisulpiride
10	2.4	topiramate
10	2.4	atomoxetine
9	2.2	tetrabenazine
8	2.0	tiapride
8	2.0	sertraline
410	100	

Comparative efficacy, tolerability, and acceptability of pharmacological interventions for the treatment of children, adolescents, and young adults with Tourette's syndrome: a systematic review and network meta-analysis

Luis C Farhat, Emily Behling, Angeli Landeros-Weisenberger, Jessica L S Levine, Pedro Macul Ferreira de Barros, Ziyu Wang, Michael H Bloch

www.thelancet.com/child-adolescent **Published online December 14, 2022** **https://doi.org/10.1016/S2352-4642(22)00316-9**

Interpretation Our analyses show that antipsychotic drugs are the most efficacious intervention for Tourette's syndrome, while α-2 agonists are also more efficacious than placebo and could be chosen by those who elect not to take antipsychotic drugs. Shared decision making about the degree of tic-related severity and distress or impairment, the trade-offs of efficacy and safety between antipsychotic drugs and α-2 agonists, and other highly relevant individual factors that could not be addressed in the present analysis, should guide the choice of medication for children and young people with Tourette's syndrome.

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https://doi.org/10.1007/s00787-021-01899-z

REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part III: pharmacological treatment

Veit Roessner[1] · Heike Eichele[2,3] · Jeremy S. Stern[4] · Liselotte Skov[5] · Renata Rizzo[6] · Nanette Mol Debes[5] · Péter Nagy[7] · Andrea E. Cavanna[8] · Cristiano Termine[9] · Christos Ganos[10] · Alexander Münchau[11] · Natalia Szejko[12,13,14] · Danielle Cath[15] · Kirsten R. Müller-Vahl[16] · Cara Verdellen[17,18] · Andreas Hartmann[19,20] · Aribert Rothenberger[21] · Pieter J. Hoekstra[22] · Kerstin J. Plessen[23,24]

Received: 28 March 2021 / Accepted: 24 October 2021

experts. The first preference should be given to psychoeducation and to behavioral approaches, as it strengthens the patients' self-regulatory control and thus his/her autonomy. Because behavioral approaches are not effective, available, or feasible in all patients, in a substantial number of patients pharmacological treatment is indicated, alone or in combination with behavioral therapy. The largest amount of evidence supports the use of dopamine blocking agents, preferably aripiprazole because of a more favorable profile of adverse events than first- and second-generation antipsychotics. Other agents that can be considered include tiapride, risperidone, and especially in case of co-existing attention deficit hyperactivity disorder (ADHD), clonidine and guanfacine. This view is supported by the results of our survey on medication preference among members of ESSTS, in which aripiprazole was indicated as the drug of first choice both in children and adults. In treatment resistant cases, treatment with agents with either a limited evidence base or risk of extrapyramidal adverse effects might be considered, including pimozide, haloperidol, topiramate, cannabis-based agents, and botulinum toxin injections. Overall, treatment of TS should be individualized, and decisions based on the patient's needs and preferences, presence of co-existing conditions, latest scientific findings as well as on the physician's preferences, experience, and local regulatory requirements.

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https://doi.org/10.1007/s00787-021-01899-z

REVIEW

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members of ESSTS, in which aripiprazole was indicated as the drug of first choice both in children and adults. In treatment resistant cases, treatment with agents with either a limited evidence base or risk of extrapyramidal adverse effects might be considered, including pimozide, haloperidol, topiramate, cannabis-based agents, and botulinum toxin injections. Overall,

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

Tamara Pringsheim, MD, MSc, Yolanda Holler-Managan, MD, Michael S. Okun, MD, Joseph Jankovic, MD, John Piacentini, PhD, Andrea E. Cavanna, MD, PhD, Davide Martino, MD, PhD, Kirsten Müller-Vahl, MD, Douglas W. Woods, PhD, Michael Robinson, Elizabeth Jarvie, MSW, LCSW, Veit Roessner, MD, and Maryam Oskoui, MD, MSc

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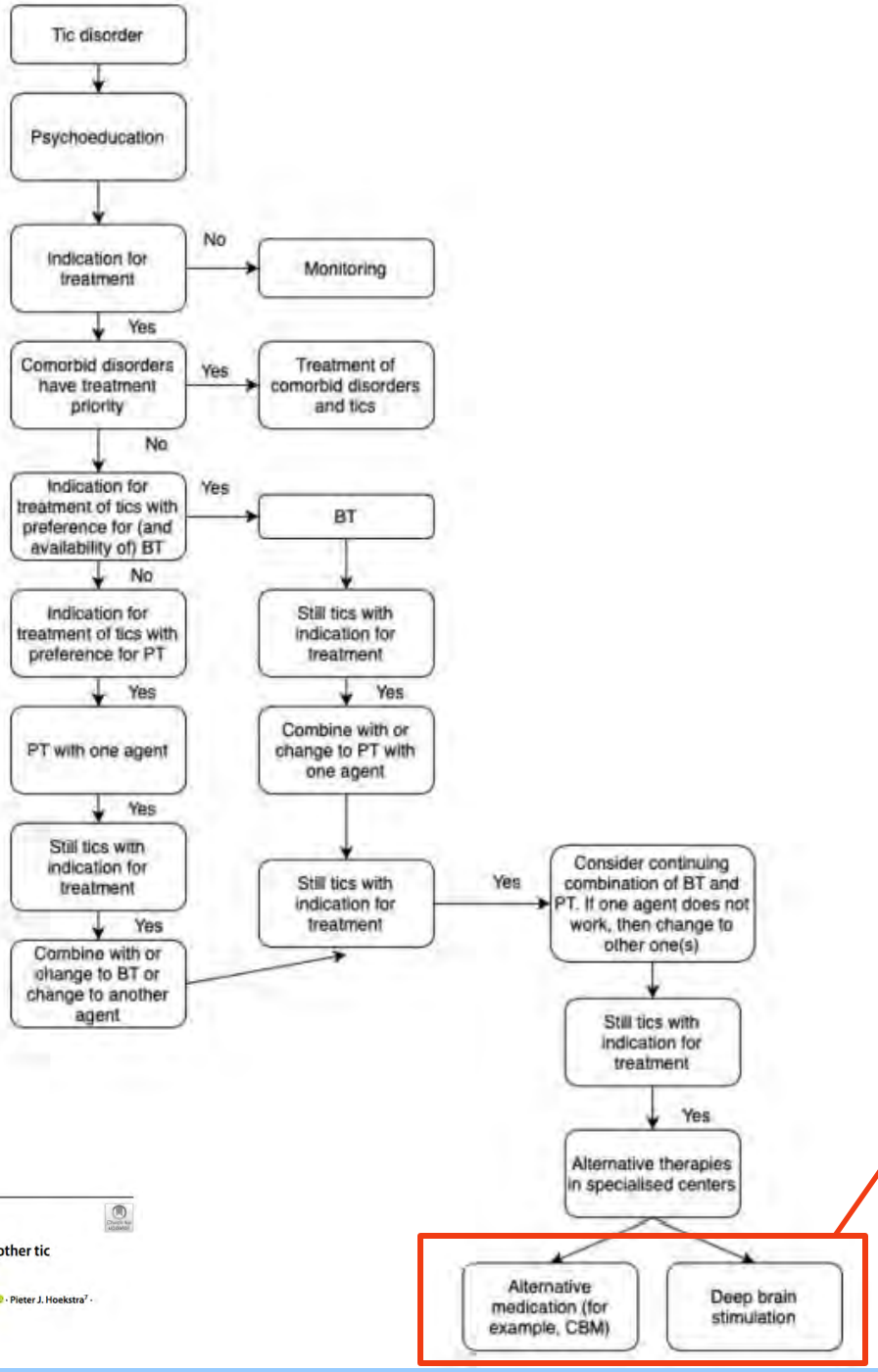
Neurology® 2019;92:907-915. doi:10.1212/WNL.0000000000007467

Results

There was high confidence that the Comprehensive Behavioral Intervention for Tics was more likely than psychoeducation and supportive therapy to reduce tics. There was moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, onabotulinumtoxinA injections, 5-ling granule, Ningdong granule, and deep brain stimulation of the globus pallidus were probably more likely than placebo to reduce tics. There was low confidence that pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinol were possibly more likely than placebo to reduce tics. Evidence of harm associated with various treatments was also demonstrated, including weight gain, drug-induced movement disorders, elevated prolactin levels, sedation, and effects on heart rate, blood pressure, and ECGs.

Fig. 1 Algorithm for the treatment of patients with TS based on shared clinician patient decision making (adapted with permission from [14], Springer). *TS* Tourette syndrome, *PT* pharmacotherapy, *BT* behaviour therapy, *CBM* cannabis-based medicine



European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-021-01832-4

REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders: summary statement

Kirsten R. Müller-Vahl[1] · Natalia Szejko[2,3,4] · Cara Verdellen[5,11] · Veit Roessner[6] · Pieter J. Hoekstra[7] · Andreas Hartmann[8] · Danielle C. Cath[9,10]

Received: 8 March 2021 / Accepted: 19 June 2021

Alternative medication (for example CBM = Cannabis based medication)

Deep Brain Simulation (DBS)

Cannabis-based Medicine

Study	Country	Number of patients	Type of study	Study medication	Efficacy
Müller-Vahl et al. (2002)	Germany	12	Randomized, double-blind, placebo-controlled, cross-over, single-dose	Oral THC	Decrease in tics, improvement in obsessive–compulsive behavior
Müller-Vahl et al. (2003)	Germany	24	Randomized, double-blind, placebo-controlled, parallel groups	Oral THC	Reduction of tics at different time points
Abi-Jaoude et al. (2022)	Israel	12	Randomized, double-blind, placebo-controlled, cross-over, single-dose	THC 10%, THC/CBD 9/9%, CBD 13%	THC and THC/CBD better than placebo, CBD ineffective
Mosley et al. (2023)	Australia	22	Randomized, double-blind, cross-over trial	oral oil 5mg/ml THC+ 5mg/ml CBD	Reduction of tics, correlation between 11-COOH-THC and primary outcome
Müller-Vahl et al. (2023)	Germany	97	Randomized, double-blind, placebo-controlled, parallel groups	Nabiximols	Non-significant tic reduction in primary endpoint, significant tic reduction in secondary endpoints
Efron et al. (2025)	Australia	10 (12-18y, mean 14.8y)	Phase I/II randomized, double-blind, cross-over pilot study	THC 10 mg/mL+ CBD 15 mg/mL	CGI-I: N=3 much improved on MC compared with N=1 on placebo at 10 weeks, no SAEs

Efficacy of cannabis-based medicine in the treatment of Tourette syndrome: a systematic review and meta-analysis

European Journal of Clinical Pharmacology (2024) 80:1483–1493
https://doi.org/10.1007/s00228-024-03710-9

Ibrahim Serag[1] · Mona Mahmoud Elsakka[2] · Mostafa Hossam El din Moawad[3,4] · Hossam Tharwat Ali[5] · Khalid Sarhan[1] · Sally Shayeb[6] · Islam Nadim[7] · Mohamed Abouzid[8,9]

Results In total, 357 articles were identified for screening, with nine studies included in the systematic review and 3 in the meta-analysis. These studies involved 401 adult patients with TS treated with cannabis. YGTSS revealed a significant reduction in total scores (MD = -23.71, 95% CI [-43.86 to -3.55], $P = 0.02$), PUTS revealed a significant decrease in scores (MD = -5.36, 95% CI [-8.46 to -2.27], $P = 0.0007$), and Y-BOCS revealed no significant difference in score reduction (MD = -6.22, 95% CI [-12.68 to 0.23], $P = 0.06$).

Conclusion The current study indicates promising and potentially effective outcomes with the use of cannabis-based medicine in mitigating the severity of tics and premonitory urges. However, there is a need for larger, placebo-controlled studies with more representative samples to validate these findings.

Cannabinoids in ADHD

	N	Patients	Product	Findings
Case reports	2	N=1 N=1	Cannabis	• Improvement of ADHD symptoms, Improvement of driving abilities • Improvement of ADHD symptoms, in particular of poor tolerance to frustration, outbursts of anger, boredom, and problems related to concentration
Case series	2	N=30 N=3	Cannabis	• Improvement of ADHD symptoms including concentration, impulsivity, sleep, • Improvement of depression, anxiety, self regulation, inattention
Survey	3	N=1,739 N=59 N=2,811	Cannabis	• Beneficial effects on symptoms of ADHD: e.g., hyperactivity, impulsivity, improvement of medication side effects (e.g., irritability, anxiety), Impaired memory • Association between cannabis dose and withdrawal from other ADHD medications, association between high dose of cannabinol (CBN) and reduction of ADHD symptoms • Higher proportion of daily users met symptom criteria for an ADHD diagnoses of the hyperactive–impulsive subtype than the inattentive subtype
Prospective study	1	N=361 veterans	Cannabis	• Veterans with ADHD symptoms: sleep disturbance motivates for cannabis use; coping with negative affect predicts cannabis use problems
RCT	1	N=30	Nabiximols	• No significant change in primary endpoint • Significant improvement in secondary endpoints: hyperactivity, impulsivity, inhibition control • Trend towards improvement in inattention

European Child & Adolescent Psychiatry
https://doi.org/10.1007/s00787-021-01881-9

REVIEW

European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part IV: deep brain stimulation

Natalia Szejko[1,2,3] · Yulia Worbe[4,5] · Andreas Hartmann[14] · Veerle Visser-Vandewalle[6] · Linda Ackermans[7] · Christos Ganos[8] · Mauro Porta[9] · Albert F. G. Leentjens[10] · Jan-Hinnerk Mehrkens[11] · Daniel Huys[12] · Juan Carlos Baldermann[12] · Jens Kuhn[12,13] · Carine Karachi[5,14,15] · Cécile Delorme[14] · Thomas Foltynie[16] · Andrea E. Cavanna[17] · Danielle Cath[18,19] · Kirsten Müller-Vahl[20]

Received: 7 March 2021 / Accepted: 15 September 2021

Abstract

In 2011 the European Society for the Study of Tourette Syndrome (ESSTS) published its first European clinical guidelines for the treatment of Tourette Syndrome (TS) with part IV on deep brain stimulation (DBS). Here, we present a revised version of these guidelines with updated recommendations based on the current literature covering the last decade as well as a survey among ESSTS experts. Currently, data from the International Tourette DBS Registry and Database, two meta-analyses, and eight randomized controlled trials (RCTs) are available. Interpretation of outcomes is limited by small sample sizes and short follow-up periods. Compared to open uncontrolled case studies, RCTs report less favorable outcomes with conflicting results. This could be related to several different aspects including methodological issues, but also substantial placebo effects. These guidelines, therefore, not only present currently available data from open and controlled studies, but also include expert knowledge. Although the overall database has increased in size since 2011, definite conclusions regarding the efficacy and tolerability of DBS in TS are still open to debate. Therefore, we continue to consider DBS for TS as an experimental treatment that should be used only in carefully selected, severely affected and otherwise treatment-resistant patients.

Anterior pallidal deep brain stimulation for Tourette's syndrome: a randomised, double-blind, controlled trial

*Marie-Laure Welter, Jean-Luc Houeto, Stéphane Thobois, Benoit Bataille, Marc Guenot, Yulia Worbe, Andreas Hartmann, Virginie Czernecki, Eric Bardinet, Jerome Yelnik, Sophie Tezenas du Montcel, Yves Agid, Marie Vidailhet, Philippe Cornu, Audrey Tanguy, Solène Ansquer, Nematollah Jaafari, Emmanuel Poulet, Giulia Serra, Pierre Burbaud, Emmanuel Cuny, Bruno Aouizerate, Pierre Pollak, Stephan Chabardes, Mircea Polosan, Michel Borg, Denys Fontaine, Bruno Giordana, Sylvie Raoul, Tiphaine Rouaud, Anne Sauvaget, Isabelle Jalenques, Carine Karachi, Luc Mallet, for the STIC study group**

Lancet Neurol 2017

Published Online
June 20, 2017
http://dx.doi.org/10.1016/
S1474-4422(17)30160-6

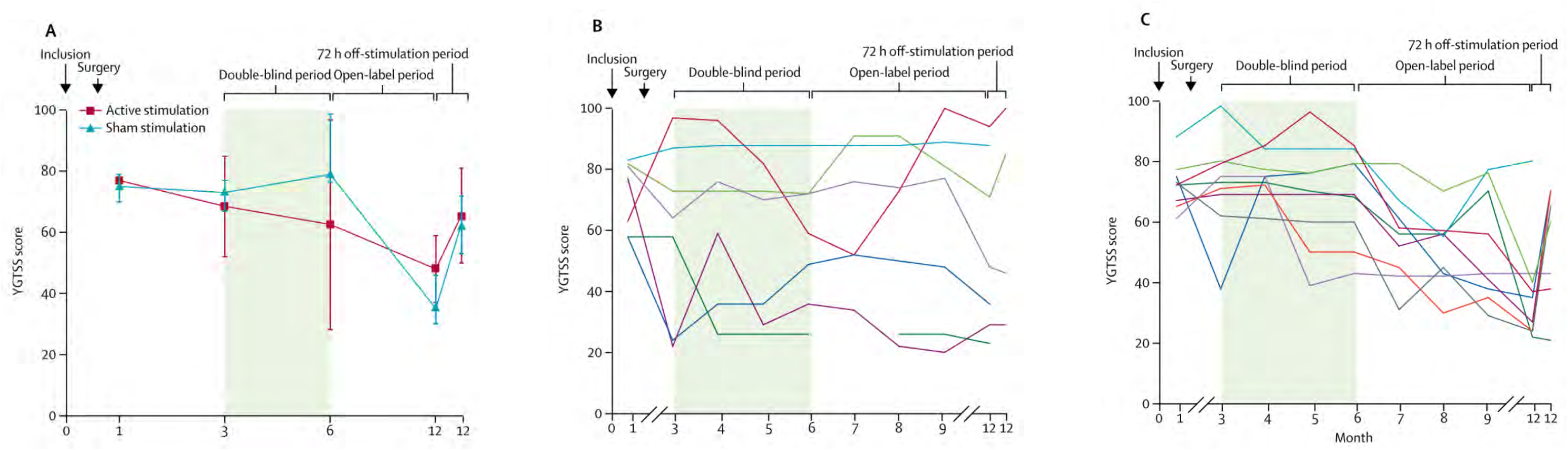


Figure 4: **Changes in YGTSS score during the study period**
(A) Median overall YGTSS scores for the active and sham stimulation groups. Error bars are IQRs. Individual YGTSS scores for the (B) active and (C) sham stimulation groups. YGTSS=Yale Global Tic Severity Scale.

Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome

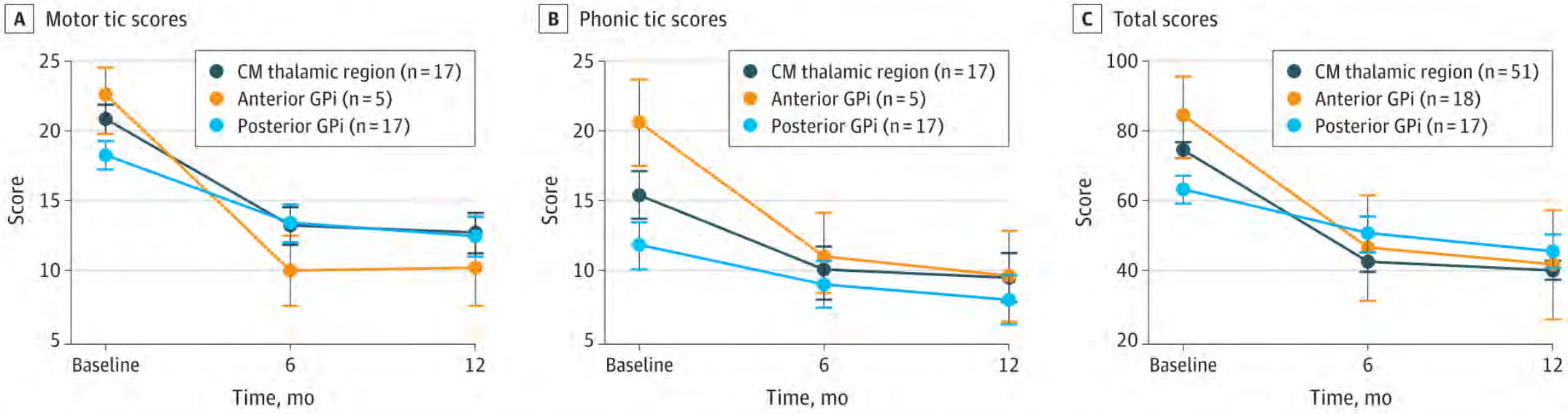
The International Tourette Syndrome Deep Brain Stimulation Public Database and Registry

Daniel Martinez-Ramirez, MD; Joohi Jimenez-Shahed, MD; James Frederick Leckman, MD; Mauro Porta, MD; Domenico Servello, MD; Fan-Gang Meng, MD; Jens Kuhn, MD; Daniel Huys, MD; Juan Carlos Baldermann, MD; Thomas Foltynie, PhD, MRCP; Marwan I. Hariz, MD, PhD; Eileen M. Joyce, MD, PhD; Ludvic Zrinzo, MD; Zinovia Kefalopoulou, MD, PhD; Peter Silburn, MD; Terry Coyne, MD; Alon Y. Mogilner, MD, PhD; Michael H. Pourfar, MD; Suketu M. Khandhar, MD; Man Auyeung, MD, FHKCP, FHKAM; Jill Louise Ostrem, MD; Veerle Visser-Vandewalle, MD; Marie-Laure Welter, MD; Luc Mallet, MD, PhD; Carine Karachi, MD, PhD; Jean Luc Houeto, MD; Bryan Timothy Klassen, MD; Linda Ackermans, MD, PhD; Takanobu Kaido, MD, PhD; Yasin Temel, MD; Robert E. Gross, MD, PhD; Harrison C. Walker, MD; Andres M. Lozano, MD, PhD; Benjamin L. Walter, MD; Zoltan Mari, MD; William S. Anderson, MD; Barbara Kelly Changizi, MD; Elena Moro, MD, PhD; Sarah Elizabeth Zauber, MD; Lauren E. Schrock, MD; Jian-Guo Zhang, MD; Wei Hu, MD; Kyle Rizer, BS; Erin H. Monari, PhD; Kelly D. Foote, MD; Irene A. Malaty, MD; Wissam Deeb, MD; Aysegul Gunduz, PhD; Michael S. Okun, MD

JAMA Neurol. doi:10.1001/jamaneurol.2017.4317
Published online January 16, 2018.

DESIGN, SETTING, AND PARTICIPANTS The prospective International Deep Brain Stimulation Database and Registry included 185 patients with medically refractory Tourette syndrome who underwent DBS implantation from January 1, 2012, to December 31, 2016, at 31 institutions in 10 countries worldwide.

Figure. Yale Global Tic Severity Scale (YGTSS) Scores by Time and Brain Target



A, YGTSS motor tic scores at baseline, 6 months, and 1 year. B, YGTSS phonic tic scores at baseline, 6 months, and 1 year. C, Total YGTSS scores at baseline, 6 months, and 1 year. CM indicates centromedian; GPi, globus pallidus internus.

Efficacy and Safety of Deep Brain Stimulation in Tourette Syndrome

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Daniel Martinez-Ramirez, MD; Joohi Jimenez-Shahed, MD; James Frederick Leckman, MD; Mauro Porta, MD; Domenico Servello, MD; Fan-Gang Meng, MD; Jens Kuhn, MD; Daniel Huys, MD; Juan Carlos Baldermann, MD; Thomas Foltynie, PhD, MRCP; Marwan I. Hariz, MD, PhD; Eileen M. Joyce, MD, PhD; Ludvic Zrinzo, MD; Zinovia Kefalopoulou, MD, PhD; Peter Silburn, MD; Terry Coyne, MD; Alon Y. Mogilner, MD, PhD; Michael H. Pourfar, MD; Suketu M. Khandhar, MD; Man Auyeung, MD, FHKCP, FHKAM; Jill Louise Ostrem, MD; Veerle Visser-Vandewalle, MD; Marie-Laure Welter, MD; Luc Mallet, MD, PhD; Carine Karachi, MD, PhD; Jean Luc Houeto, MD; Bryan Timothy Klassen, MD; Linda Ackermans, MD, PhD; Takanobu Kaido, MD, PhD; Yasin Temel, MD; Robert E. Gross, MD, PhD; Harrison C. Walker, MD; Andres M. Lozano, MD, PhD; Benjamin L. Walter, MD; Zoltan Mari, MD; William S. Anderson, MD; Barbara Kelly Changizi, MD; Elena Moro, MD, PhD; Sarah Elizabeth Zauber, MD; Lauren E. Schrock, MD; Jian-Guo Zhang, MD; Wei Hu, MD; Kyle Rizer, BS; Erin H. Monari, PhD; Kelly D. Foote, MD; Irene A. Malaty, MD; Wissam Deeb, MD; Aysegul Gunduz, PhD; Michael S. Okun, MD

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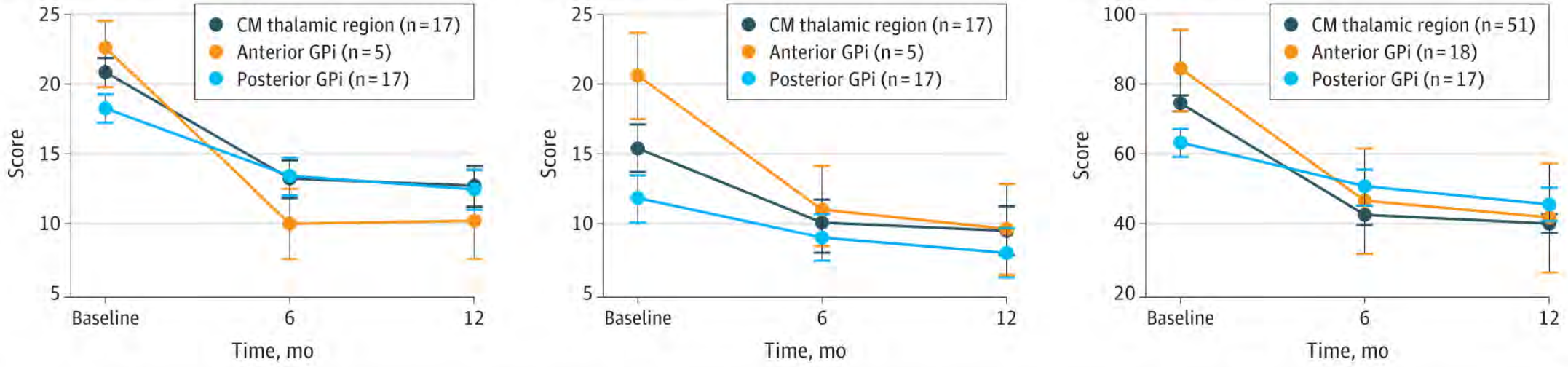
Most data from open uncontrolled (case) studies



A, YGTSS motor tic scores at baseline, 6 months, and 1 year. B, YGTSS phonic tic scores at baseline, 6 months, and 1 year. C, Total YGTSS scores at baseline, 6 months, and 1 year. CM indicates centromedian; GPi, globus pallidus internus.

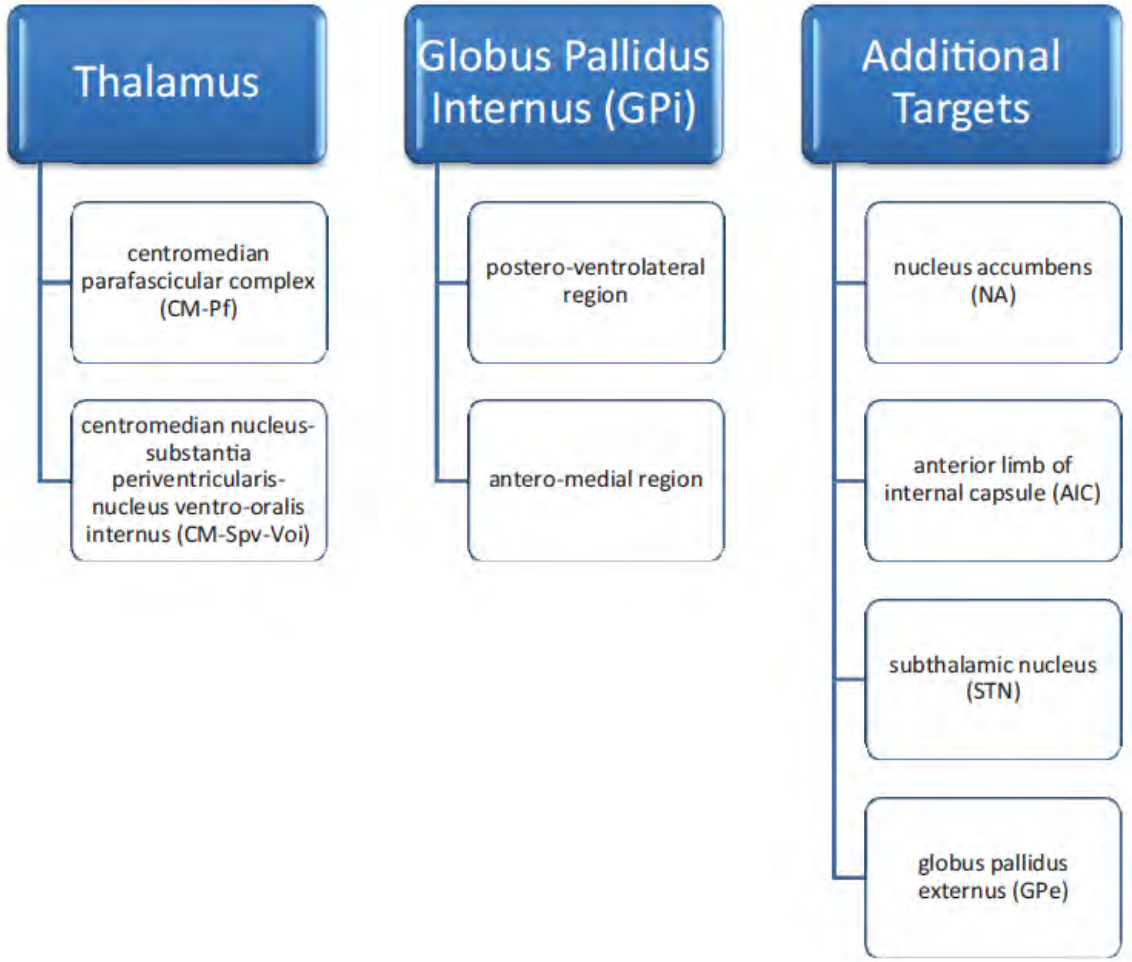
DBS: optimal target unclear

Deep brain stimulation in Tourette's syndrome

Avram Fraint and Gian Pal*

frontiers in Neurology

REVIEW
published: 04 August 2015
doi: 10.3389/fneur.2015.00170



Recent studies: promising new treatments

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

Donald L. Gilbert, MD,[1*] Tanya K. Murphy,[2] Joseph Jankovic, MD,[3] Cathy L. Budman, MD,[4] Kevin J. Black, MD,[5] Roger M. Kurlan, MD,[6] Keith A. Coffman, MD,[7] James T. McCracken, MD,[8] Jorge Juncos, MD,[9] Jon E. Grant, MD[10], and Richard E. Chipkin, PhD[11]

Movement Disorders, Vol. 33, No. 8, 2018

Double blind
Placebo controlled
N=40
Age: 7-17 years

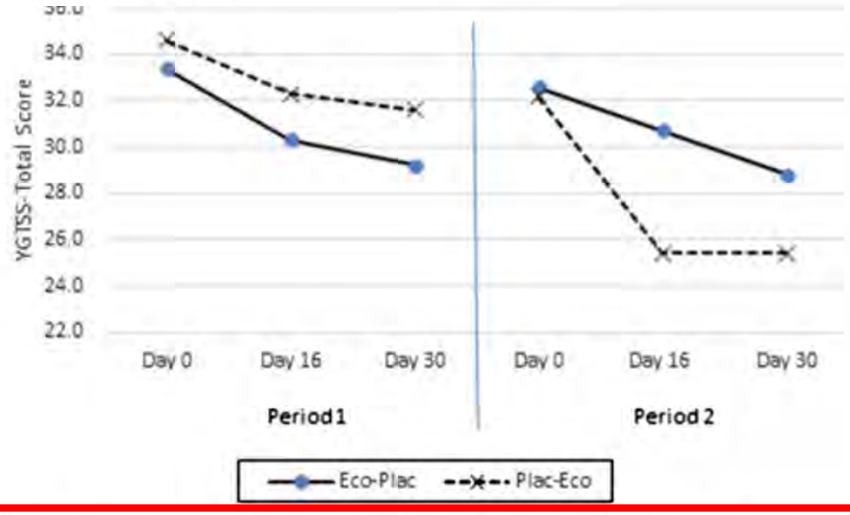


FIG. 2. Treatment effects by period. YGTSS, Yale Global Tic Severity Scale; YGTSS-total score, motor and phonic tic scores, the primary outcome for the trial; Eco-Plac, ecopipam in period 1, followed by placebo in period 2; Plac-Eco, placebo in period 1, followed by ecopipam in period 2. Means are from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

Ecopipam for Tourette Syndrome: A Randomized Trial

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]

PEDIATRICS Volume 151, number 2, February 2023:e2022059574

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

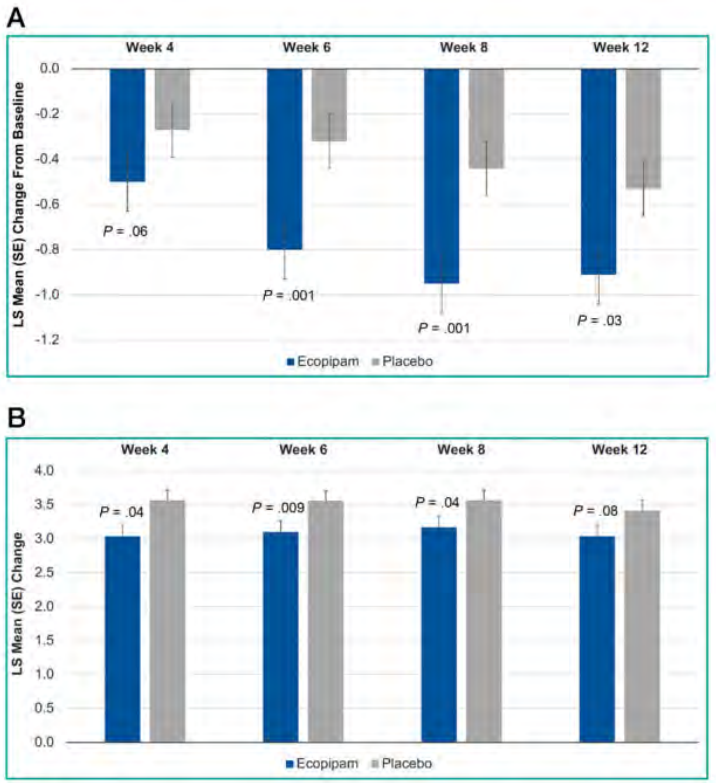


FIGURE 3
(A) CGI-TS-S LS mean (SE) change from baseline to week 4, 6, 8, and 12 and (B) CGI-TS-I LS mean (SE) change from baseline to week 4, 6, 8, and 12.

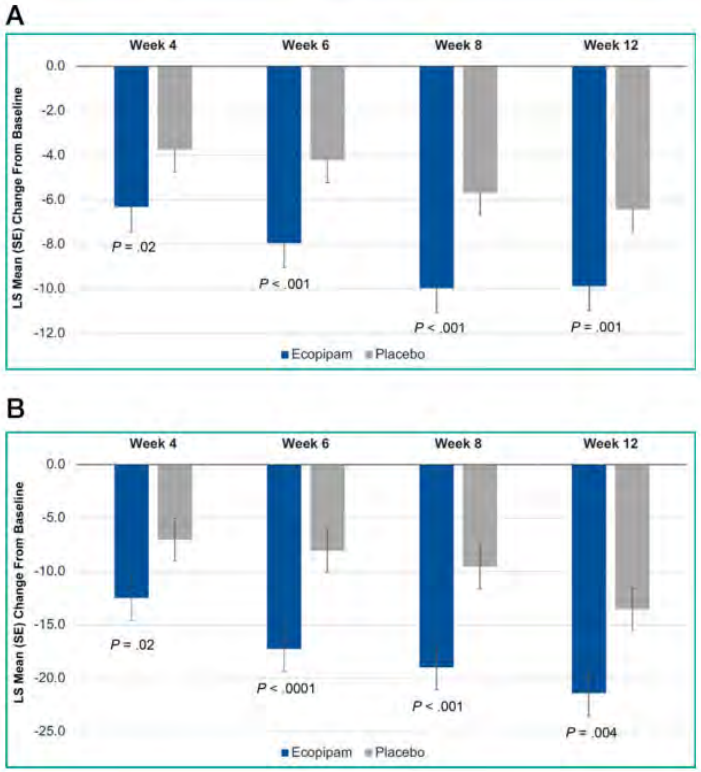


FIGURE 2
(A) YGTSS-TTS LS mean (SE) change from baseline to week 4, 6, 8 and 12 and (B) YGTSS-GS LS mean (SE) change from baseline to week 4, 6, 8, and 12. *P* values from MMRM analysis.

Emalex Biosciences' Lead Candidate Meets Primary and Secondary Endpoints in Phase 3 Tourette Syndrome Study

February 25, 2025

Topline data from Phase 3 study in patients with Tourette syndrome shows statistical significance between ecopipam and placebo for both the primary efficacy endpoint in pediatric subjects (p = 0.0084) and secondary efficacy endpoint in pediatric and adult subjects (p=0.0050)

ESSTS

Emalex Biosciences' Lead Candidate Meets Primary and Secondary Endpoints in Phase 3 Tourette Syndrome Study

February 25, 2025

Topline data from Phase 3 study in patients with Tourette syndrome shows statistical significance between ecopipam and placebo for both the primary efficacy endpoint in pediatric subjects (p = 0.0084) and secondary efficacy endpoint in pediatric and adult subjects (p=0.0050)

Emalex eyes FDA approval for Tourette syndrome therapy after Phase III success

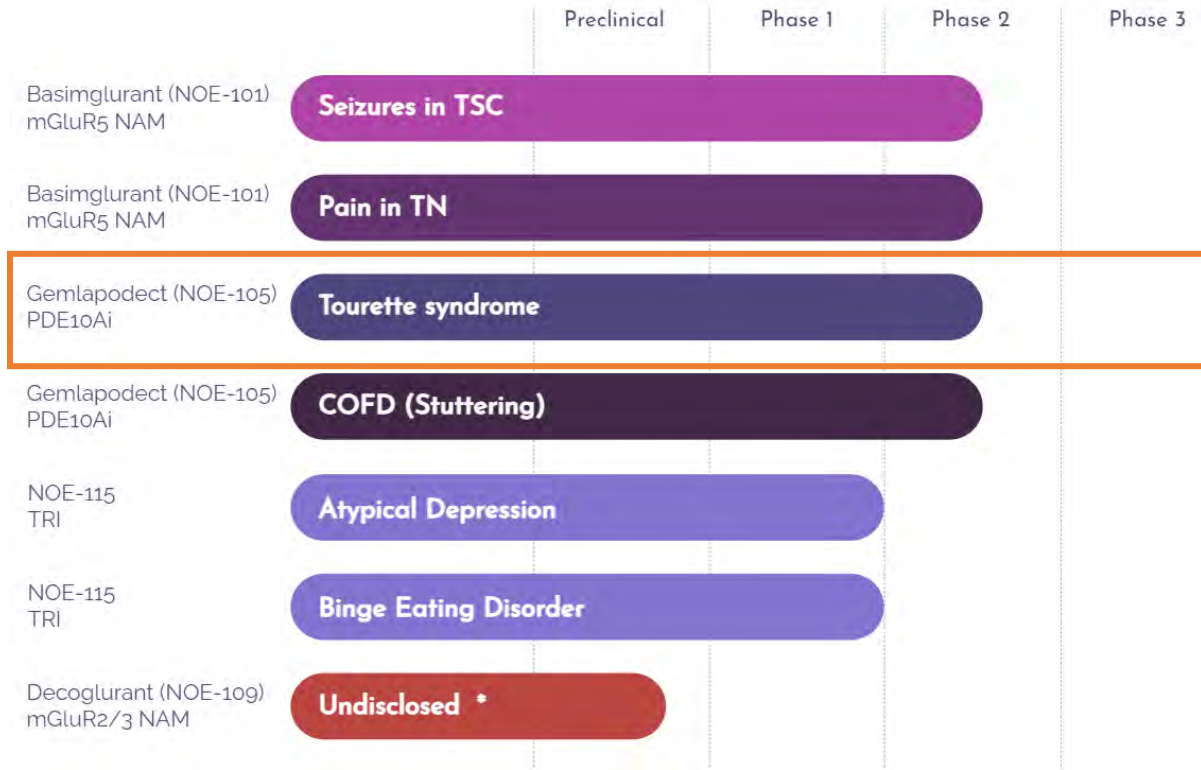
The Phase III DIAMOND trial met both its primary and secondary endpoints of reducing tics in both children and adult patients.

Joshua Silverwood | February 26, 2025

NOEMA PHARMA

Our Pipeline

Click an asset below to learn more.



Gemlapodect (NOE-105)

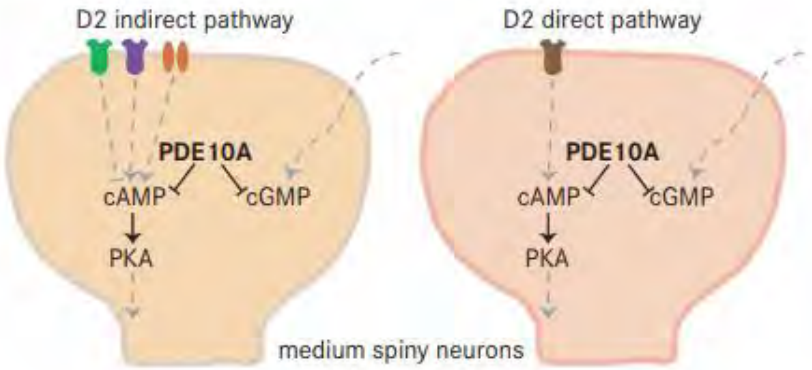
PDE10A inhibitor

For the management of Tourette Syndrome (TS) tics

Clinical stage: Phase 2a

Noema Pharma initiates Phase 2a Allevia study of PDE10A inhibitor NOE-105 in Tourette Syndrome

FIGURE. PDE10A Inhibition[4]



cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; D1, dopamine type 1 receptor; D2, dopamine type 2 receptor; PDE10A, phosphodiesterase 10A; PKA, protein kinase A. PDE10A is one of the main phosphodiesterases expressed in corticostriatal circuits, primarily localized to the medium spiny neurons. PDE10A inhibition activates cAMP/PKA signaling, leading to inhibition of D1 and D2 receptor signaling. Effects of PDE10A inhibition predominate the indirect pathway.

PDE10A Inhibition in Tourette Syndrome

By Jennifer S. Sun, PhD

NeurologyLive.com
Vol. 5 | No. 2 | April 2022

Inactivtion of PDE10A by Gemlapodect (NOE-105)

- enhances the effect of dopamine D1 receptor activation in the striatonigral (direct) pathway
- counteracts the inhibitory effect of D2 receptor signaling in the striatopallidal (indirect) pathway

Noema Pharma Announces NOE-105 (gemlapodect) Phase 2a Study in Tourette Syndrome met Primary and all Key Secondary Endpoints

Nearly 60% of all patients treated with gemlapodect and 88% of patients completing the study at the target clinical dose range were responders based on the primary efficacy assessment

The Yale Global Tics Severity Scale Total Tic Score (YGTSS-TTS) showed a statistically significant improvement of -7.8 points for all patients, and -12.8 points for patients completing the study at the target clinical dose

No weight gain, events of metabolic marker increase, or serious adverse events were reported

Session 2, Friday 23 May 2025, 1:30 PM

3. Results of ALLEVIA 1 (NOE-TTS-211), a Phase 2a study assessing safety and tolerability of gemlapodect (NOE-105), a first-in-class investigational product, in patients with Tourette Syndrome
Kirsten Müller-Vahl

Recruiting

Efficacy and Safety of Gemlapodect (NOE-105) in Adults and Adolescents With Tourette Syndrome (ALLEVIA2)

ClinicalTrials.gov ID NCT06315751

Sponsor Noema Pharma AG

Information provided by Noema Pharma AG (Responsible Party)

Last Update Posted 2025-05-15

Official Title

A Double-blind, Placebo-controlled, Phase 2b, Multi-center, Twelve-week Prospective Study to Evaluate the Efficacy and Safety of Gemlapodect in Adult and Adolescent Patients With Tourette Syndrome

Friday, 23 May 2025
Afternoon session, 14:30-15:15

P37 Design of ALLEVIA-2 study (NOE-TTS-201), a Phase 2b study assessing efficacy and safety of gemlapodect (NOE-105), a first-in-class investigational PDE10A inhibitor, in patients with Tourette Syndrome
Amine Tahiri

Randomized, Sham-Controlled Trial of Real-Time Functional Magnetic Resonance Imaging Neurofeedback for Tics in Adolescents With Tourette Syndrome

ESSTS

Denis G. Sukhodolsky, Christopher Walsh, William N. Koller, Jeffrey Eilbott, Mariela Rance, Robert K. Fulbright, Zhiying Zhao, Michael H. Bloch, Robert King, James F. Leckman, Dustin Scheinost, Brian Pittman, and Michelle Hampson

Biological Psychiatry June 15, 2020; 87:1063–1070 www.sobp.org/journal

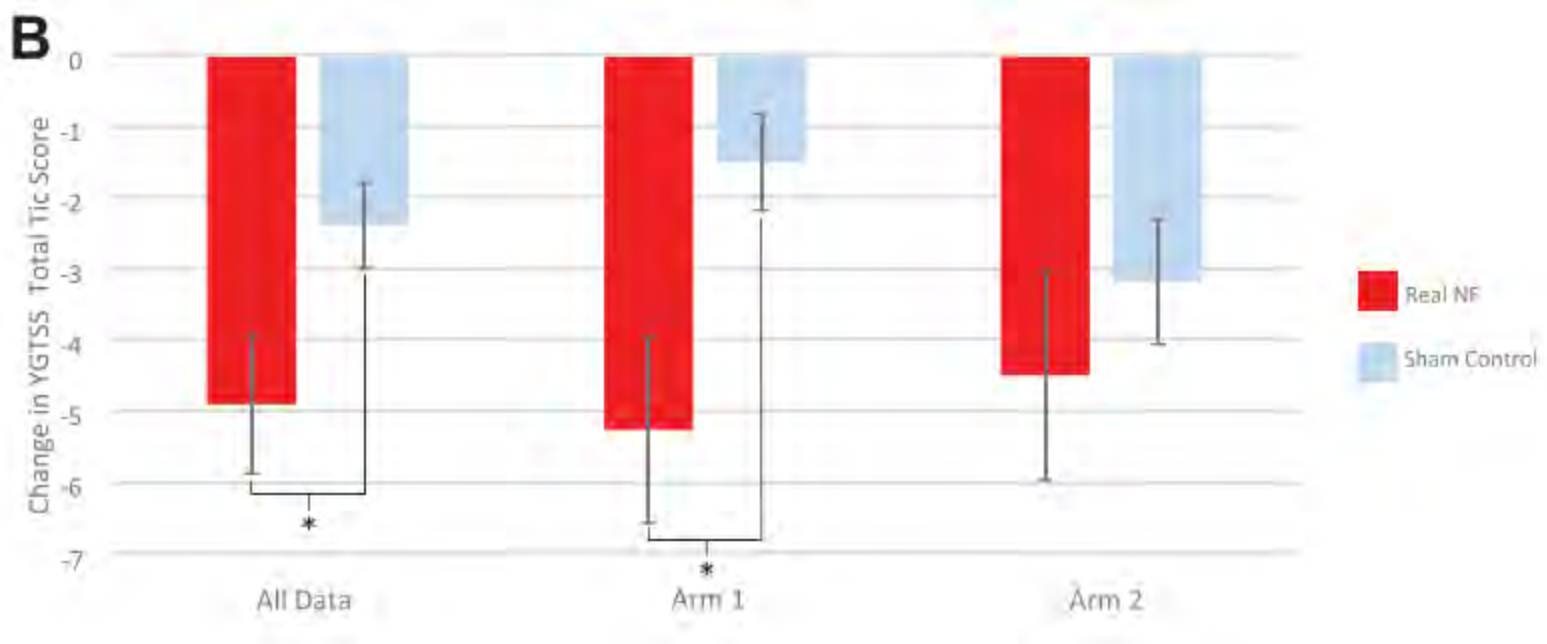


Figure 2. **(A)** Yale Global Tic Severity Scale (YGTSS) Total Tic score at baseline and end point by treatment condition (real neurofeedback [NF], sham control) and study arm (arm 1: before crossover; arm 2: after crossover). The group that was randomized to receive real NF first (real NF first followed by sham) is shown with a solid line. The group that was randomized to receive the sham control first (sham first followed by real NF) is shown with a dashed line. Error bars represent SE. **(B)** Change in YGTSS Total Tic score by treatment condition (real NF, sham control) and study arm (arm 1: before crossover; arm 2: after crossover; all data: arm 1 and arm 2 combined). Change scores were calculated by subtracting preintervention scores from postintervention scores. A more negative value reflects greater clinical improvement from preintervention to postintervention. Error bars represent SE. Asterisk indicates significant differences between conditions.

N=21

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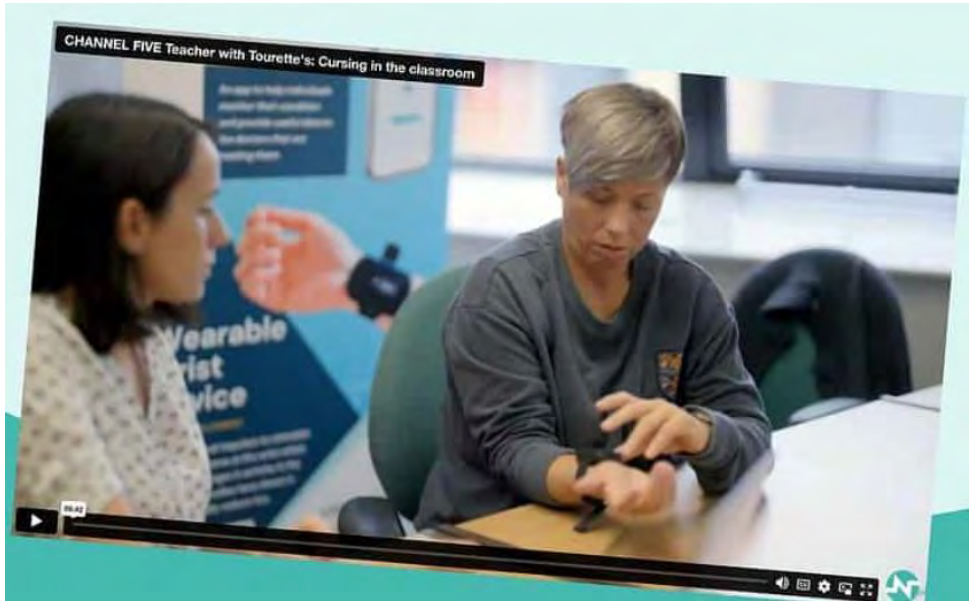
A double-blind, sham-controlled, trial of home-administered rhythmic 10Hz median nerve stimulation for the reduction of tics, and suppression of the urge-to-tic, in individuals with Tourette syndrome and chronic tic disorder

Barbara Morera Maiquez, Caitlin Smith, Katherine Dyke, Chia-Ping Chou, Belinda Kasbia, Ciara McCready, Hannah Wright, Jessica K. Jackson, Isabel Farr, Erika Badinger, Georgina M. Jackson, Stephen R. Jackson

doi: https://doi.org/10.1101/2023.03.06.23286799



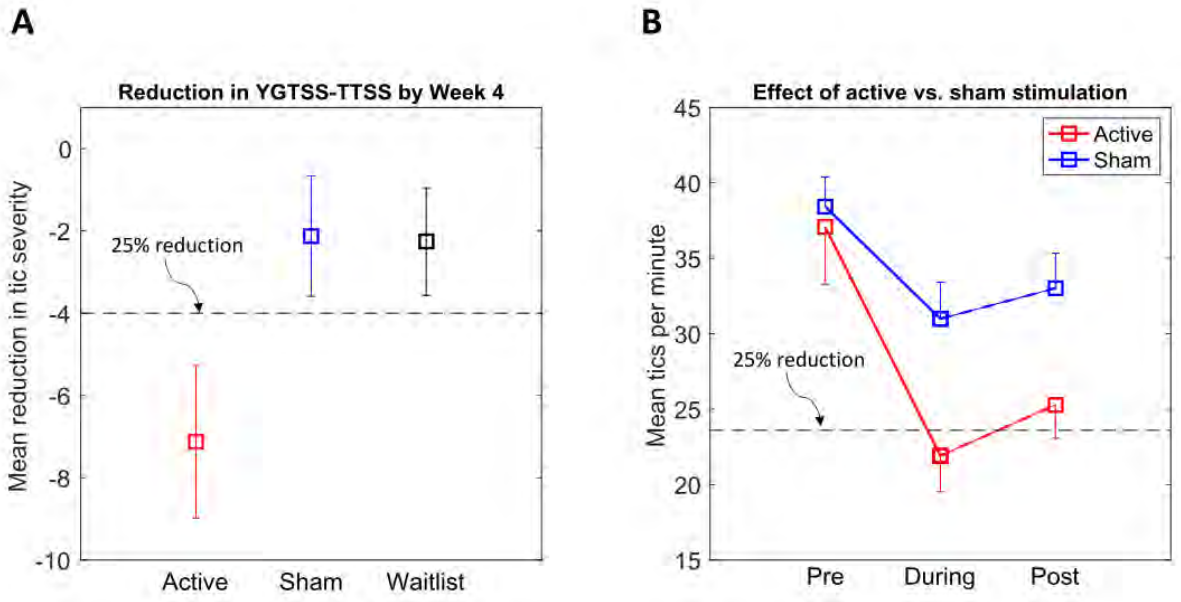


Figure 2: **A.** Mean reduction in total tic severity score (YGTSS-TTSS) for each group after 4 weeks of stimulation relative to baseline levels. The dotted line represents a 25% reduction in YGTSS-TTSS. Error bars are standard errors. **B.** Mean reduction in tics per minute (TPM) for active and sham stimulation sessions immediately prior to, during, and post stimulation. The dotted line represents a 25% reduction in TPM. Error bars are standard errors.

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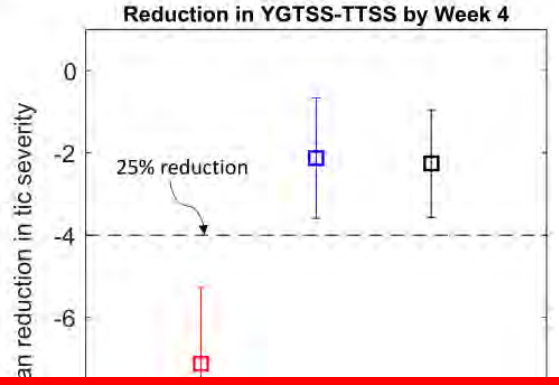
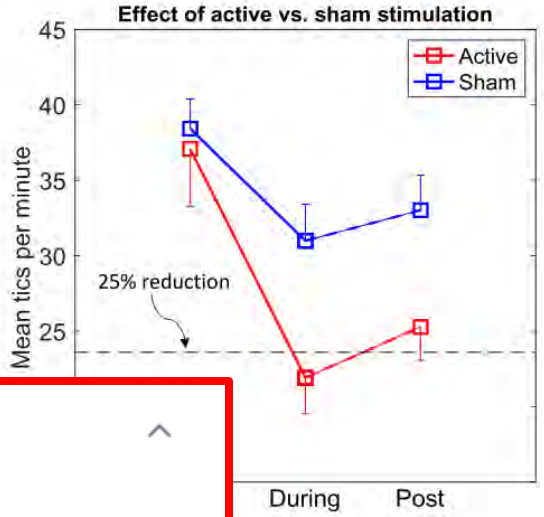
NEUPULSE®

A double-blind, sham-controlle
median nerve stimulation for t
tic, in individuals with Tourette syndrome and chronic tic disorder

Barbara Morera Maiquez
Hannah Wright, Jessica K

doi: https://doi.org/10.1

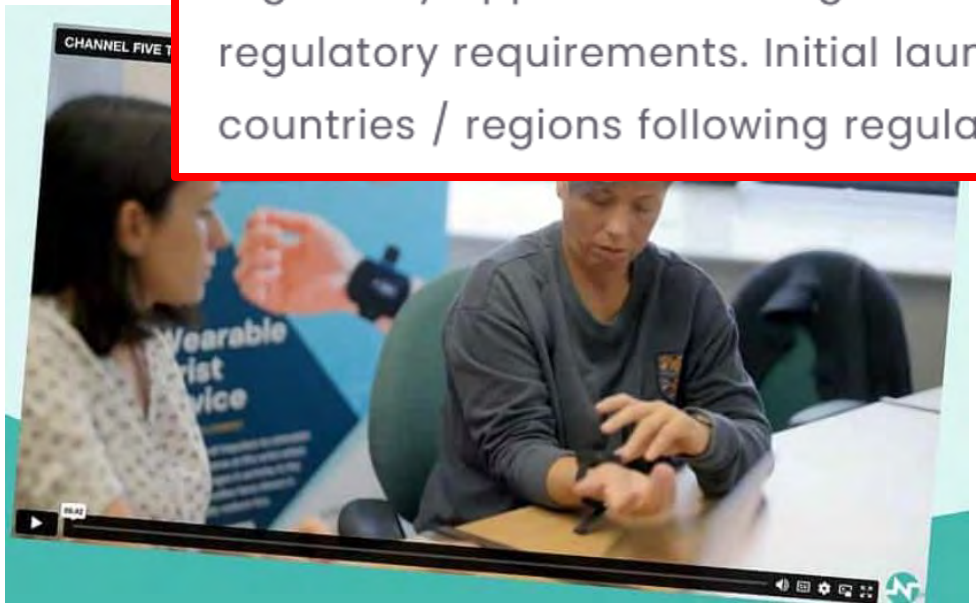




to baseline levels. The dotted line
or active and sham stimulation
ars are standard errors.

When will the Neupulse device be available?

We are aiming to launch the device called 'Neupulse' in 2026 following regulatory approval ensuring its compliance to all relevant safety, quality and regulatory requirements. Initial launch will be in the UK with expansion to other countries / regions following regulatory approval.



A Phase-2 Pilot Study of a Therapeutic Combination of Δ^9-Tetrahydracannabinol and Palmitoylethanolamide for Adults With Tourette's Syndrome

Michael H. Bloch, M.D., M.S., Angeli Landeros-Weisenberger, M.D., Jessica A. Johnson, B.A., James F. Leckman, M.D., Ph.D.

J Neuropsychiatry Clin Neurosci 33:4, Fall 2021

Objective: There are few effective pharmacological treatments for Tourette's syndrome. Many patients with Tourette's syndrome experience impairing tic symptoms despite use of available evidence-based treatments. The investigators conducted a small, uncontrolled trial to examine the safety, tolerability, and dosing of THX-110, a combination of Δ^9-tetrahydracannabinol (Δ^9-THC) and palmitoylethanolamide (PEA), in Tourette's syndrome.

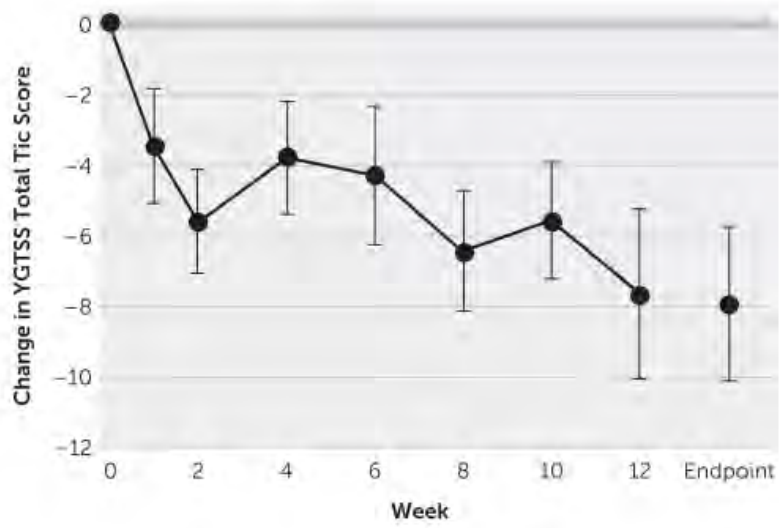
Methods: A 12-week uncontrolled trial of THX-110 (maximum daily Δ^9-THC dose, 10 mg, and a constant 800-mg dose of PEA) in 16 adults with Tourette's syndrome was conducted. The primary outcome was improvement on the Yale Global Tic Severity Scale (YGTSS) total tic score. Secondary outcomes included measures 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 Δ^9-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.

J Neuropsychiatry Clin Neurosci 2021; 33:328–336; doi: 10.1176/appi.neuropsych.19080178

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



Starting soon:

SciSparc Advances Its Phase IIb Clinical Trial in Patients with Tourette Syndrome with its Proprietary Drug Candidate SCI-110

USA - English

The Dual-Site Study Will Be Conducted at the Hannover Medical School in Germany, and Israel's Tel-Aviv Sourasky Medical Center

SCI-110 = combination of dronabinol (THC) and the endocannabinoid palmitoylethanolamide (PEA).
SCI-110 was designed to increase THC efficacy, thereby increasing the efficiency of oral administration while decreasing dosage requirements, side effects and adverse events.

Recent studies: negative results

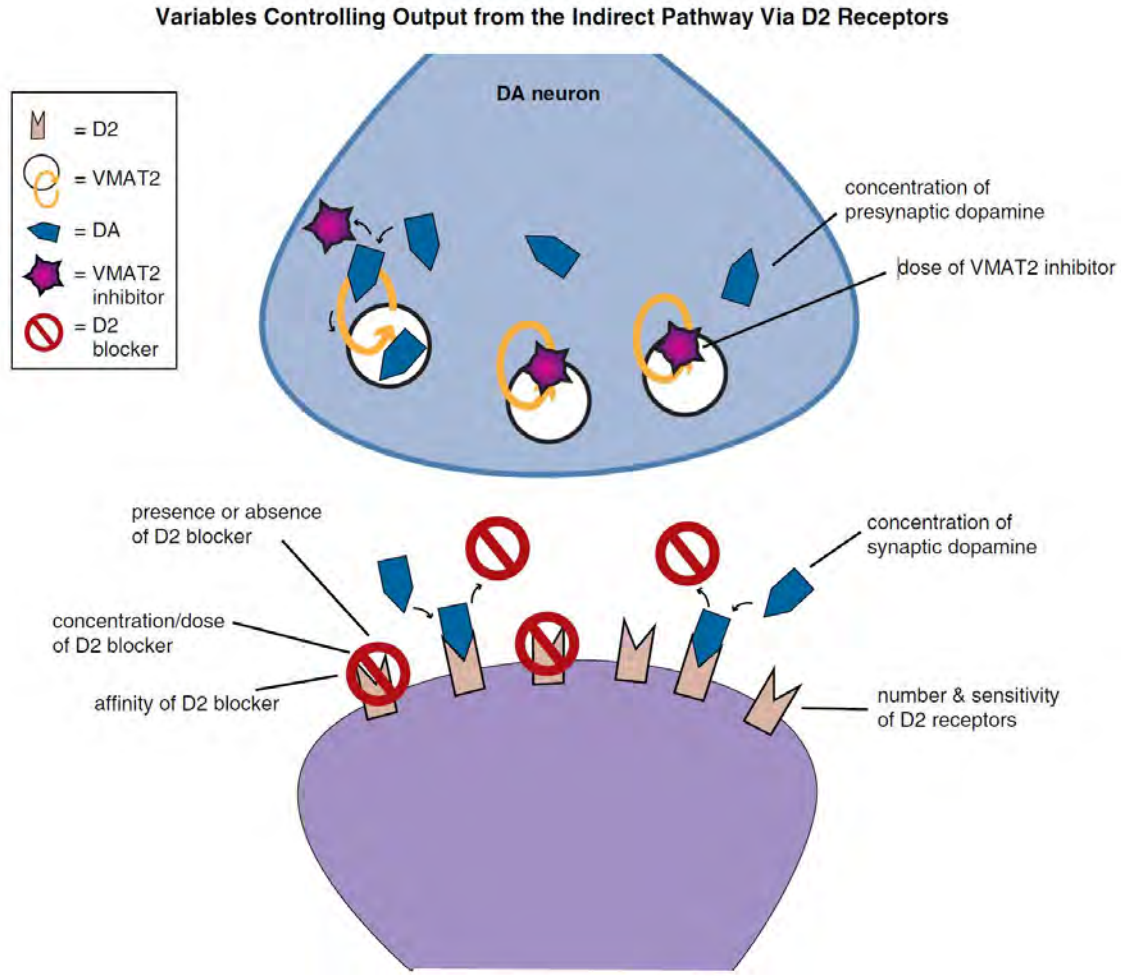
Vesicular monoamine transporter (VMAT2) Inhibitors

Tetrabenazine
Deutetrabenazine
Valbenazine

VMAT2 inhibitors reduce:

- DA storage
- DA release

→ ↓ Dopamine



JAMA Network Open

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

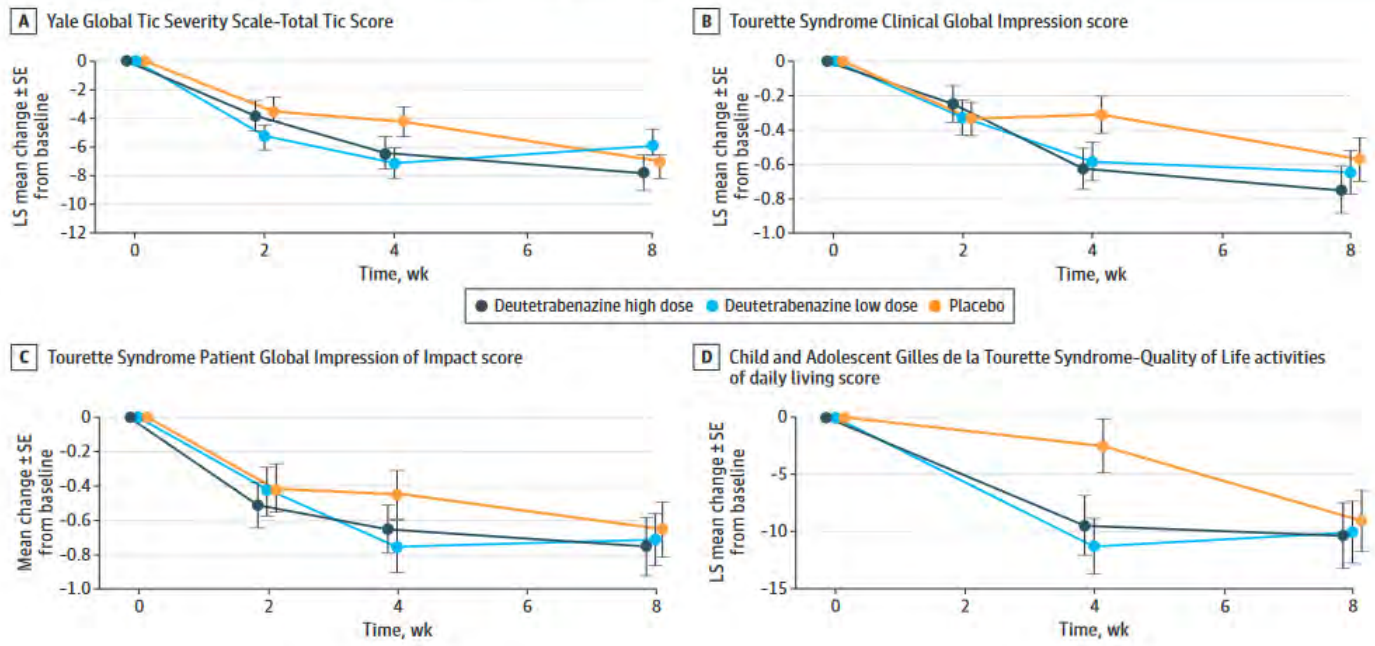
Original Investigation | Neurology

Efficacy and Safety of Fixed-Dose Deutetrabenazine in Children and Adolescents for Tics Associated With Tourette Syndrome

A Randomized Clinical Trial

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

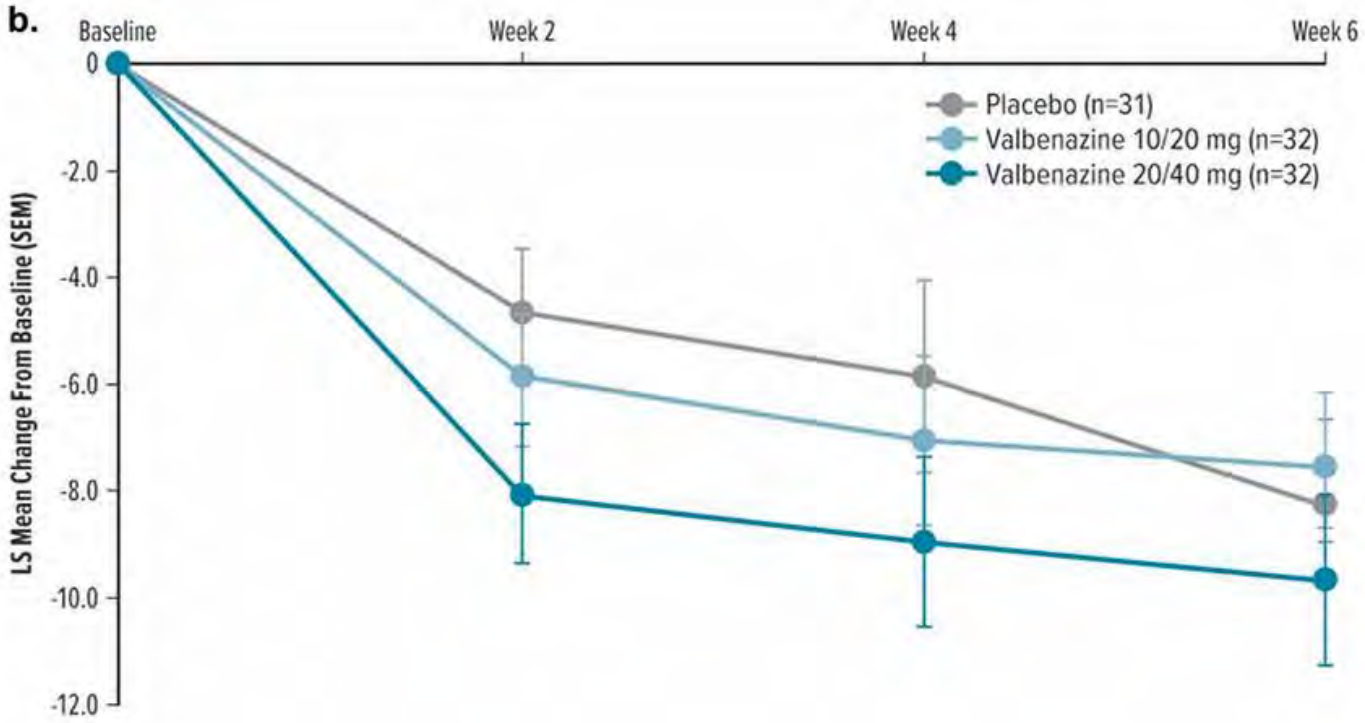
Figure 2. Change From Baseline Through Week 8 in Primary and Key Secondary Efficacy End Points



Clinical development of valbenazine for tics associated with Tourette syndrome

EXPERT REVIEW OF NEUROTHERAPEUTICS
2021, VOL. 21, NO. 4, 393-404
https://doi.org/10.1080/14737175.2021.1898948

Robert H. Farber, Angel Angelov, Kristine Kim, Tara Carmack, Dao Thai-Cuarto, and Eiry Roberts



Expert opinion: Due to the failure to meet the primary endpoint in these trials, further investigation of valbenazine for TS is unlikely. Given the need for safe and effective TS therapies and the key role of VMAT2 in modulating dopaminergic activity, it is reasonable for future studies to investigate other VMAT2 inhibitors as potential treatments for TS.

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

:SSTS

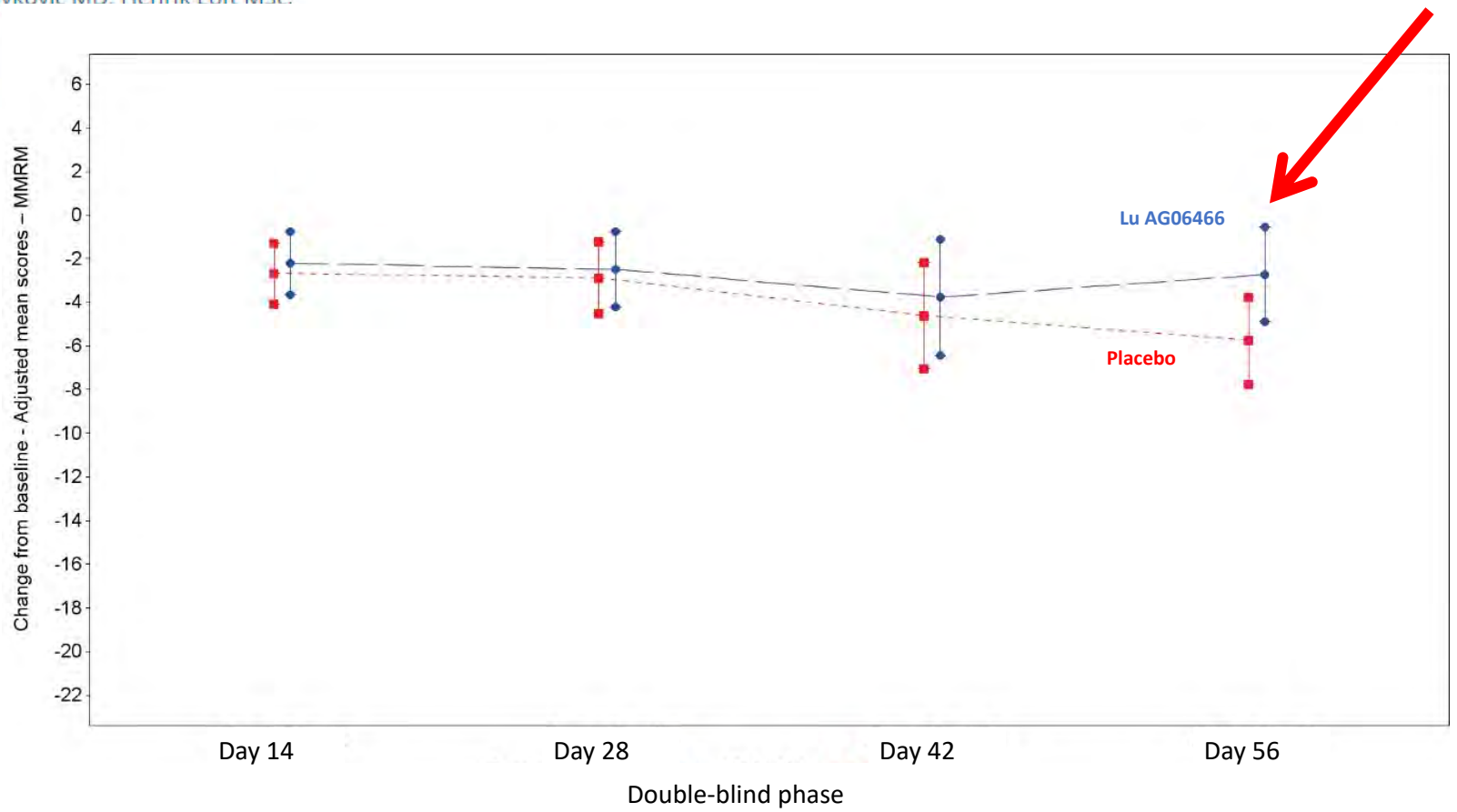
BRIEF REPORT | Open Access

Monoacylglycerol Lipase Inhibition in Tourette Syndrome: A 12-Week, Randomized, Controlled Study

Kirsten R. Müller-Vahl MD, Carolin Fremer MSc, Chan Beals MD, Jelena Ivkovic MD, Henrik Loft MSc, PhD, Christoph Schindler MD.

First published: 12 June 2021 | https://doi.org/10.1002/mds.28681

Adjusted mean change from baseline in YGTSS–Total Tic Scores
(Double-blind phase)



NULL HYPOTHESIS

Association of Group A *Streptococcus* Exposure and Exacerbations of Chronic Tic Disorders

A Multinational Prospective Cohort Study

Davide Martino, MD, PhD, Anette Schrag, MD, PhD, Zacharias Anastasiou, PhD, Alan Apter, MD, Noa Benaroya-Milstein, MD, PhD, Maura Buttiglione, PhD, Francesco Cardona, MD, Roberta Creti, PhD, Androulla Efstratiou, PhD, Tammy Hedderly, MD, Isobel Heyman, MBBS, PhD, FRCPsych, Chaim Huyser, MD, PhD, Marcos Madruga, MD, Pablo Mir, MD, PhD, Astrid Morer, MD, PhD, Nanette Mol Debes, MD, PhD, Natalie Moll, MSc, Norbert Müller, MD, Kirsten Müller-Vahl, MD, Alexander Munchau, MD, Peter Nagy, MD, Kerstin Jessica Plessen, MD, PhD, Cesare Porcelli, MD, Renata Rizzo, MD, PhD, Veit Roessner, MD, PhD, Jaana Schnell, MSc, Markus Schwarz, MD, PhD, Liselotte Skov, MD, Tamar Steinberg, MD, Zsanett Tarnok, PhD, Susanne Walitza, MD, MSc, Andrea Dietrich, PhD, and Pieter J. Hoekstra, MD, PhD, on behalf of the EMTICS Collaborative Group

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Dr. Martino
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Neurology® 2021;96:e1680-e1693. doi:10.1212/WNL.0000000000011610

Results

A total of 405 exacerbations occurred in 308 of 715 (43%) participants. The proportion of exacerbations temporally associated with GAS exposure ranged from 5.5% to 12.9%, depending on GAS exposure definition. We did not detect any significant association of any of the 4 GAS exposure definitions with tic exacerbations (odds ratios ranging between 1.006 and 1.235, all p values >0.3). GAS exposures were

Treatment of Tics: Summary

- Psychoeducation
- Treatment of comorbidities indicated?
- Behavioral therapy: HRT, CBIT, ERP
- Pharmacotherapy:
  - 1. choice: antipsychotics
    - aripiprazole
    - others: risperidone, tiapride
  - 2. choice:
    - cannabis-based medicine
    - clonidine (when ADHD comorbid)
    - Other antipsychotics
    - in carefully selected patients: botulinum toxine
- DBS