TS-school Brussels | training course on Tourette Syndrome

Tuesday 6 June 2023

Royal Museum for Central Africa

Pharmacological Treatment (for Tics)

Kirsten Müller-Vahl, MD

Department of Psychiatry, Socialpsychiatry and Psychotherapy

Hannover Medical School, Germany

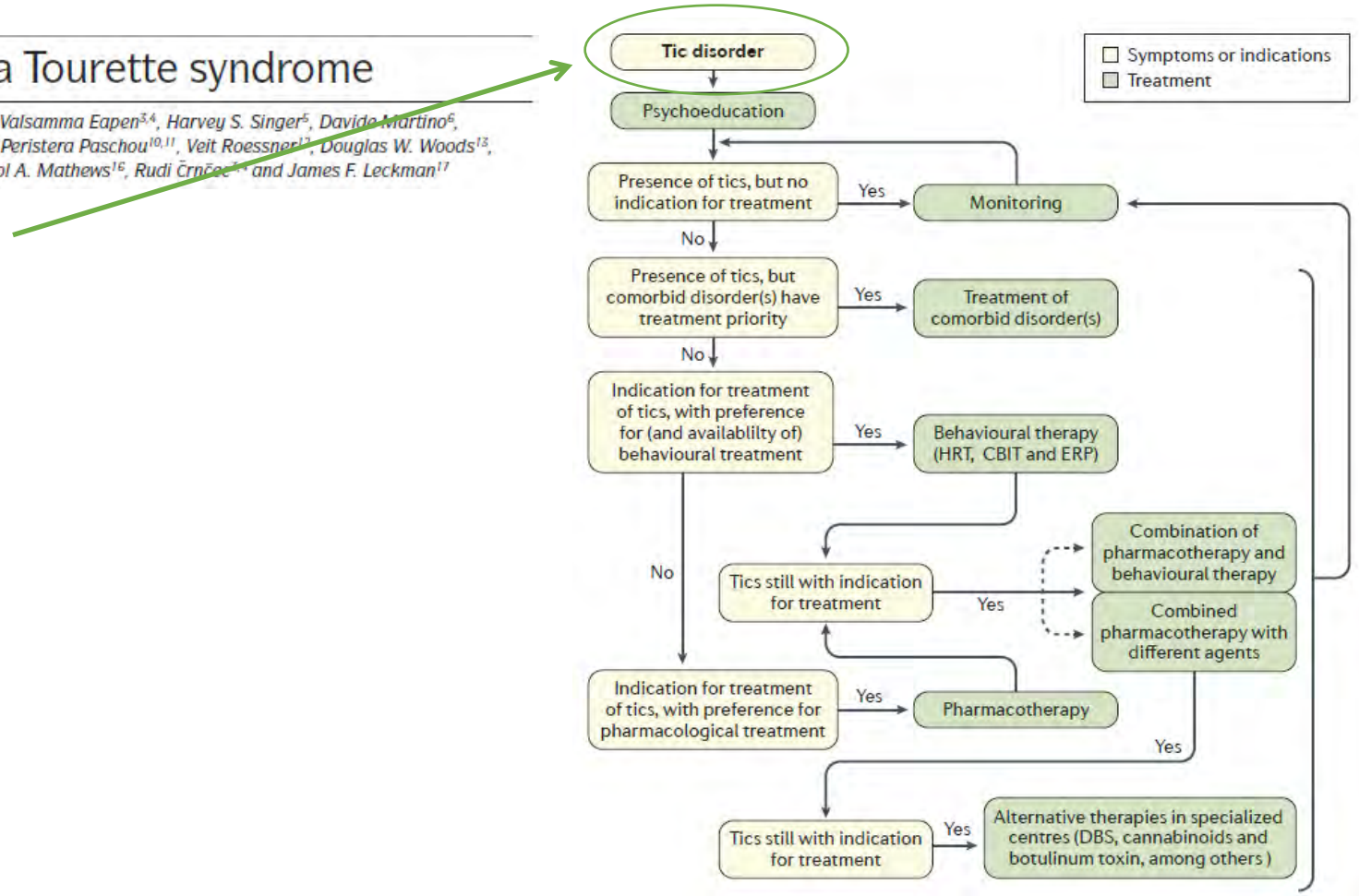
Mueller-vahl.Kirsten@mh-hannover.de

2023 Brussels

Treatment of Tics

Gilles de la Tourette syndrome

Mary M. Robertson[1,2], Valsamma Eapen[3,4], Harvey S. Singer[5], Davide Martino[6], Jeremiah M. Scharf[7–9], Peristera Paschou[10,11], Veit Roessner[12], Douglas W. Woods[13], Marwan Hariz[14,15], Carol A. Mathews[16], Rudi Črnčec[3,4] and James F. Leckman[17]



DSM-5: Tic disorders

- 307.20 Other specified tic disorder (specify reason)
- 307.20 Unspecified tic disorder
- 307.21 Provisional tic disorder
- 307.22 Persistent (chronic) motor or vocal tic disorder (specify motor or vocal)
- 307.23 Tourette's disorder

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

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]

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

Summary statement
Patients' perspectives
Editorial

2023 ISSELS

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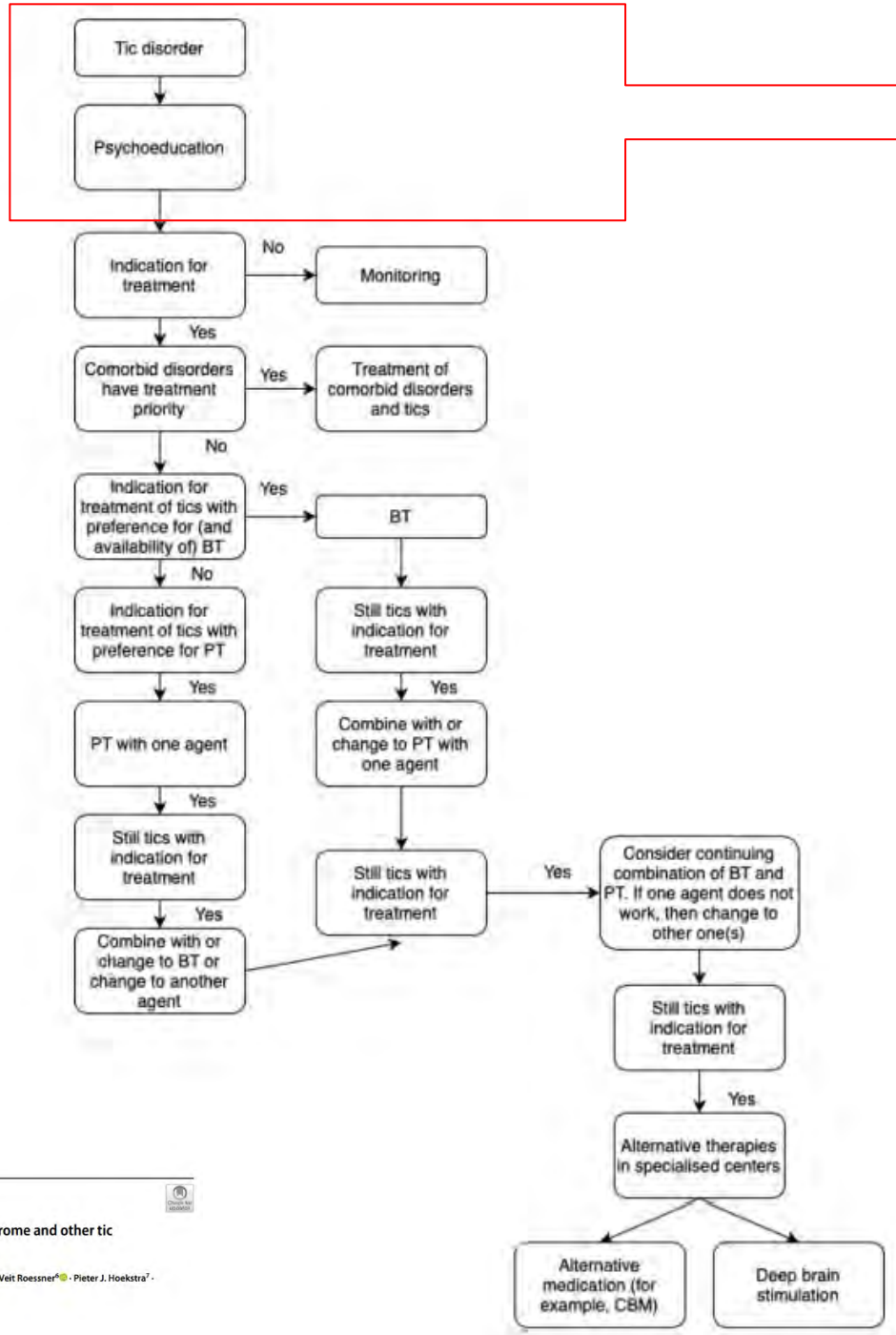

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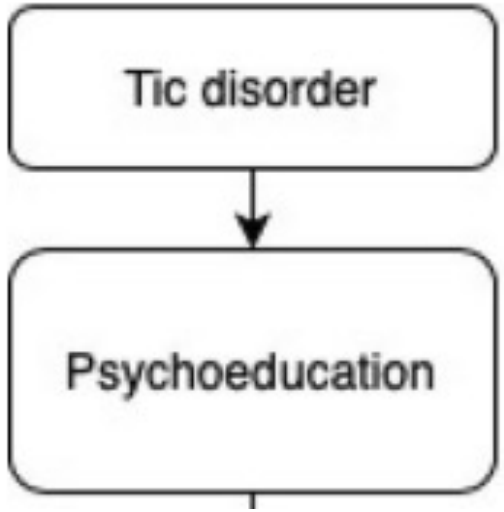

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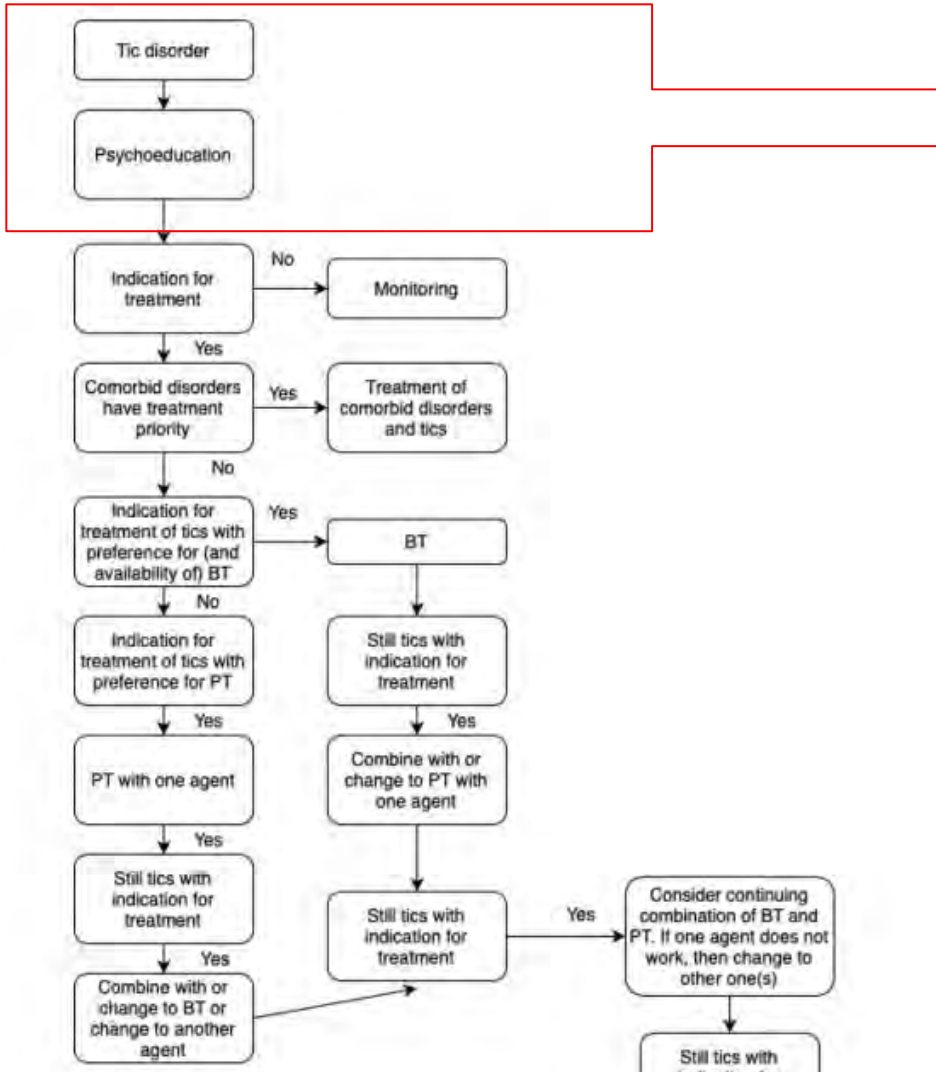

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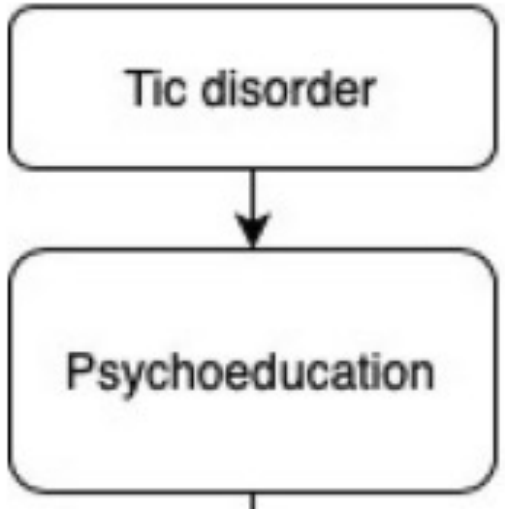

- Typical course of tics
- Prognosis
- Comorbidities
- Treatment options
- Presentation in TV/social media
- Advocacy groups
- Information for school/work

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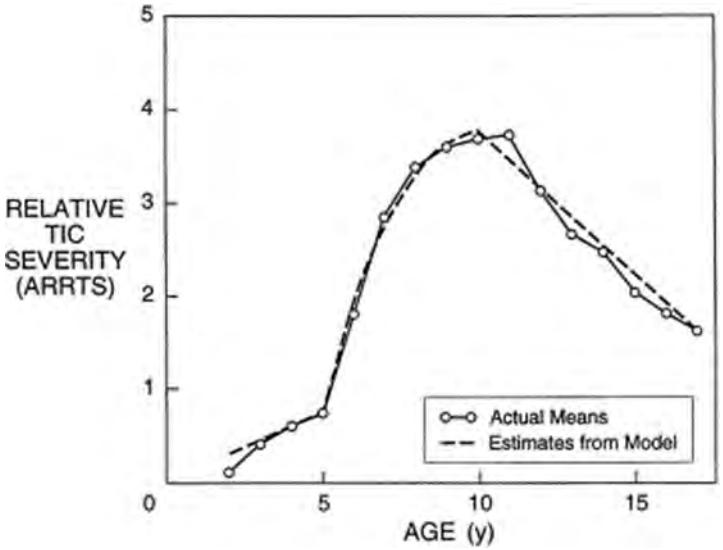
Course of Tics

- 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

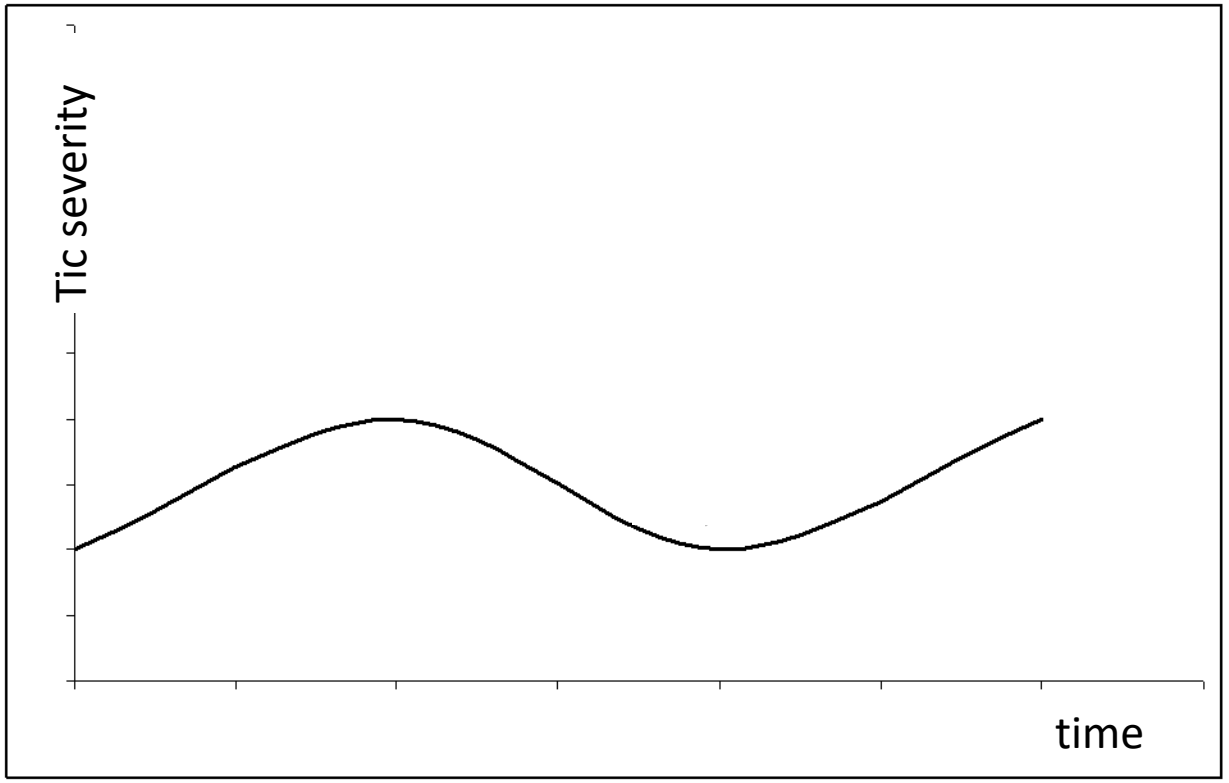
Ann M. Iverson [1] and Kevin J. Black [2,*]

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	

Waxing and waning



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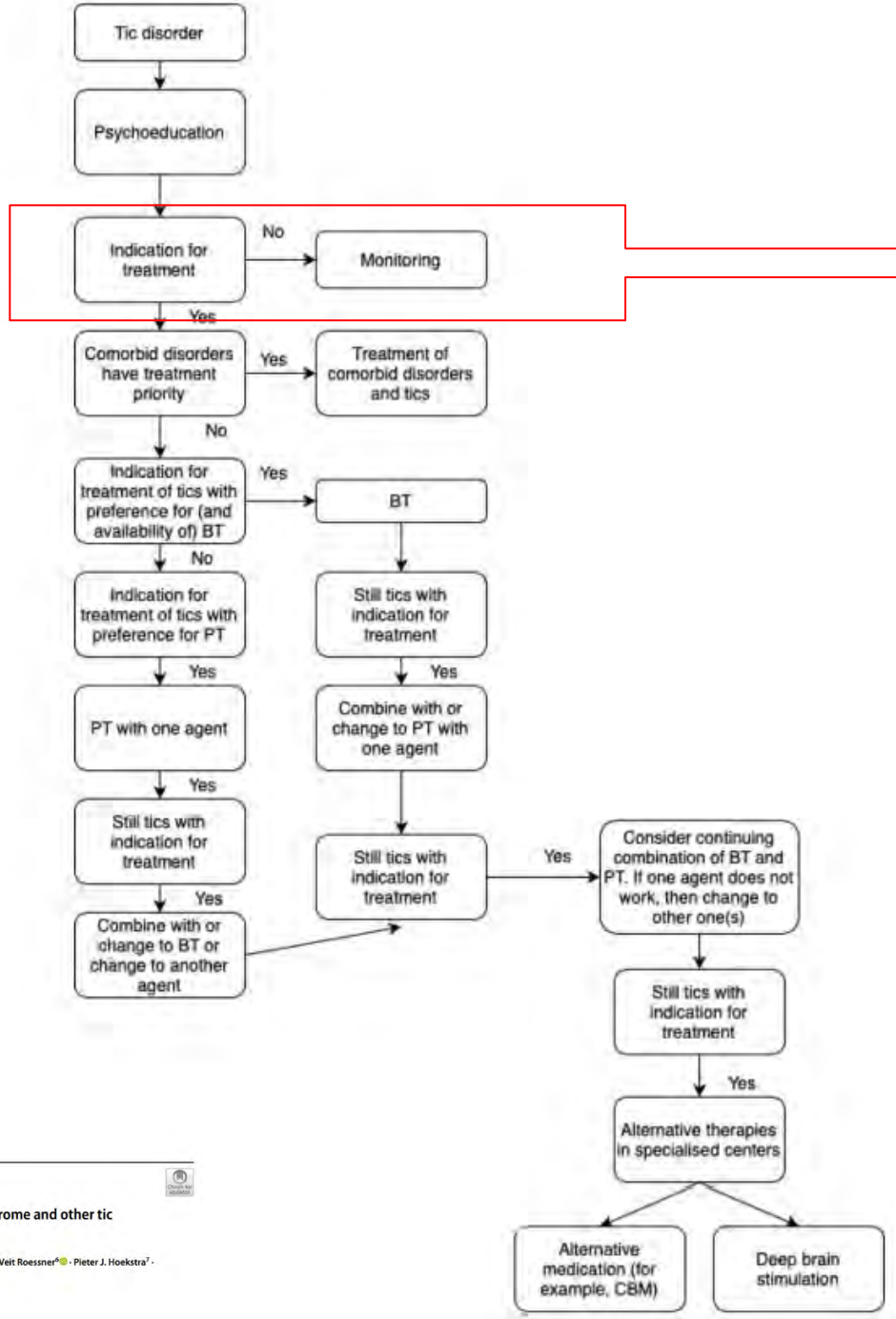

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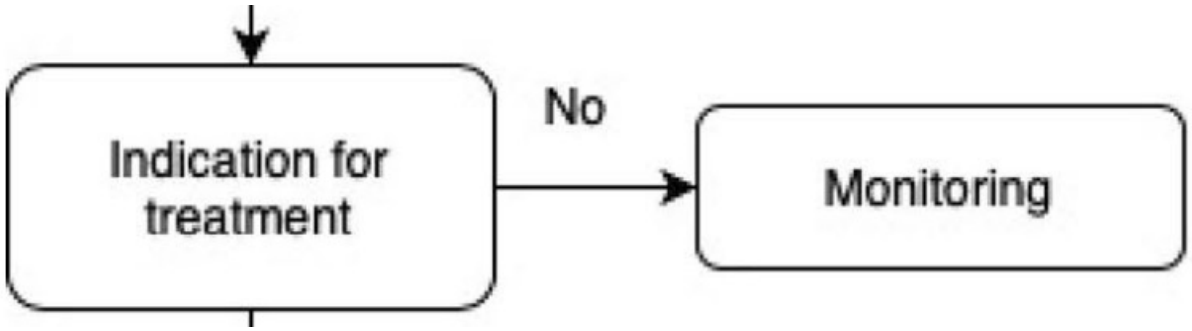
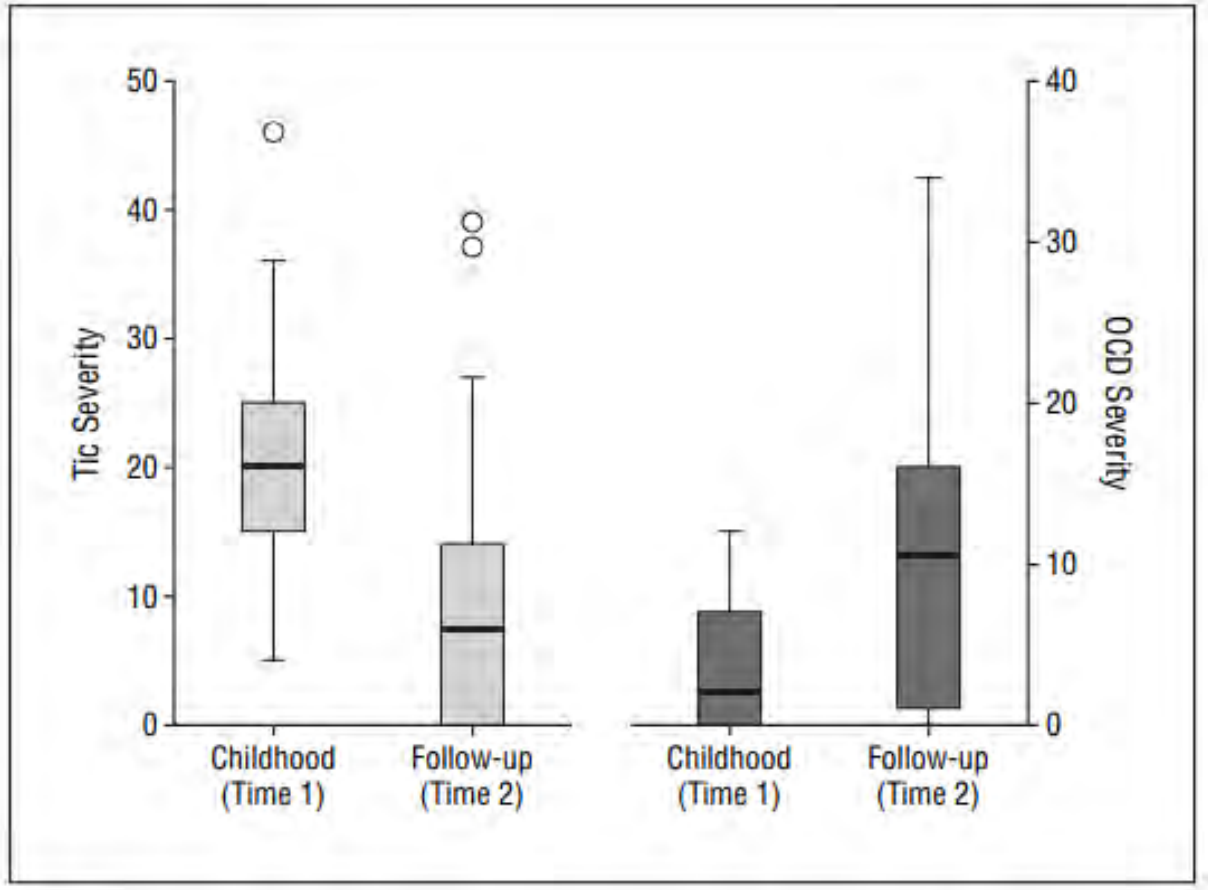


Course of Tourette Syndrome



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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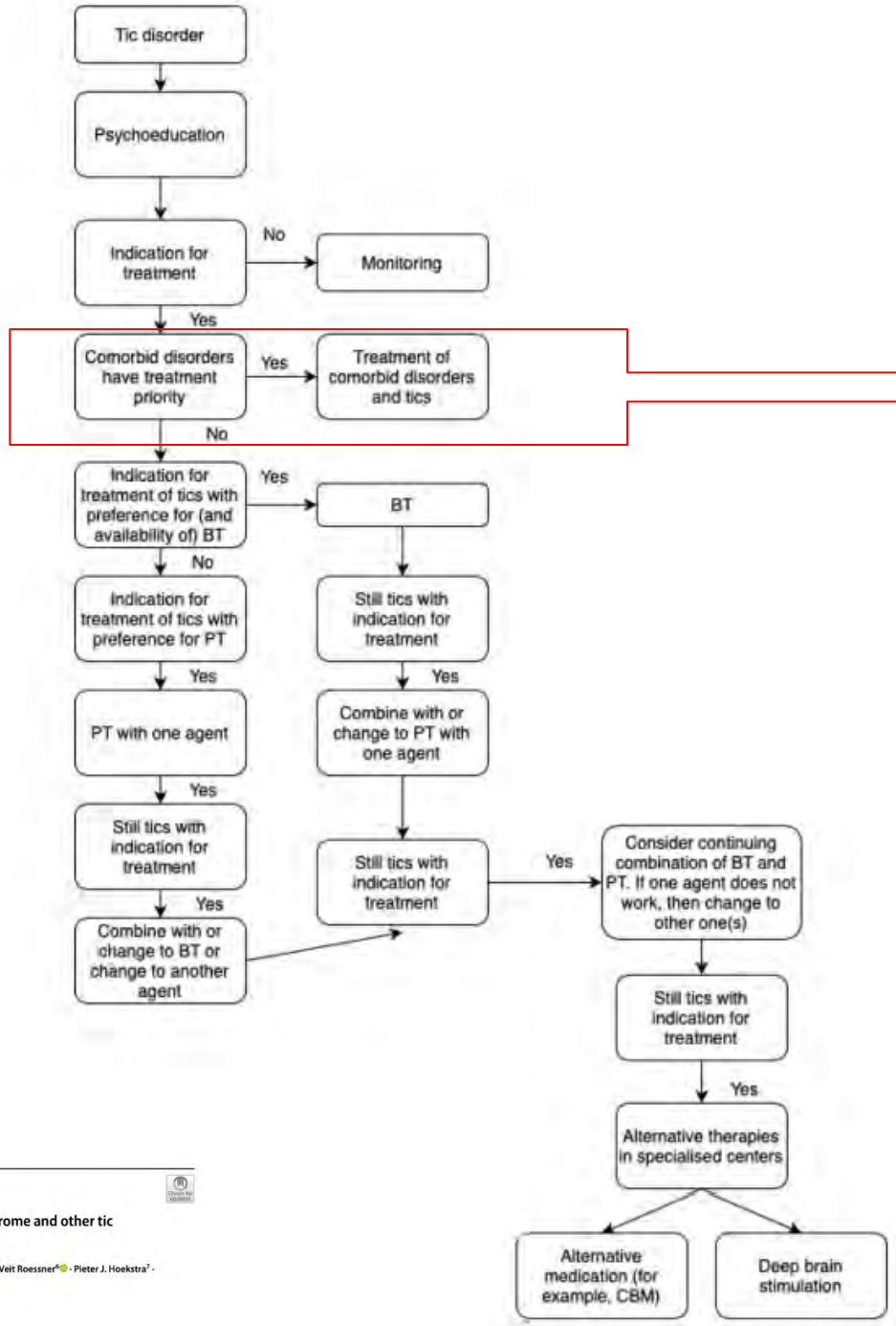

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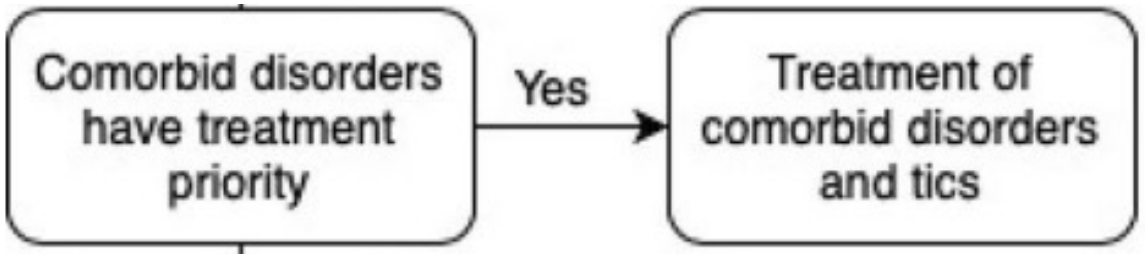

Effects of comorbidity on Tourette's tic severity and quality of life

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]

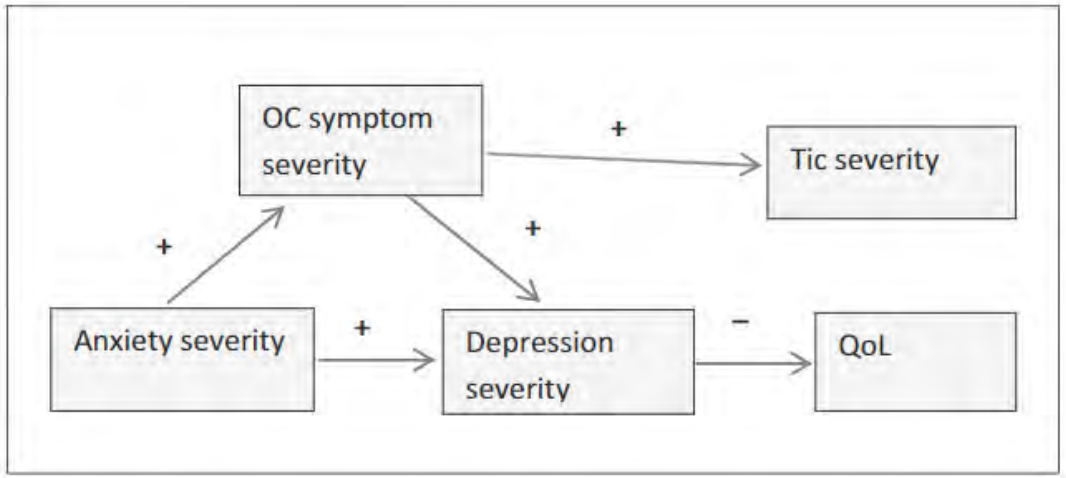

FIGURE 3 Graphic representation of a potential model combining the results of our study. +, Positive effect; –, Negative effect

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.

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.

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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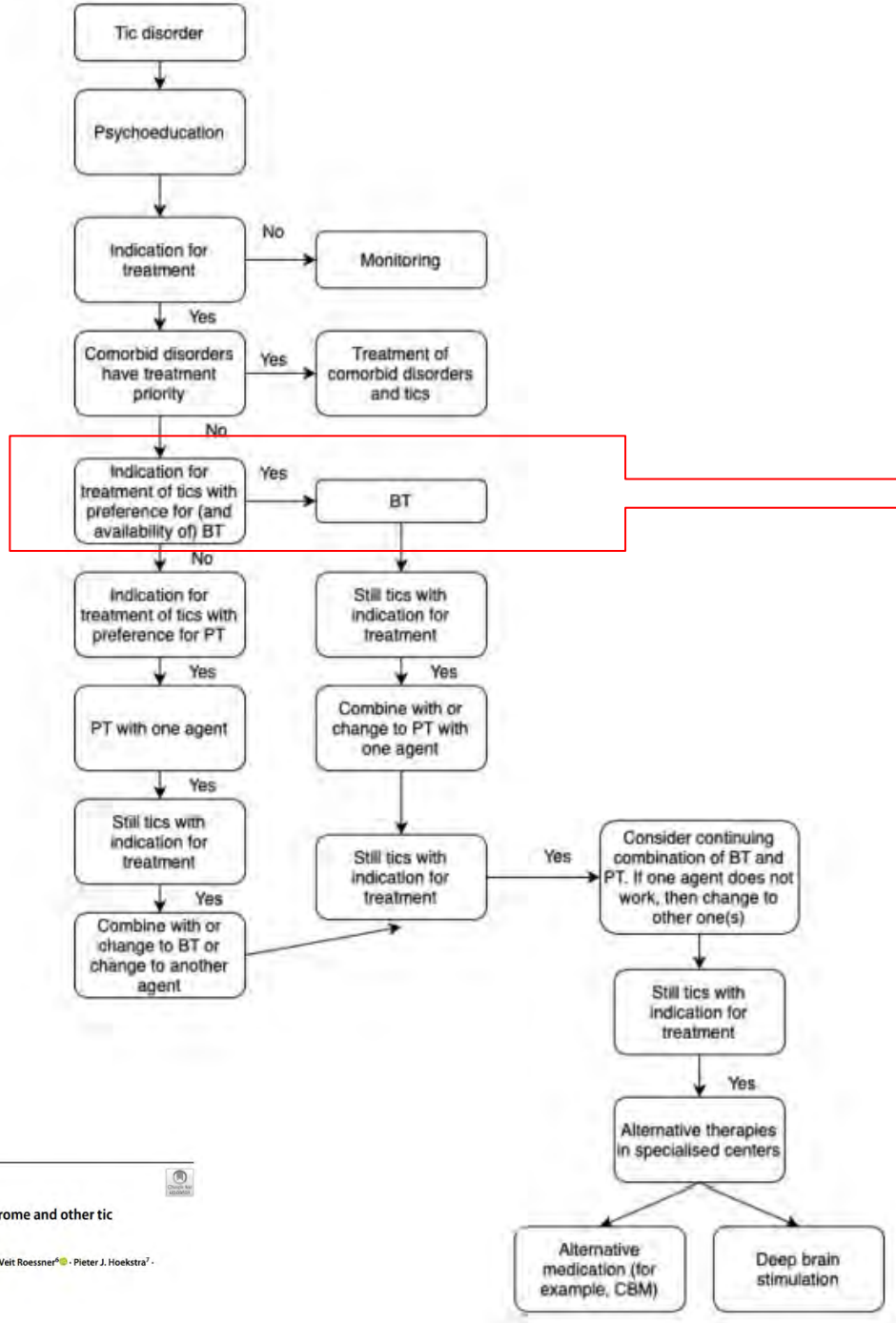

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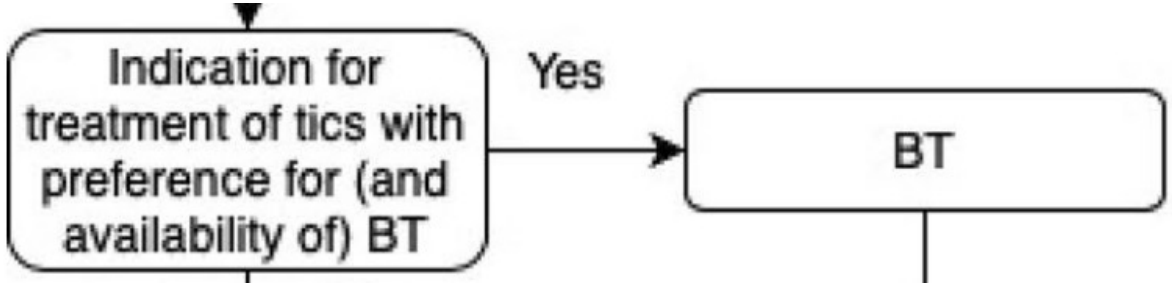

BT=Behavioral Therapy

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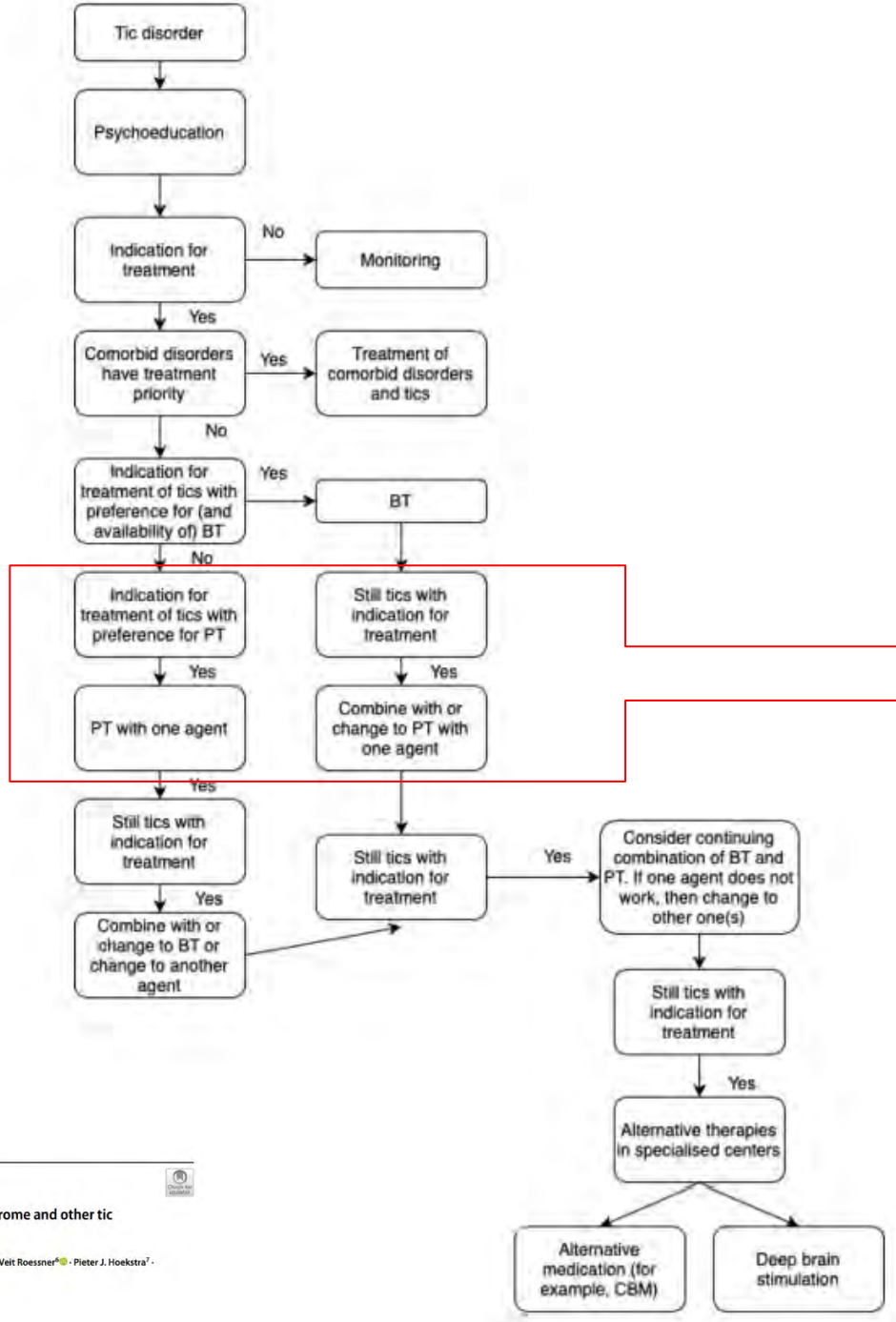

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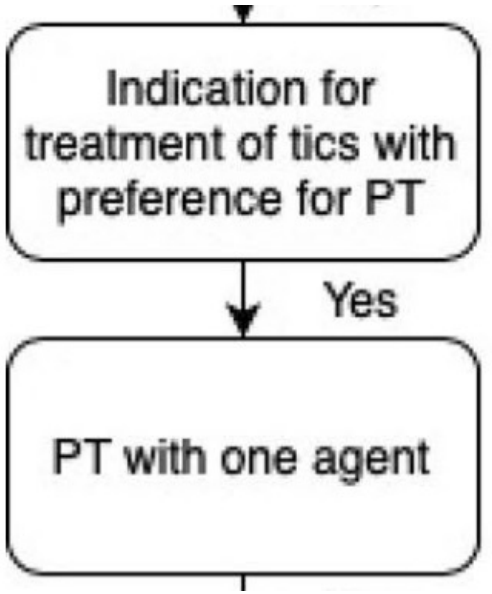

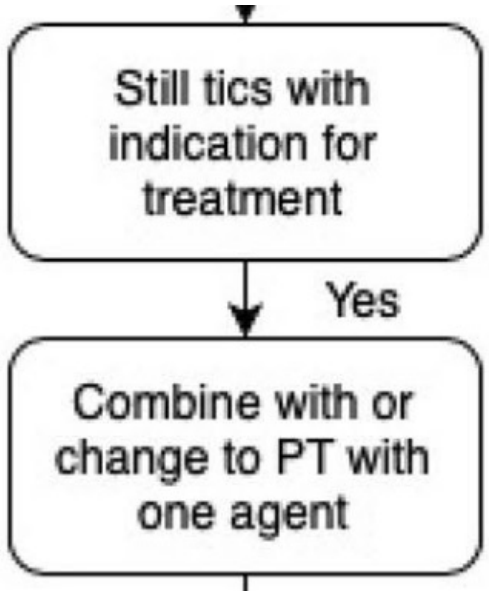

Licensed for Treatment of Tics/Tourette Syndrome

- 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.

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REVIEW

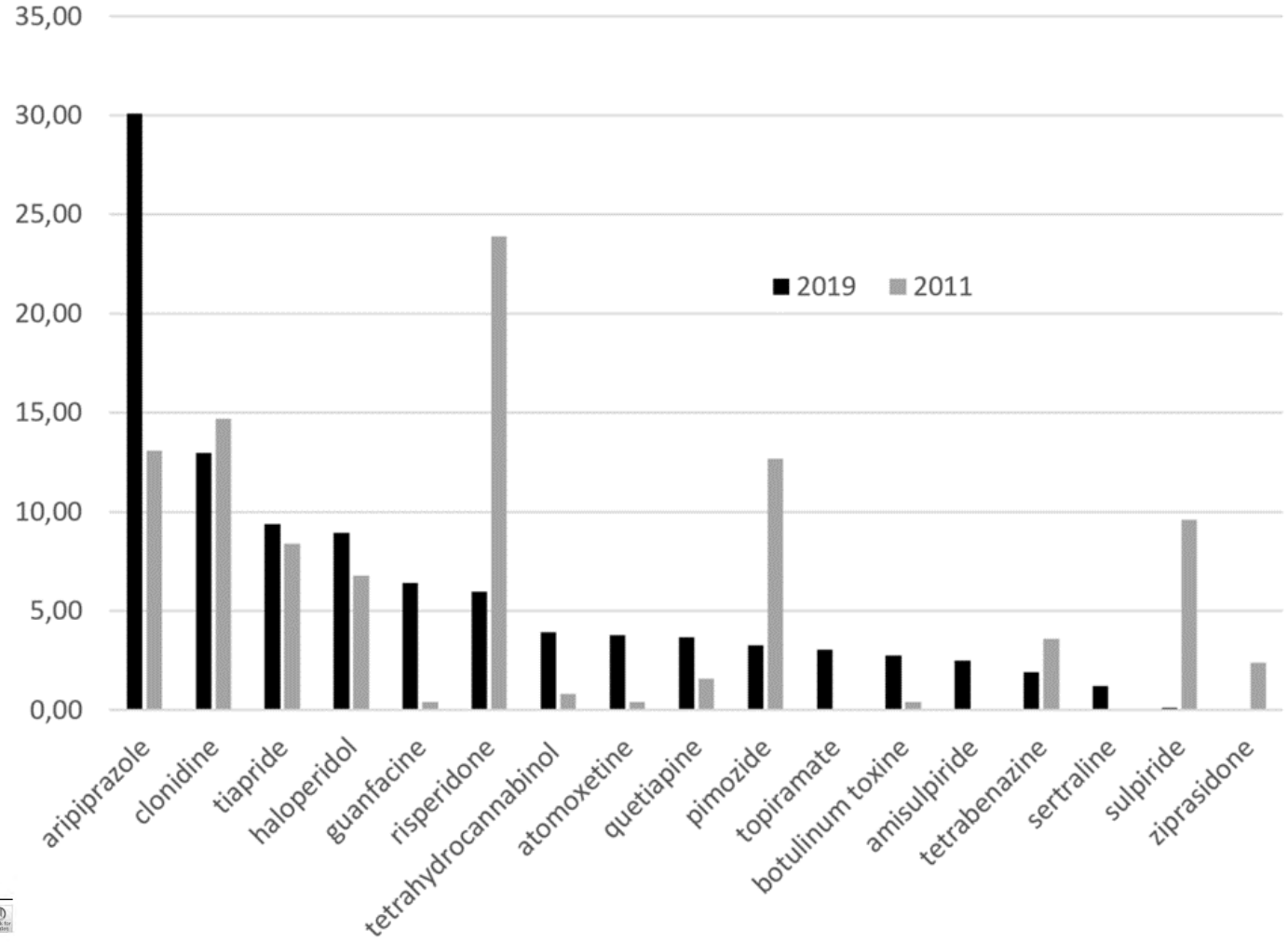
European clinical guidelines for Tourette syndrome and other tic disorders—version 2.0. Part III: pharmacological treatment

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.

ESSTS Survey: clinical practice: 2011 vs. 2019



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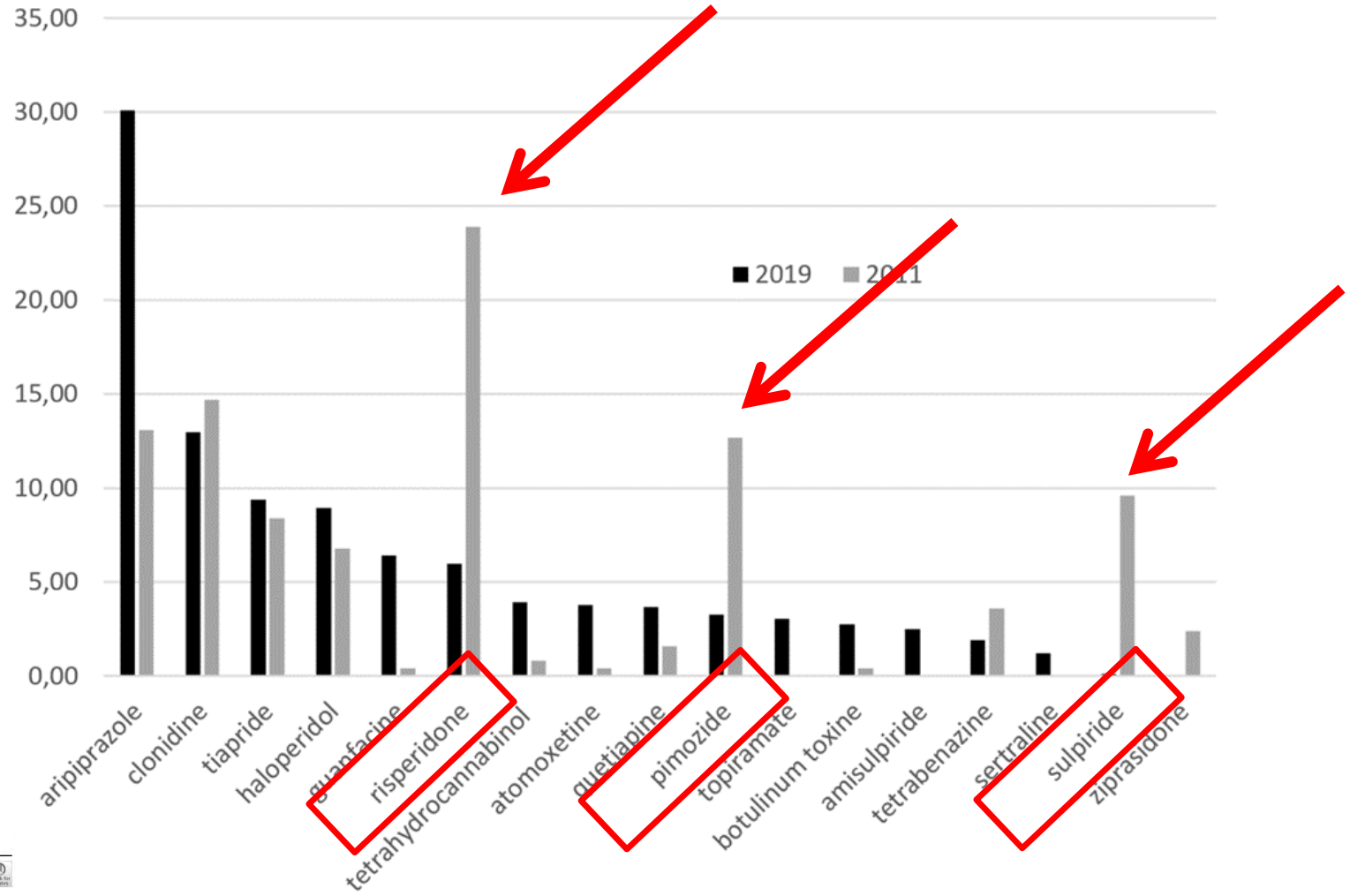

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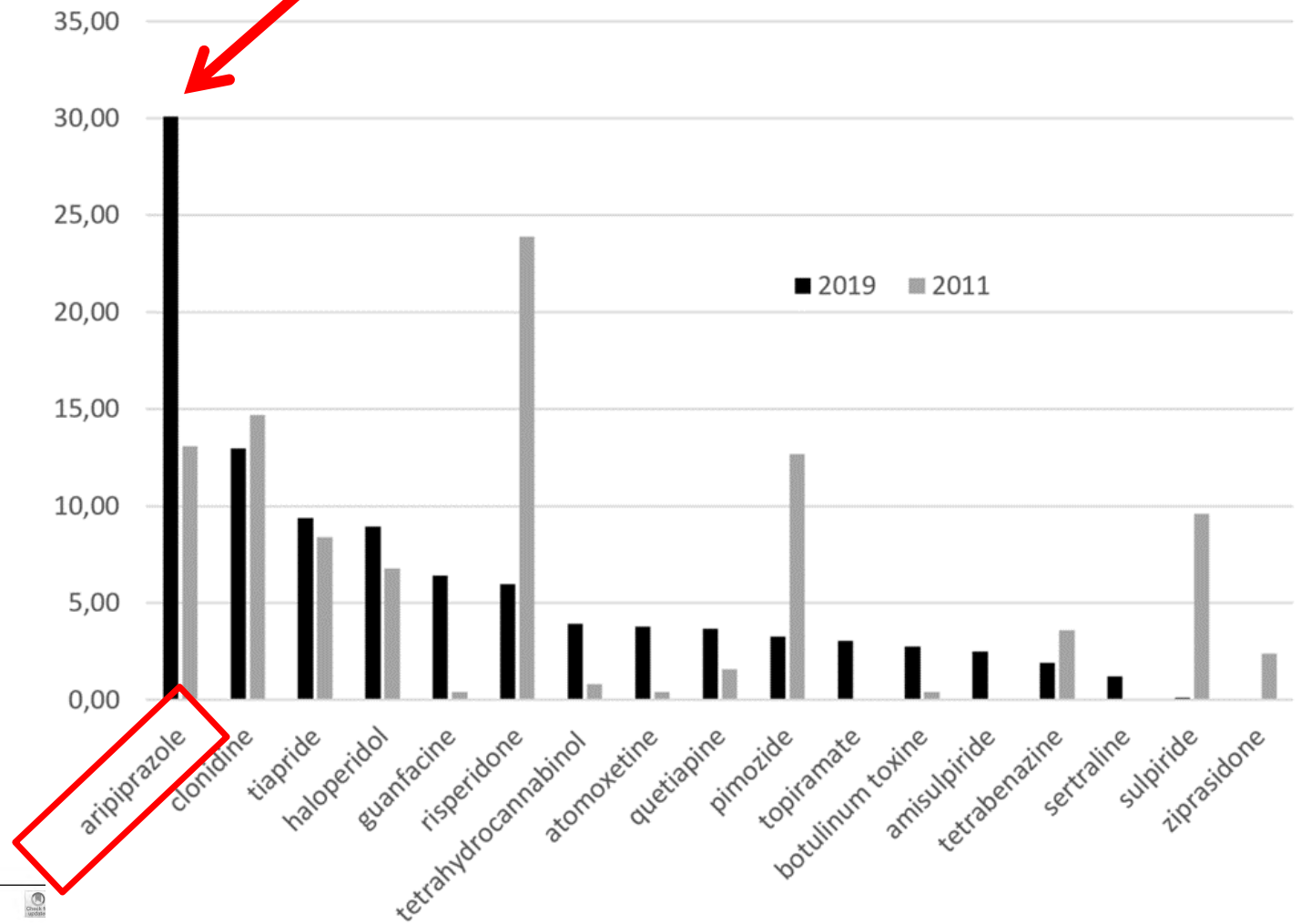

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Veit Roessner[1] · Heike Eichele[2,3] · Jeremy S. Stern[4] · Liselotte Skov[5] · Renata Rizzo[6] · Nanette Mol Debes[5] · Péter Nagy[7] · Andrea E. Cavanna[8] · Cristiano Termine[9] · Christos Ganos[10] · Alexander Münchau[11] · Natalia Szejko[12,13,14] · 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]

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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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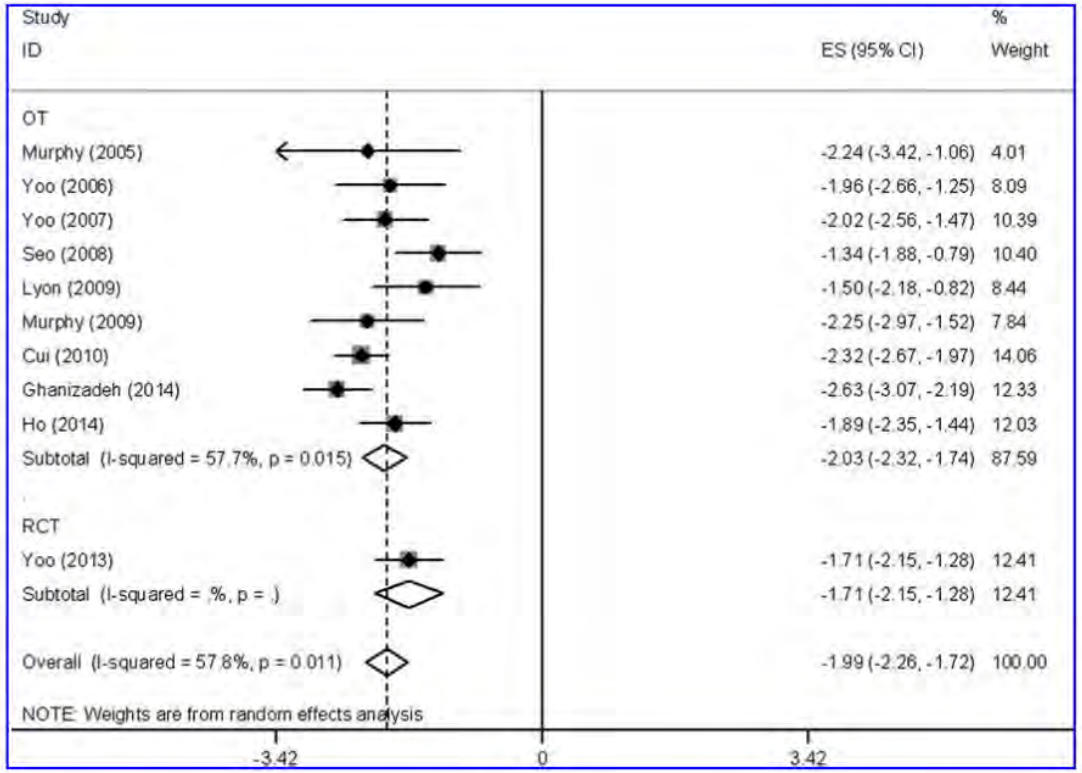
Original Article

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]

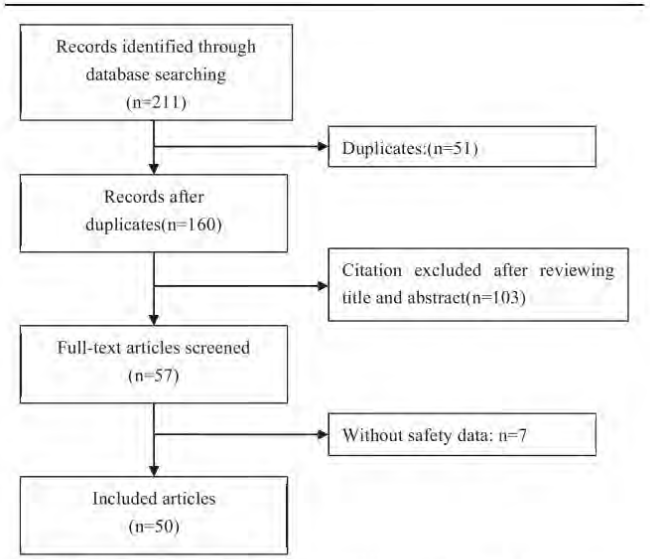


Figure 1. Flow chart of literature screening and the selection process.

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: how to do?

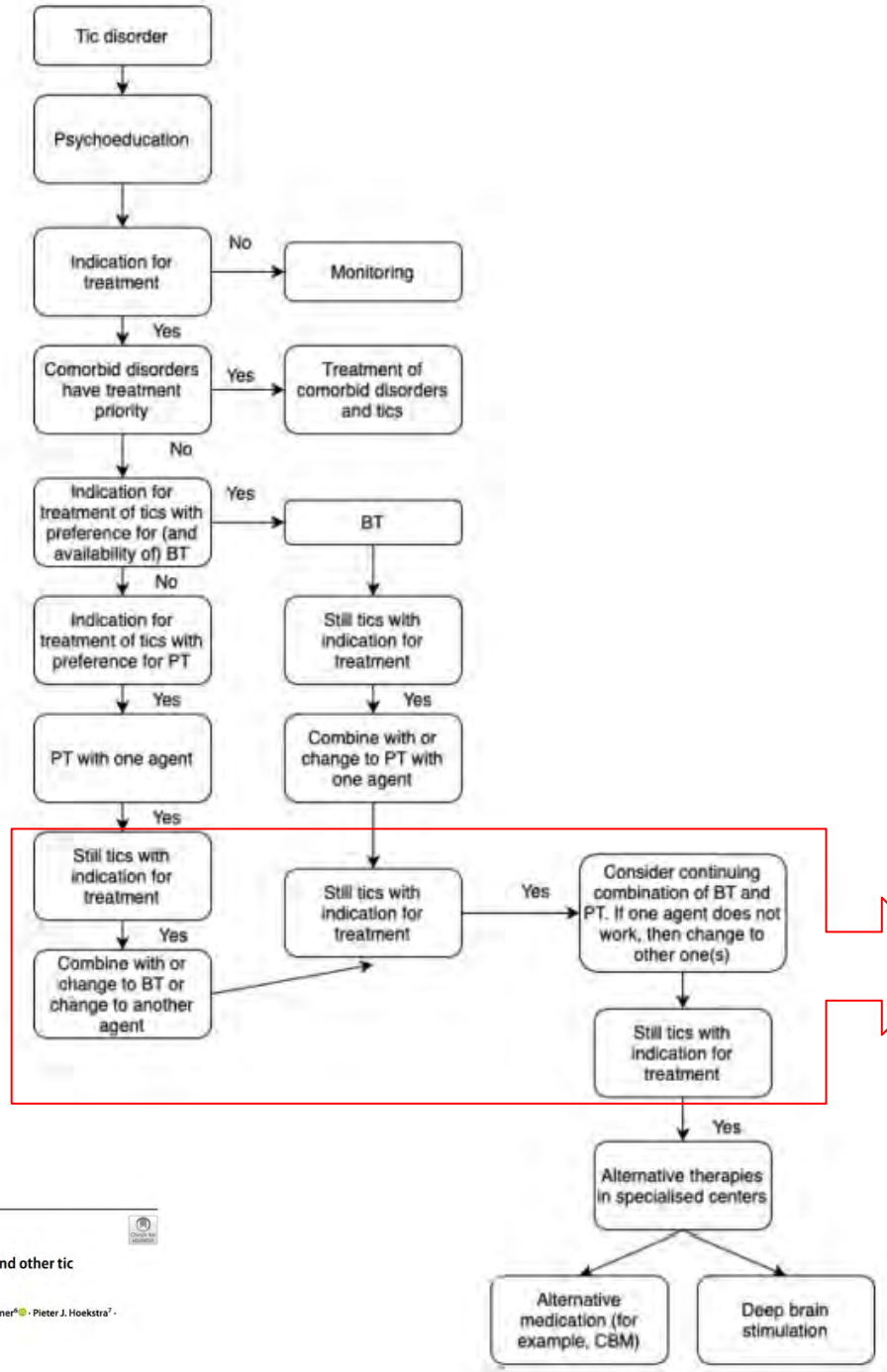
- Start low
- Go slow
- Increase dosage until tics decrease or intolerable side effects occur
- Find the individually optimal dose together with the patient/parents
- Adapt the dose depending on kind and severity of tics

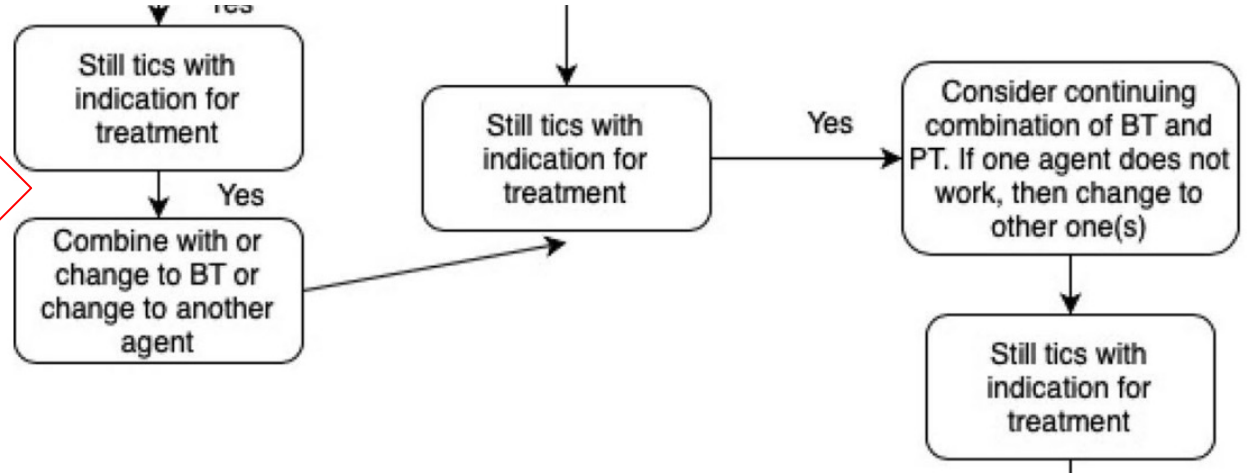
Treatment with Antipsychotics: what to expect?

Antipsychotics

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

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

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]

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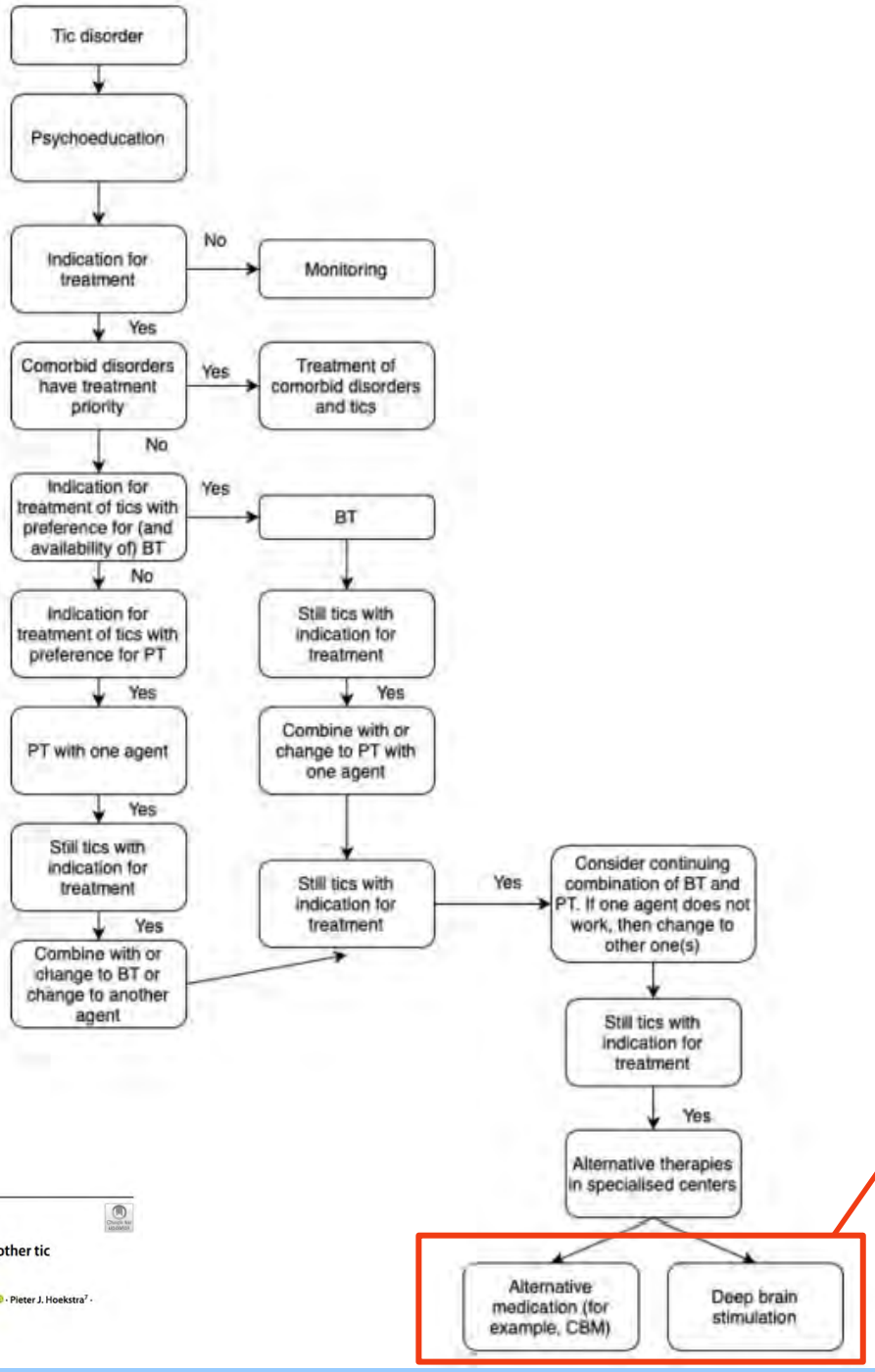
Fig. 1 Algorithm for the treatment of patients with TS based on shared clinician patient decision making (adapted with permission from [14], Springer). *TS* Tourette syndrome, *PT* pharmacotherapy, *BT* behaviour therapy, *CBM* cannabis-based medicine



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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
Müller-Vahl et al. (2023)	Germany	97	Randomized, double-blind, placebo-controlled, parallel groups	Nabiximols	Non-significant tic reduction: Primary endpoint (responder criterion 25% tic reduction) narrowly missed Several secondary endpoints reached

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.

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

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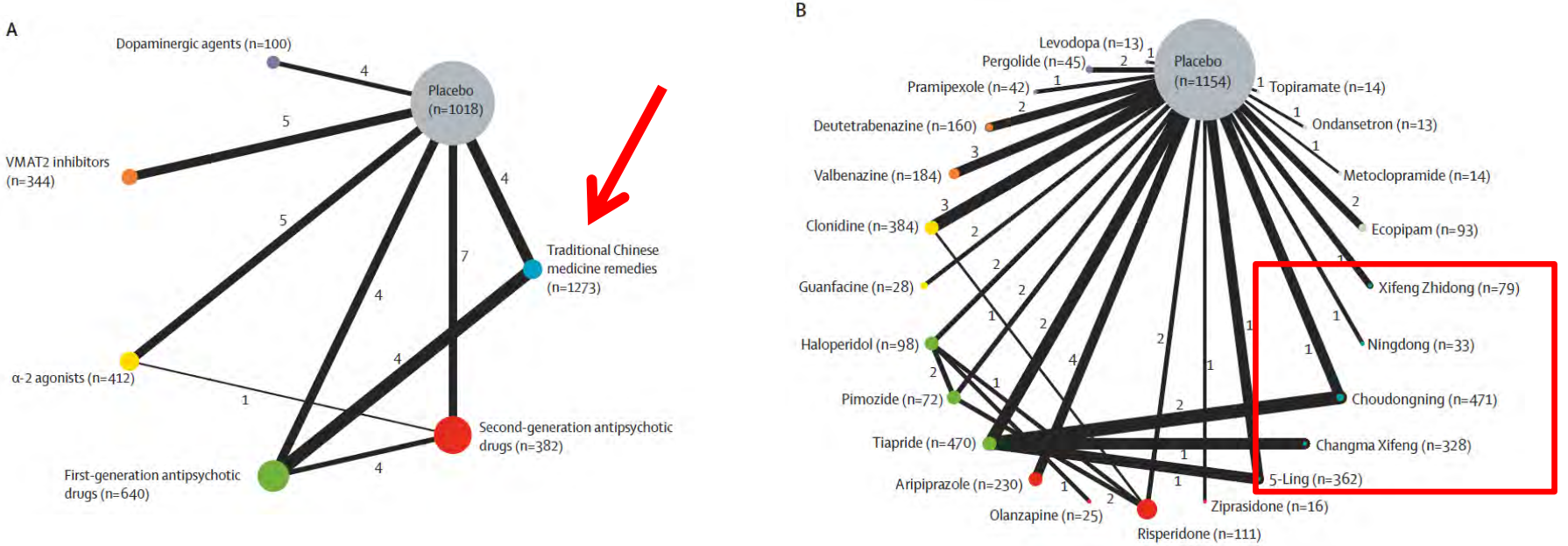


Figure 2: **Network plots for efficacy for medication categories (A) and medications individually (B)**
The nodes are coloured according to their medication category, and their size is proportional to the number of groups that included that treatment. The number of studies for each comparison is illustrated by the number besides the black line, and its thickness is proportional to the precision of the direct estimate for that comparison. The number of participants who were included in the analyses for each treatment are shown in parentheses. VMAT2=vesicular monoamine transporter 2.

Recent studies: promising new compounds

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

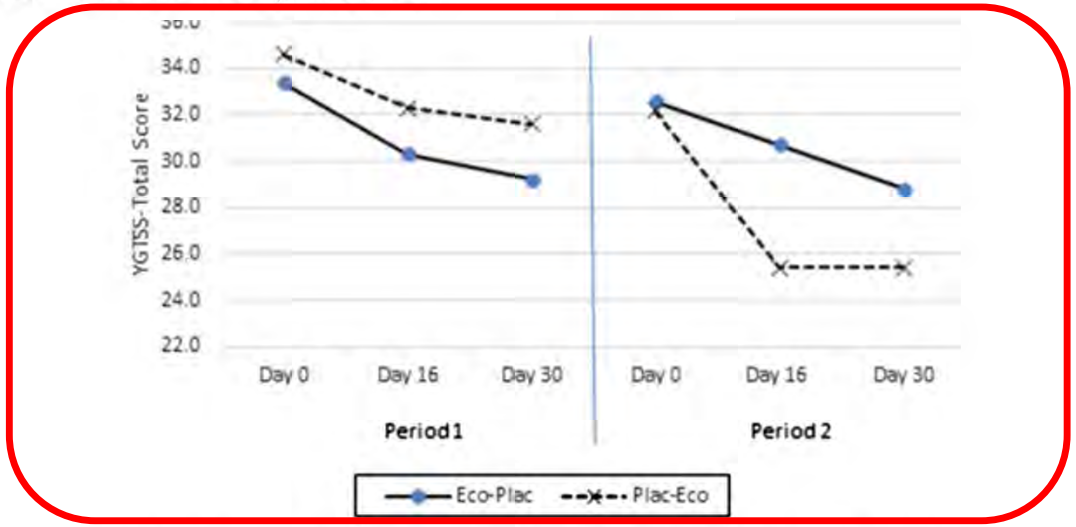


FIG. 2. Treatment effects by period. YGTSS, Yale Global Tic Severity Scale; YGTSS-total score, motor and phonic tic scores, the primary outcome for the trial; Eco-Plac, ecopipam in period 1, followed by placebo in period 2; Plac-Eco, placebo in period 1, followed by ecopipam in period 2. Means are from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

Brussels 2023

Paragon's Portfolio Company Emalex Biosciences Announces Positive Topline Results from Phase 2b Clinical Study Evaluating Ecopipam for Pediatric Tourette Syndrome

November 10, 2021

The D1AMOND Study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of ecopipam in 153 children and adolescents (ages 6 to < 18) conducted at 63 sites across the U.S., Canada and Europe. Patients were randomized to receive either ecopipam tablets at a dose of 2 mg/kg/day or placebo tablets. Study medication was titrated to the target dose over four weeks and then maintained for an eight-week treatment period. The primary efficacy endpoint was the change from Baseline to Week 12 in the Yale Global Tic Severity Score-Total Tic Score (YGTSS-TTS). Statistically significant and clinically meaningful results were obtained on this primary endpoint at all timepoints, from Week 4 to Week 12. The key secondary endpoint, the Clinical Global Impression of Tourette Syndrome Severity (CGI-TS-S), was also statistically significant at all timepoints from Week 6 to Week 12.

Emalex Biosciences Announces First Patient Dosed in Phase 3 Trial of Ecopipam for Tourette Syndrome

Enrolled patients will receive medication for up to 24 weeks; 90 sites planned for North America and Europe

CHICAGO, March 1, 2023 /PRNewswire/ -- Emalex Biosciences announced that the first patient was dosed in its Phase 3 clinical trial evaluating ecopipam for the treatment of Tourette Syndrome.

Participants in the trial receive ecopipam for 12 weeks in the open-label phase of the study. Those with at least a 25% reduction in the Yale Global Tic Severity Scale-Total Tic Score (YGTSS-TTS) at both week 8 and 12 will be randomized to continue on ecopipam or placebo in the double-blind phase of the study until they relapse, up to an additional 12 weeks. Efficacy will be assessed as the difference in time-to-relapse between groups.

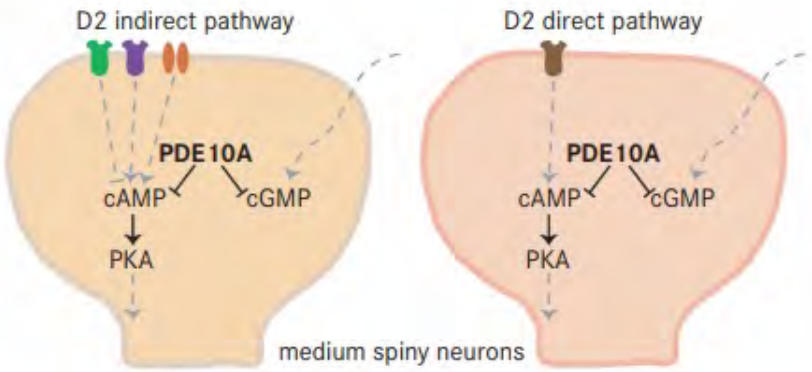
Noema Pharma initiates Phase 2a Allevia study of PDE10A inhibitor NOE-105 in Tourette Syndrome

PDE10A = Phosphodiesterase 10A

- PDE10A has very limited distribution and is mainly expressed in medium spiny neurons (MSNs) of the **striatum** and **substantia nigra**
- Synergistic dopamine type D1 and D2 receptors are also expressed on striatal MSNs
- PDE10A acts **postsynaptically on dopamine signaling** by controlling the availability of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)

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

Recent studies: negative results

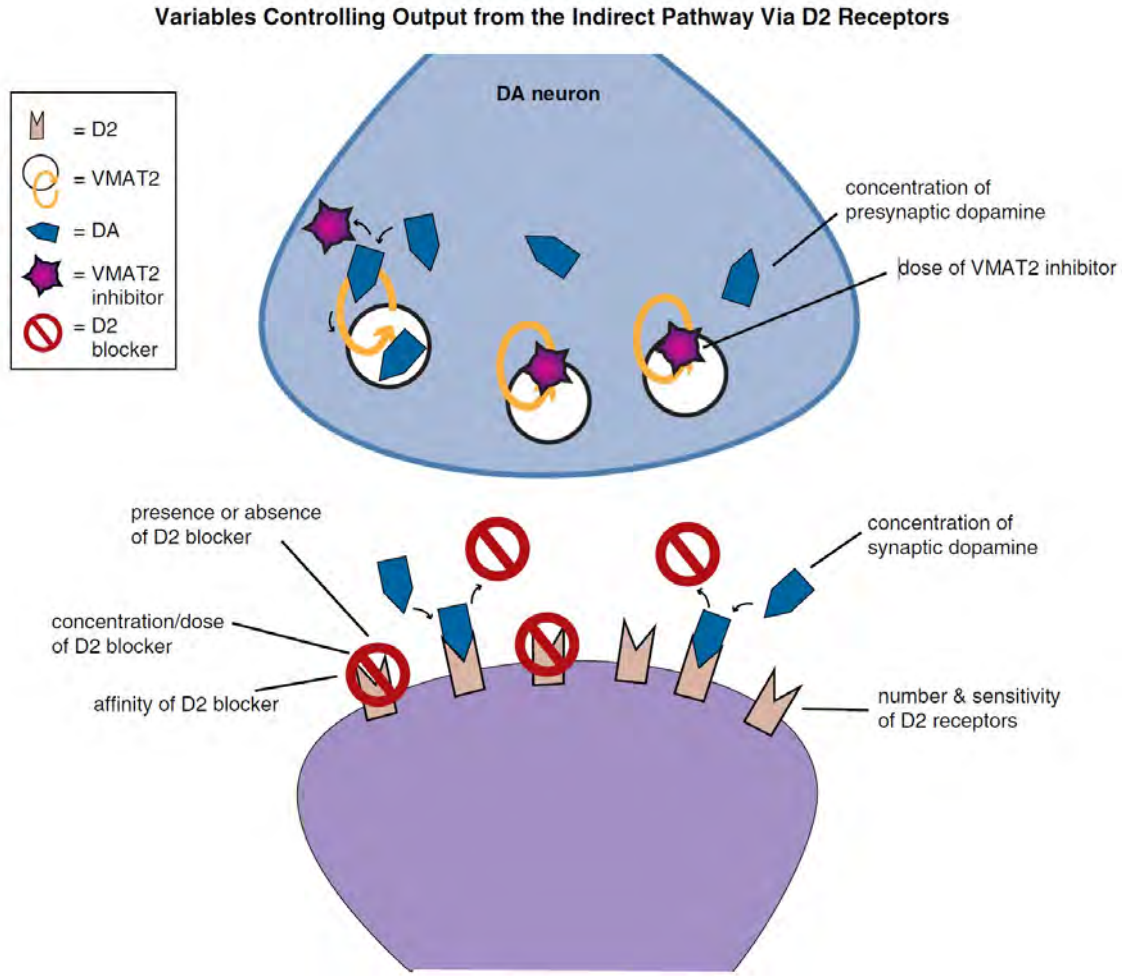
Vesicular monoamine transporter (VMAT2) Inhibitors

Tetrabenazine
Deutetrabenazine
Valbenazine

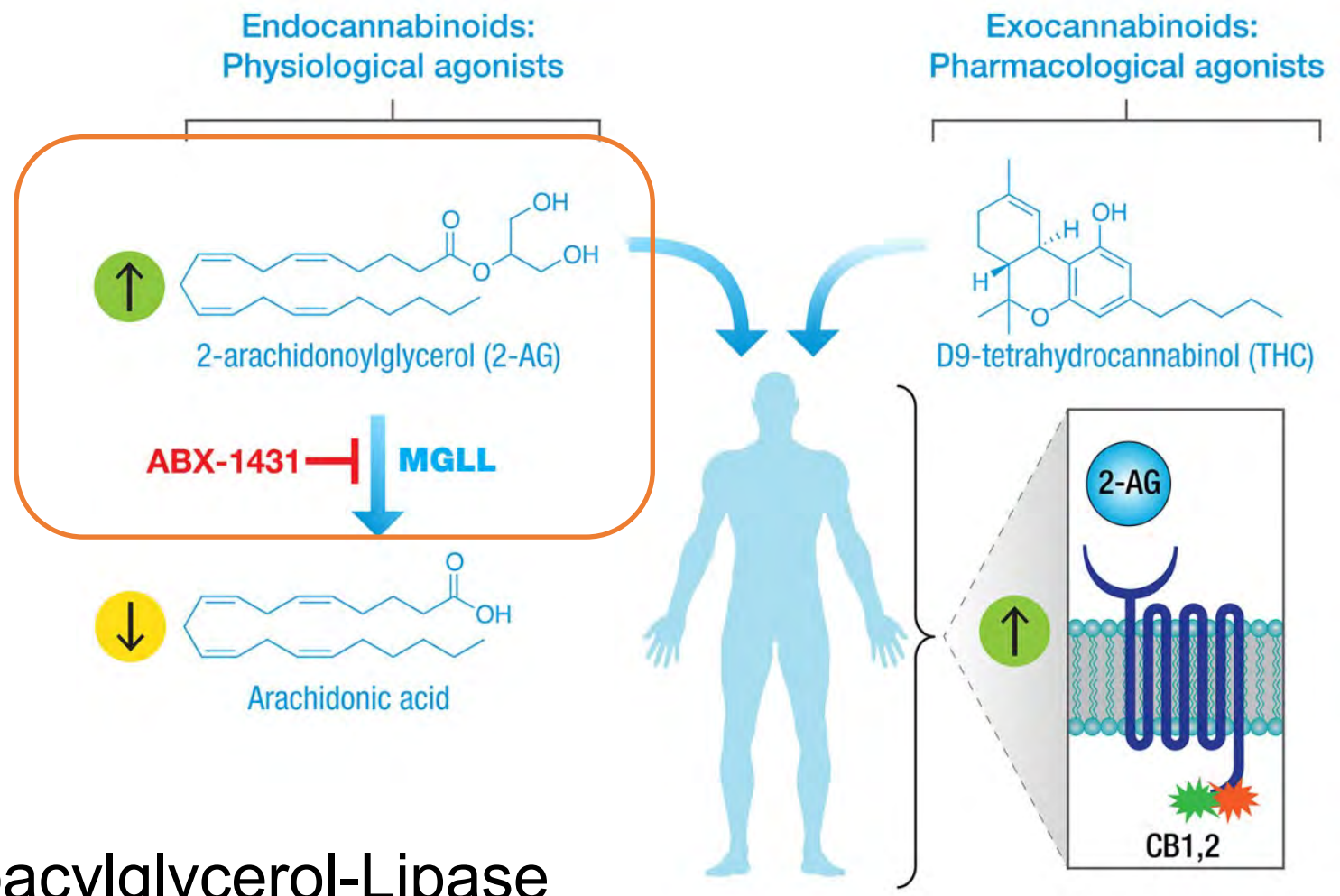
VMAT2 inhibitors reduce:

- DA storage
- DA release

→ ↓ Dopamine

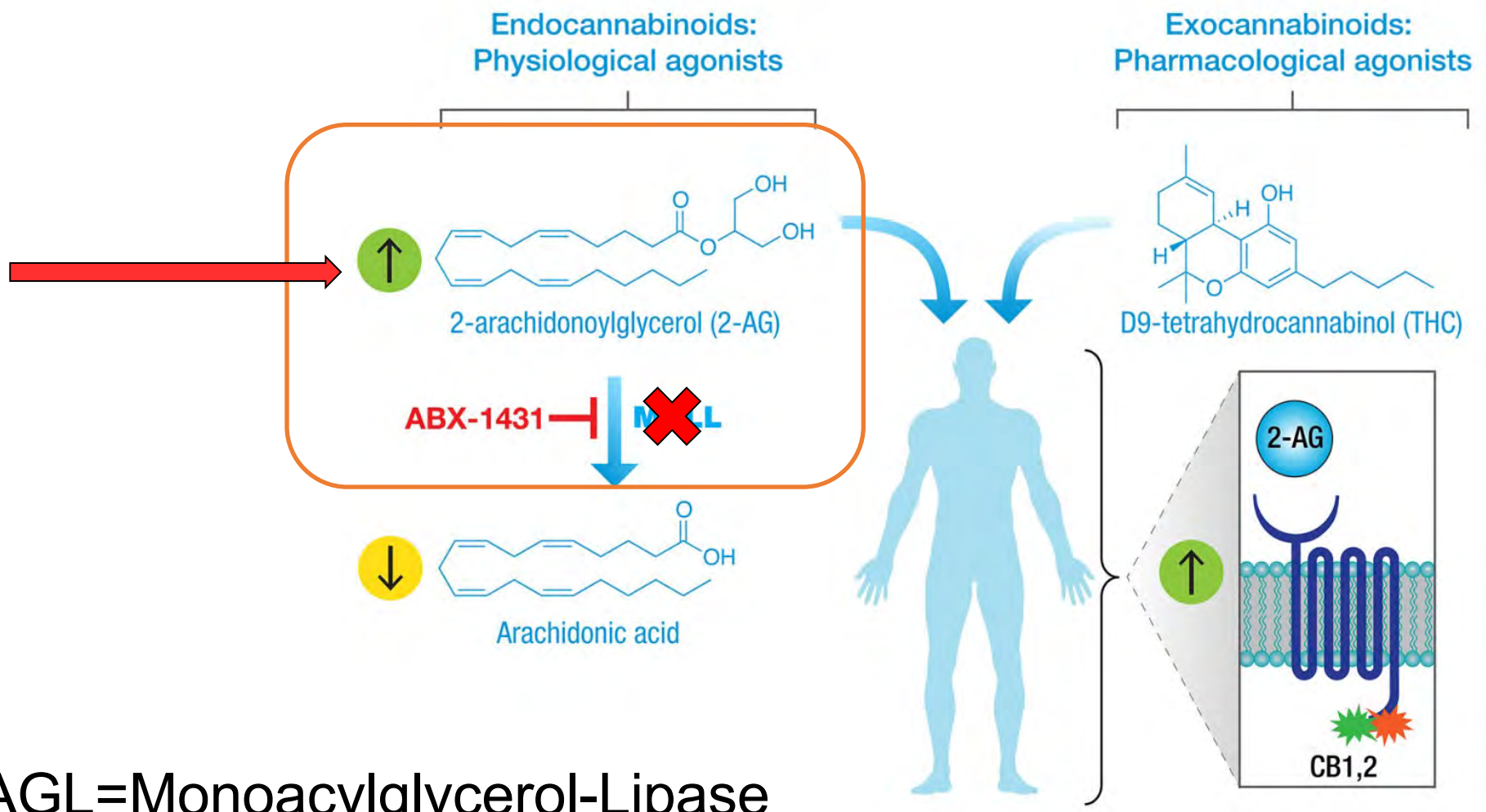


Endocannabinoid Modulator: MAGL Inhibitor: ABX-1431 (Lu AG06466)



MAGL=Monoacylglycerol-Lipase

Endocannabinoid Modulator: MAGL Inhibitor: ABX-1431 (Lu AG06466)



MAGL=Monoacylglycerol-Lipase

„PANDAS Diagnostic Guidelines"

1. Presence of OCD and/or tics, particularly multiple, complex or unusual tics
2. Age Requirement (Symptoms of the disorder first become evident between 3 years of age and puberty)
3. Acute onset and episodic (relapsing-remitting) course
4. **Association with Group A Streptococcal (GAS) infection**
5. Association with Neurological Abnormalities

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

Correspondence
Dr. Martino
davide.martino@ucalgary.ca

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

Pharmacotherapy of Tics

- **1. choice: antipsychotics**
  - aripiprazole
  - others: risperidone, tiapride
- **2. choice:**
  - in adults: cannabis based medicine
  - in children: clonidine (when ADHD comorbid)
  - in carefully selected patients: botulinum toxine
- **3. choice:**
  - topiramate (?)
  -